Atrial fibrillation and heart rate at long-term electrocardiograms

Persson, Anders P

2025

Document Version:
Publisher's PDF, also known as Version of record

Atrial Fibrillation and Heart Rate at Long-term Electrocardiograms

ANDERS PERSSON
DEPARTMENT OF CLINICAL SCIENCES MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

Atrial Fibrillation and Heart Rate at Long-term Electrocardiograms

Atrial Fibrillation and Heart Rate at Long-term Electrocardiograms

Anders Persson

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University. To be publicly defended in room 2007, Skånes Universitetssjukhus, Malmö, Inga Marie Nilssons gata 47 floor 2 Thursday 22nd May 2025 at 13.00.

Faculty opponent
Docent Nils Edvardsson MD, PhD Gothenburg University

Organization: LUND UNIVERSITY

Document name: Doctoral dissertation **Date of issue** 22 May 2025

Author(s): Anders Persson **Sponsoring organization:**

Title and subtitle: Atrial fibrillation and heart rate at long-term electrocardiograms

Abstract:

Atrial fibrillation (AF) is common condition among the elderly, and leads to increased risks of stroke, heart failure, dementia, and death. Diagnosing AF requires electrocardiograms (ECGs), and long recordings may be necessary since AF often occurs intermittently in its early stages. During AF, the heart rate is irregular, and sometimes inappropriately fast. This thesis includes four papers that study long-term ECGs for AF prediction and management.

In Paper I we used the population-based Swedish CArdioPulmonary bioImage Study to establish normal ranges for ambulatory heart rate during sinus rhythm. The normal range was wide, and largely independent of clinical correlates.

In Paper II and III we used the population-based Malmö Diet and Cancer Study to show that low heart rates at 24hECGs are associated with increased incidence of AF and that patients with short, irregular supraventricular tachycardias (SVTs) without discernible P-waves had substantially increased risk of AF (adjusted hazard ratio 4.95, 95% confidence interval (CI) 2.06-11.9).

Electrocardiograms are also used to measure resting heart rates during AF, to dose rate controlling drugs. In Paper IV we repeatedly sampled resting heart rate measurements in patients with at least 2 days of ambulatory ECGs with AF (n=832). A single measurement differed on average by 10% compared to the average resting heart rate.

The conclusions are that low heart rates and short, irregular SVTs without P-waves are predictors of incident AF, that the resting heart rate during AF varies within the same individual, and that the range of normal ambulatory heart rate is wide.

Key words:

Atrial fibrillation, heart rate, ambulatory ECG, long-term electrocardiograms, premature atrial contractions, micro AF, supraventricular tachycardia

Classification system and/or index terms (if any) Supplementary bibliographical information

Language **Number of pages**: 90

ISSN and key title: 1652-8220

ISBN: 978-91-8021-714-9

Recipient's notes Price Security classification

Signature Date 2025-04-10

Atrial Fibrillation and Heart Rate at Long-term Electrocardiograms

Anders Persson

LUND
UNIVERSITY

Faculty of Medicine
Department of Clinical Sciences Malmö

ISBN 978-91-8021-714-9
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2025

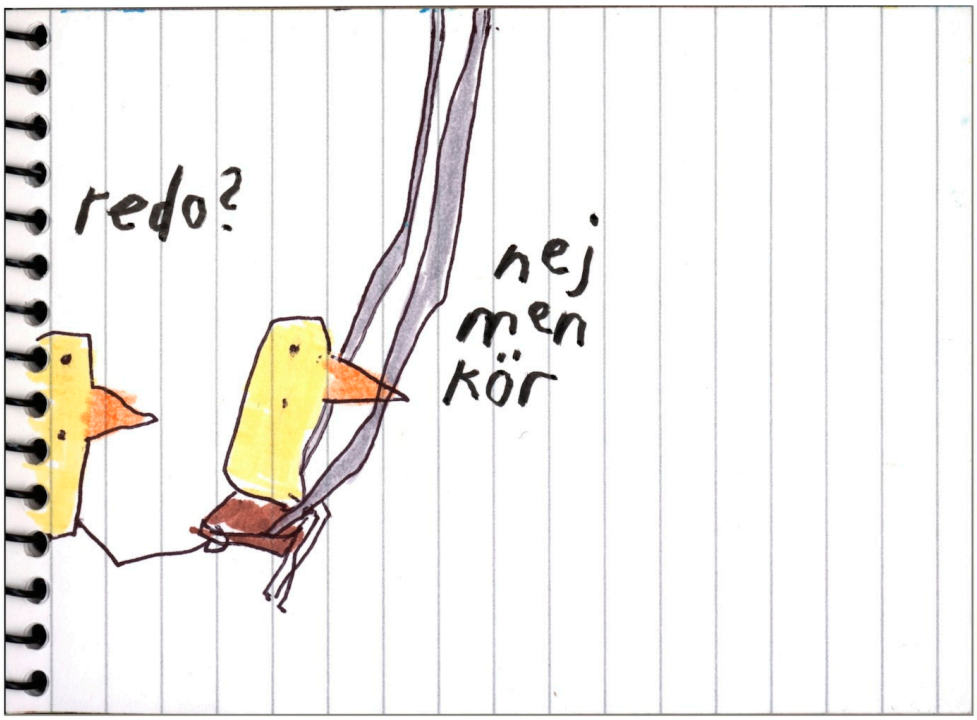

Table of Contents

List of Papers

This thesis is based on the following four original papers. The first three have been published and are reproduced with permission from the publishers. The fourth paper has not yet been submitted. The papers are referred to by their roman numbers in the text of this thesis.

Paper I: Persson AP, Måneheim A, Economou Lundeberg J, Fedorowski A, Healey JS, Sundström J, Engström G, Johnson LSB. Reference ranges for ambulatory heart rate measurements in a middle-aged population. Heart 2024;110(12):831-837. DOI: 10.1136/heartjnl-2023-323681.

Paper II: Persson AP, Fedorowski A, Hedblad B, Persson M, Juul-Möller S, Engström G, Johnson LSB. Heart rate and premature atrial contractions at 24hECG independently predict atrial fibrillation in a population-based study. Heart 2020;106(4):287-291. (In eng). DOI: 10.1136/heartjnl-2019-315119.

Paper III: Johnson LSB, Persson AP, Wollmer P, Juul-Möller S, Juhlin T, Engström G. Irregularity and lack of p waves in short tachycardia episodes predict atrial fibrillation and ischemic stroke. 2018 Jun;15(6):805-811 (In eng). DOI: 10.1016/j.hrthm.2018.02.011

Paper IV: Persson AP, Mcintyre WF, Glotzer T, Andrade JG, D. Conen, Fedorowski A, Måneheim A, Juhlin T, Edegran A, Grotek-Cuprjak A, Healey JS, Engström G, Rienstra M, Johnson LSB. Reliability of resting heart rate measurements in atrial fibrillation

Abstract

Atrial fibrillation (AF) is common condition among the elderly, and leads to increased risks of stroke, heart failure, dementia, and death. Diagnosing AF requires electrocardiograms (ECGs), and long recordings may be necessary since AF often occurs intermittently in its early stages. During AF, the heart rate is irregular, and sometimes inappropriately fast. This thesis includes four papers that study long-term ECGs for AF prediction and management.

In **Paper I** we used the population-based Swedish CArdioPulmonary bioImage Study to establish normal ranges for ambulatory heart rate during sinus rhythm. The normal range was wide, and largely independent of clinical correlates.

In **Paper II and III** we used the population-based Malmö Diet and Cancer Study to show that low heart rates at 24hECGs are associated with increased incidence of AF and that patients with short, irregular supraventricular tachycardias (SVTs) without discernible P-waves had substantially increased risk of AF (adjusted hazard ratio 4.95, 95% confidence interval (CI) 2.06-11.9).

Electrocardiograms are also used to measure resting heart rates during AF, to dose rate controlling drugs. In **Paper IV** we repeatedly sampled resting heart rate measurements in patients with at least 2 days of ambulatory ECGs with AF (n=832). A single measurement differed on average by 10% compared to the average resting heart rate.

The conclusions are that low heart rates and short, irregular SVTs without P-waves are predictors of incident AF, that the resting heart rate during AF varies within the same individual, and that the range of normal ambulatory heart rate is wide.

Populärvetenskaplig sammanfattning

Förmaksflimmer är en vanlig hjärtrytmrubbning, som framför allt drabbar äldre personer och leder till ökad risk för stroke, hjärtsvikt, dödsfall och demens. För att ställa diagnosen förmaksflimmer behövs ett elektrokardiogram (EKG). Eftersom förmaksflimmer i tidiga skeden ofta kommer och går omväxlande med normal sinusrytm, kan det krävas långa registreringar för att fånga förmaksflimret och ställa diagnos. Under flimmer slår hjärtat oregelbundet och hjärtfrekvensen blir hos en del så hög att hjärtat får försämrad pumpfunktion. EKG registreringar används ofta för att mäta hjärtfrekvensen under flimmer, och patienter med olämpligt hög hjärtfrekvens kan erbjudas behandling med frekvenskontrollerande läkemedel.

I den här avhandlingen presenteras fyra studier som undersöker hur långtids EKG kan användas för att hitta individer med förhöjd risk att drabbas av förmaksflimmer och för att förbättra vården för patienter med etablerad förmaksflimmerdiagnos.

I den första studien (Paper I) använder vi data från den stora svenska kohorten Swedish CArdioPulmonary bioImage Study (SCAPIS) för att ta fram normalvärden för hjärtfrekvens hos personer med normal sinusrytm, det vill säga när hjärtat slår regelbundet. I den andra studien (Paper II) analyserar vi data från Malmö Kost och Cancer-kohorten och visar att låga hjärtfrekvenser vid 24-timmars EKG-mätningar är kopplade till en ökad risk för att utveckla förmaksflimmer under en uppföljning på över 15 år.

I den tredje studien (Paper III), också baserad på Malmö Kost och Cancer-kohorten, undersöker vi hur olika typer av korta, förmaksutlösta hjärtrusningar – så kallade supraventrikulära takykardier (SVT) – hänger samman med framtida förmaksflimmer. Vi fann att personer med korta, oregelbundna SVT-episoder utan tydliga P-vågor på EKG hade en kraftigt ökad risk för förmaksflimmer (nästan fem gånger högre risk jämfört med andra). Detta kan hjälpa läkare att identifiera vilka patienter som behöver följas upp noggrannare.

Slutligen, i den fjärde studien (Paper IV), tittar vi på hur tillförlitliga vilopulsmätningar är hos patienter med förmaksflimmer. Vi analyserade upprepade mätningar av vilopuls hos 832 patienter med förmaksflimmer med hjälp av långvariga EKG och rörelsedata från accelerometer. Resultaten visar att en enskild mätning av vilopulsen i genomsnitt skiljer sig med 10% från patientens genomsnittliga vilopuls. Detta är viktigt eftersom vilopulsen används för att dosera läkemedel som kontrollerar hjärtrytmen – en mätning som varierar för mycket kan alltså leda till felaktig dosering av läkemedel.

Sammanfattningsvis visar avhandlingen hur långvariga EKG-mätningar kan ge ny kunskap om hjärtflimmer: från att förstå normala hjärtfrekvenser och tidiga risktecken till att förbättra diagnos och behandling. Detta kan i framtiden leda till bättre vård och förebyggande insatser för dem som riskerar att drabbas.

Abbreviations

ABC score	Risk score for stroke in AF patients
AF	Atrial Fibrillation
AF burden	% of time in atrial fibrillation
AF-CARE	Treatment considerations in atrial fibrillation according to European Society of Cardiology
BMI	Body Mass Index
bpm	beats per minute
$CHADS_2$	Risk score for stroke in AF patients
CHA_2DS_2-VASc	Risk score for stroke in AF patients
CHARGE-AF	Risk score for AF
CI	Confidence Intervals
DDAF	Device Detected Atrial Fibrillation
DOAC	Direct Oral AntiCoagulants
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
ESUS	Embolic Strokes of Undetermined Source
FEV1	Forced Expiratory Volume in 1 second
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
MDCS	Malmö Diet and Cancer Study
Mirco AF	Supraventricular tachycardia with atrial fibrillation characteristics and duration less than 30 seconds
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAC	Premature Atrial Contractions
PocketECG	An ambulatory ECG device produced by MEDICALgoritmics
SCAPIS	Swedish CArdioPulmonary Imaging Study
SVT	SupraVentricular Tachycardia
VKA	Vitamin K Antagonist

Context of this thesis

Atrial fibrillation (AF) is a disease that can be asymptomatic, and have a long sub-clinical phase. Adverse outcomes can occur already in this phase, and for this reason ECG-based screening for AF in elderly populations is a topic of considerable debate. When AF is established, it often occurs intermittently, and the amount of AF influences the risk of adverse outcomes for an individual patient. The heart rate during AF is also important in that it influences patient symptoms and potentially outcomes. For these reasons, diagnostic methods, in particular long-term ambulatory ECG recordings, are key throughout the chain of care of AF, not only to predict and detect AF but to provide appropriate treatment to patients with established disease and evaluate treatment effects. This thesis includes studies that examine the use of ambulatory ECG recordings for different aspects of AF prediction and care.

I have come to learn that many things regarding AF are not as straight forward as they first might seem.

Introduction

This thesis consists of four papers using ambulatory electrocardiogram (ECG) to evaluate heart rate and AF. Ambulatory ECG is a common and increasingly used method to find intermittent arrhythmias. Despite this, reference values for heart rate were lacking (**Paper I**). We also studied and identified ambulatory-ECG-based risk markers for AF (**Paper II and Paper II**). By identifying novel risk markers for AF with ambulatory ECG, it may be possible to classify individuals into high and low risk categories, potentially improving the efficiency of AF detection.

AF is known to increase stroke risk,[1] and this risk can be reduced with oral anticoagulation.[2] Finding and treating AF before stroke events occur is an important pursuit. However, this is not as straightforward as it might seem.

> "It's a fool's errand to try and sort out causes of stroke in AF"
> -Hearsay: Loose quote from a prominent AF researcher

The effect of detecting AF to reduce strokes depends on the causal relationship between stroke and AF, sorting this out is a complex task. But given its importance in both the treatment of AF and in the effect of detecting AF, I will attempt to provide a thorough background regarding the relationship between AF and stroke in the introduction of this thesis.

In **Paper IV**, the reliability of heart rate measurements at ambulatory ECG was examined. Heart rate is used to evaluate the need and treatment effect of 'rate control', which is one treatment option for AF that many patients will need at some point. To provide context, I will also give a brief introduction to other treatment options.

The Heart and Atrial Fibrillation

Heart contractions are initiated by electrical impulses, originating in specialized cells in the sinus node, located in the right atrium.[3] From the sinus node, regular electrical impulses travel through the atria and then via the atrioventricular (AV) node to the ventricles. In the AV-node, the electrical impulses slow down, allowing atria to complete their contractions that pump blood into the ventricles before the ventricles contract and pump blood to the body.

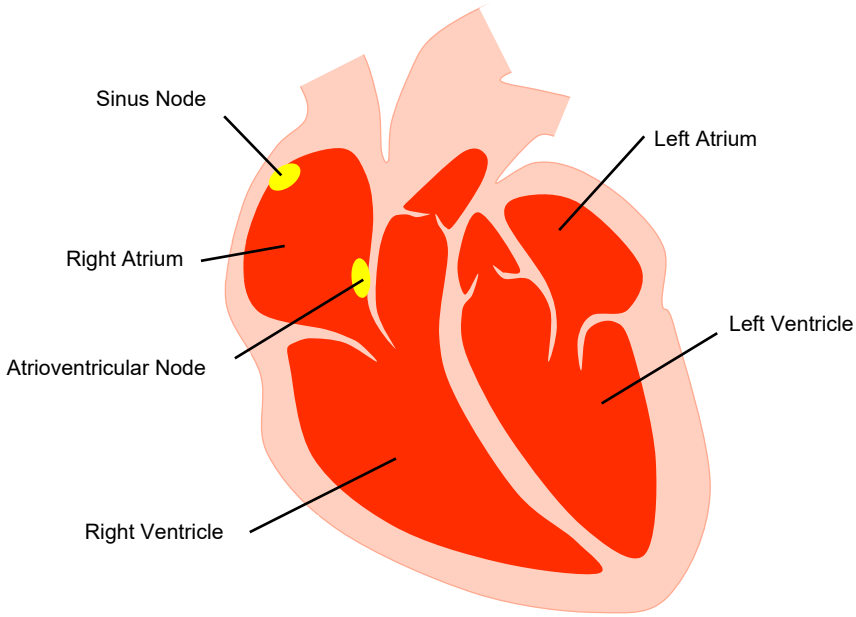

Illustration of the heart

In AF, the sinus node is set out of order by rapid, chaotic atrial impulses.[4] This causes ineffective, uncoordinated muscle twitches, or "fibrillations" in the atria, reducing ventricular filling and the amount of blood pumped with each heartbeat.[5] Fortunately, these chaotic electrical impulses do not reach the ventricles, where fibrillation would cause mechanical cardiac arrest without any cardiac output. After each electrical impulse, cells enter a refractory period during which they cannot react to new impulses. The refractory period in the AV-node protects the ventricles from fibrillation in patients with AF.

The rapid atrial impulses in AF are ready to depolarize the AV node shortly after the refractory period ends. But many impulses only reach parts of the AV node, causing these areas to become refractory and preventing of subsequent impulses from reaching the ventricles.[6] This results in a varying number of impulses successfully reaching the ventricles, leading to an irregular rhythm.

In sinus rhythm, the heart rate is regulated by signals from the autonomic nervous system, which can increase (sympathetic innervation) or decrease (vagal innervation) the heart rate. In AF, the regulation of heart rate is more complex and depends on the speed of impulses and refractory periods within the pathways of the AV node.[7] The AV node is also innervated by autonomic nervous system, and blocking sympathetic innervation with beta-blockers can reduce heart rate in AF.

AF often leads to a fast heart rate,[4] likely due to increased sympathetic activity to compensate for the lower blood volume pumped with each heartbeat.[8] The rapid impulses in AF decrease the refractory periods in atria,[9] and it is possible that refractory periods in the AV node are also shortened by these frequent impulses, resulting in higher heart rates.

Types of Atrial Fibrillation

AF is typically categorised into paroxysmal, persistent and permanent types:

Paroxysmal AF: The rhythm spontaneously switches between normal sinus rhythm and AF.

Persistent AF: The rhythm remains in AF for at least one week. Sinus rhythm can be restored with intervention but does not revert spontaneously.

Permanent AF: Sinus rhythm cannot be restored.

Newly diagnosed AF is sometimes considered a separate category of AF because it is difficult to determine which category it belongs to initially.

Device detected AF (DDAF), also known as subclinical AF (**SCAF**) or atrial high-rate episodes (**AHRE**), refers to AF detected by pacemakers or other implanted devices.

To diagnose AF, there is a consensus that the duration must be at least 30 seconds. Shorter episodes are referred to as "**Micro AF**". **Paper III** in this thesis was the first to study the association between Micro AF and clinical AF.

Prevalence of Atrial Fibrillation

The lifetime risk of AF in 45–50-year-olds is over 30% in Europe and United States of America.[10-12] The prevalence of AF increases exponentially with age, doubling each decade.[13] While the age-adjusted prevalence has remained stable over the last three decades,[14] the overall prevalence of AF diagnoses is rising because people are living longer. It has been estimated that the prevalence of AF in Europe will double between 2000 and 2060.[15]

Reports on AF-prevalence account only for diagnosed AF, but AF can be asymptomatic, and the total prevalence is higher:

$$\text{Total AF } prevalence = Diagnosed\ AF + Undiagnosed\ AF$$

Technological advancements have improved the availability and performance of long-term ECG monitoring. In 1990s, effective anticoagulation therapy with vitamin K antagonist (VKA) was introduced to reduce stroke risk in AF patients.[16] The importance of paroxysmal AF as a risk factor for stroke was established in 2010.[17] Increased detection, effective treatment and recognition of the risks with paroxysmal AF likely contributed to more frequent AF diagnosis.

The total prevalence of AF includes both diagnosed and undiagnosed cases. The age-adjusted total AF prevalence has decreased, as the age-adjusted AF prevalence have remained stable while undiagnosed AF declined for reasons mentioned earlier. Since AF and stroke share many risk factors, reducing these risk factors would lower the incidence of both conditions. The rapid decrease in age-adjusted stroke rates (**Figure 1**) also support a reduction in in the total age-adjusted AF prevalence.

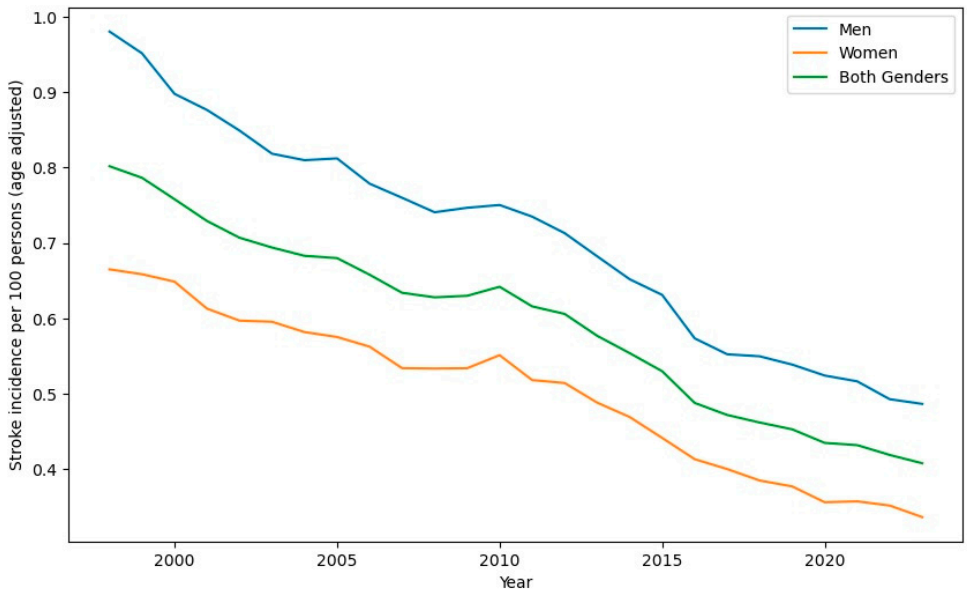

Figure 1
Age adjusted stroke incidence for individuals at least 50 years old in Sweden 1998-2023.
Graph created using Co-Pilot with data from Diagnosis in in-patients in Sweden: National Board of health and welfare database. Available from https://www.socialstyrelsen.se/en/statistics-and-data/statistics/statistical-databases/

Projecting AF prevalence in 2060 and beyond is complex and depends on factors such as life expectancy, changes in AF-risk factors (e.g. smoking), and the use of ECG monitoring. It can be expected that a larger proportion of patients diagnosed with AF will have short-lasting AF and be elderly.

Risk Factors for Atrial Fibrillation

Identifying risk factors for AF are important for three reasons. First, by identifying individuals at high risk of AF, effective AF screening could possibly be implemented. Second, if risk factors are not just predictors but also the causes of AF, treating these would decrease AF prevalence. If paroxysmal AF develops, the causal risk factors would increase the frequency of AF episodes and thereby cause AF progression. However, if the risk factors were removed or decreased through treatment, it is possible that fewer AF episodes would occur. Third, individuals with AF risk factors could be motivated to adhere to medications and reduce risk factors, knowing it could prevent AF from occurring (both as a primary prevention and in patients with paroxysmal AF).

The CHARGE-AF score is the most well-known risk prediction model for AF and includes age, height, systolic blood pressure, use of medication for hypertension, smoking status, precordial murmur, ECG signs of left ventricular hypertrophy and/or left atrial enlargement, coronary artery disease (CAD) and HF.[18,19]

A few other AF risk factors that have been identified are family history,[13,20] male sex,[13] obesity,[21] obstructive sleep apnea,[21] alcohol,[21] COPD and low forced expiratory volume during 1 second,[22,23] biomarkers (such as N-terminal pro-B-type natriuretic peptide (NT-proBNP)),[24] low resting heart rate,[25] vigorous physical activity,[26,27] physical inactivity,[28] premature atrial contractions (PAC),[29] supraventricular tachycardias,[30] and premature ventricular contractions (PVC).[29]

We studied low average daily heart rate (**Paper II**) and Micro AF (**Paper III**) at 24-hour ECG as novel risk factors for AF.

Natural History of Atrial Fibrillation

Once AF occurs, it can create conditions in the heart that make future episodes more likely. The concept "AF begets AF" originates from a study in goats, where increasing duration of artificially induced AF with pacemakers led to longer AF episodes after pacing was stopped.[9] Paroxysmal AF often progresses with increasing AF burden (% of time in AF) and eventually progresses to persistent AF.[31,32] The 30-second duration cut-off for AF-diagnosis is arbitrary, and AF often progresses. In **Paper III** we examined whether Micro AF is associated with a risk for future clinical AF. Progression of AF ultimately leads to persistent and permanent AF, which are associated with higher rates of thromboembolism, heart failure and death.[33,34] However, there are also reports that AF burden can decrease;[31,35,36] on average, the AF burden decreased by 35% at 6 months in the sham arm of the SHAM-PVI trial, which tested real pulmonary vein isolation procedures against cardioversion + sham

procedures (where patients underwent a surgical procedure without performance of pulmonary vein isolation).[36] AF burden varies over time, and therefore the measurement of it is subject to some error. Reduced AF burden in some individuals is probably at least in part an effect of regression to the mean. Life-style interventions may also reduce AF burden and recurrence rates; exercise has been shown to reduce AF recurrences and symptoms in patients with paroxysmal or persistent AF,[37] and in the observational LEGACY study, individuals with body mass index (BMI) at least 27 kg/m2 who achieved weight loss experienced a reduction in AF burden.[38]

Atrial Fibrillation Screening

Examining individuals to detect asymptomatic conditions is called screening. The goal of screening programs is to reduce mortality and morbidity. To reduce morbidity the risk and discomfort of the test and the potential benefit in terms of treatment effect need to be considered. The risk of finding individuals that would stay asymptomatic and never develop any morbidities also need to be considered since any treatment could possibly increase overall risks in these individuals, reducing the net benefit.

The most effective screening programs use a simple low-cost examination, and search for a common condition with high morbidity, mortality and costs, that can be treated effectively.

AF is a common disease that can go undetected with potential severe consequences. ECG examinations to detect AF can be performed at low cost, and anticoagulation effectively reduces stroke risk. In light of this there has been a lot of interest in studies of AF screening. Two large screening trials (LOOP and STROKESTOP) were published in 2021.[39,40]

The LOOP trial used implanted loop recorders and found no significant effect of screening in reducing strokes. In contrast, the STROKESTOP trial found a small but significant effect in the composite primary end point (ischemic or hemorrhagic stroke, systemic embolism, major bleeding leading to hospitalization or death from any cause). However, screening did not significantly reduce stroke or systemic embolisms in STROKESTOP II (published 2024), which utilized the biomarker NT-proBNP to guide the duration of ECG screening.[41]

LOOP-study

The Danish LOOP-study invited and included individuals aged 70-90 years without AF and at least one additional stroke risk factor (hypertension, diabetes, previous heart failure or stroke), resulting in a population in whom anticoagulation was

indicated according to the CHA_2DS_2-VASc score. These individuals were randomized to an implantable loop recorder (a small ECG-recorder that is placed under the skin and can monitor for several years) or usual care. If AF was found anticoagulation was recommended. The LOOP-study was powered to find a 35% reduction of stroke with 80 % certainty, this may have been an optimistic estimate of screening effect considering that approximately 15-20 % of stroke events have been attributed to diagnosed AF.[1] The inclusion criteria, which included hypertension (91%), diabetes (21%) and previous stroke (17%) could also possibly have caused a population of individuals at particularly high risk of strokes not caused by AF. During a mean follow up of 5.4 years AF was diagnosed in 32% of individuals with a loop recorder and 12% in the control arm, and the annular rate of stroke or systemic embolism was non-significantly reduced from 1.1% in usual care to 0.9% with loop recorder monitoring, resulting in a non-significant hazard ratio of 0.8 (0.61-1.05) in favor of monitoring.

STROKESTOP

The Swedish STROKESTOP study randomized all 75–76-year-olds in two regions in Sweden into AF-screening with intermittent ECG for 14 days, or a control arm with no invitation to screening. In the screening group 51.3% of invitees accepted participation in the screening activities. The study used an intention-to-screen analysis: the comparison was between those who were invited to screening (regardless of whether they participated or not) to those in the control group. Intention to screen in STROKESTOP reduced the primary endpoint with a hazard ratio 0.96 (0.92-1.00), an impressive result considering that almost half of invitees did not participate. Individuals randomized to screening had non-significantly fewer bleeding events contributing to the significant decrease of the primary endpoint. The lower bleeding rate in the screening group is perhaps a chance finding but a bit surprising considering that detection of AF increases anticoagulation use. Direct oral anticoagulants (DOAC) have lower risk of bleeding that VKA,[42] it is possible that screening at a time when DOAC replaced VKA as the first line anticoagulation increased the ratio of DOAC/VKA and decreased bleeding rate.

Comparison of Atrial Fibrillation Detection in the Control Arms of LOOP and STROKESTOP

The mean age in the Danish LOOP study was 75 years, AF was found in 12% of the control arm over a follow-up period of 5.4 years. In the Swedish STROKESTOP study, the baseline AF prevalence in the control arm of 75–76-year-olds was 12.8%, which increased to just over 20% during a 7-year follow-up. The relative risk of new AF was 50% higher in the control arm of the LOOP study compared to the STROKESTOP study (12% vs 8%), despite the shorter follow up.

Differences in AF detection in the control arms could be attributed to various factors, including different risks in Danes and Swedes, the wider age-span in LOOP (as AF increases exponentially with age), and the inclusion criteria with at least one risk factor being required in LOOP compared to age-only based recruitment for STROKESTOP. Another difference between the control groups is that controls in STROKESTOP were never contacted, whereas all participants in LOOP were invited and then randomized to either the control or intervention group. It is possible that being invited to participate in LOOP and then randomized to the control arm caused participants to undergo ECG examinations more frequently than they would have otherwise, which may have contributed to the non-significant finding in the LOOP study.

LOOP and STROKESTOP

These two studies underscore the importance of conducting trials before implementing interventions. Screening for AF seemed straight-forward, but these large trials reveal that it is more complex than initially thought. When interventions are already established clinically despite a lack of evidence, studying them can be challenging. An example is the ISCHEMIA trial, where revascularization in chronic coronary syndrome did not reduce a composite of death or ischemic cardiovascular events.[43] However, 15% of the control group underwent revascularization before the primary endpoint occurred. The high rate of revascularization in the control group is likely due to its establishment in clinical practice, which may have contributed to the non-significant findings.

Morbidities Related to Atrial Fibrillation

Stroke is perhaps the most well-known and dreaded consequence of AF. However, AF is also associated with increased risk of death,[44] heart failure, dementia, and reduced quality of life.

Stroke and Systemic Embolism

Stroke rates in persistent or permanent AF have been reported to be 4-5 times higher than in individuals without AF.[1] Anticoagulation with VKA decreases stroke rates by approximately 60%,[2] and DOAC are associated with further reductions.[42,45] Most anticoagulation studies in AF assess the reduction of a composite of ischemic stroke and systemic embolism. Strokes can also be haemorrhagic, but for simplicity "stroke" will be used in this section to describe ischemic strokes or a composite of ischemic strokes and systemic embolism unless stated otherwise.

Causes of Stroke in Atrial Fibrillation

AF patients may experience strokes due to embolisms from thrombi formed in the left atrium. The mechanism by which AF causes thromboembolic strokes to occur has been questioned in recent years. Previously, it was thought that the mechanical dysfunction in the atria during an AF episode caused blood clots to form in the atria and atrial appendages. Stroke events would then happen at the time of an AF episode. These ideas were disrupted by data from the TRENDS and ASSERT studies in pacemaker patients, in which no temporal relationship between DDAF and stroke was found.[46,47] This has led to a theory that AF may not directly cause strokes, but that the underlying structural and mechanical changes in the atria do.[48] However, despite these data from TRENDS and ASSERT there is evidence that a temporal relationship between AF and stroke is likely to exist, at least to some degree.

No Temporal Relationship between Atrial Fibrillation and Stroke

There are several reasonable explanations why no clear temporal relationship for DDAF was found in TRENDS and ASSERT. First, regardless of whether there is a temporal relationship between AF episodes and stroke risk, not all strokes in AF patients are caused by AF. Stroke and AF share many risk factors, and AF patients also have an increased risk of non-cardioembolic strokes, which are not caused by AF and for which a temporal relationship can't be expected. In the TRENDS study, 27 patients with DDAF or previous AF diagnosis had a thromboembolic event, 10 of these were on anticoagulation.[49] In ASSERT 4 out of 26 patients were on anticoagulation before their stroke. This use of anticoagulation in TRENDS and ASSERT likely reduced the subset of strokes that were causally related to AF, further contributing to the difficulty in finding a clear temporal relationship between AF and stroke. Two large recent trials (ARTESiA and NOAH-AFNET 6)[50,51] showed that stroke rates for patients with DDAF was approximately 1% per year, much lower risk than in clinical AF. In a meta-analysis of the two trials randomization to anticoagulants (apixaban in ARTESiA and rivaroxaban in NOAH-AFNET 6) was associated with a 32% risk reduction for stroke,[52] indicating that most strokes were not caused by AF. In ARTESiA, the reduction in severe strokes (modified Rankin scale 3-6) that are more likely to be caused by AF, was higher, at 49%, but these events were more rare overall, 0.53% per year in the aspirin group and 0.27% per year in the apixaban group.

Finally, it is possible that thrombi formed during AF can remain in the atrium for long periods before dislodging and causing a stroke. An indication that this can be the case is that thrombi can be found during sinus rhythm in patients with patients with paroxysmal AF.[53,54]

Therefore, it is perhaps not surprising that only a few DDAF episodes are detected before the occurrence of stroke in the ASSERT and TRENDS trials, and this doesn't necessarily indicate that no temporal relationship exists.

Evidence of a Temporal Relationship between AF and Stroke

A case-crossover study of stroke patients compared the number of AF episodes lasting at least 5.5 hours 30 days before the stroke to those 91-120 days before the stroke.[55] In discordant causes (where AF was present in one period but not the other), 13 patients had AF in the 30 days before stroke compared to 3 patients in the 91-120 days before the stroke (warfarin-adjusted odds ratio 4.2; 95% CI 5.4-73.1), indicating a temporal relationship between AF and stroke.

Electrical or pharmaceutical cardioversion is sometimes performed to restore sinus rhythm in AF patients. Rhythm control procedures increase the risk of thromboembolism, and to reduce this risk a period of anticoagulation, or a transesophageal echocardiography to rule out left atrial thrombi, is recommended prior to the procedure. However, acute cardioversion without anticoagulation or transesophageal echocardiography can be considered in patients without other thromboembolic risk factors if performed within 24 hours of AF onset.[56] Longer durations of AF before cardioversion increase the stroke rate,[57] indicating that thrombi formed during AF cause strokes and further supporting the evidence of a temporal relationship between AF and stroke.

Who is at Risk of Stroke

Stroke risk in AF is increased, but some AF patients have a low risk even without anticoagulation. To assess the need for anticoagulation, various risk scores are used, of which the CHA_2DS_2-VASc is the most well-known and commonly used.[58] The ABC score, which includes age, biomarkers and clinical history, has been shown to outperform the CHA_2DS_2-VASc score.[59,60]

CHA_2DS_2-VASc

The CHA_2DS_2-VASc score assesses the risk of stroke in AF-patients not taking anticoagulation but it does not perform particularly well, with a C statistic of 0.6 (where 0.5 is as good as flipping a coin and 1.0 is prefect discrimination) in the original study.[58] In clinical practice anticoagulation is usually considered in patients with a score of ≥1 in men in and ≥2 in women, and an observational study reported C statistic of 0.89 when CHA_2DS_2-VASc was dichotomized into 0, 1 or ≥ 2 over a 10 year follow up.[61]

The CHA_2DS_2-VASc score was developed to predict the risk of any ischemic stroke or systemic embolism. But AF patients have a risk factor profile that puts them at risk for all types of strokes, and simply predicting stroke in AF might not be sufficient to inform the need for anticoagulation. Additionally, several components of CHA_2DS_2-VASc are strong predictors for all types of strokes, yet anticoagulation is not indicated for reduction of strokes of vascular or unknown origin.

The components of **CHA_2DS_2-VASc** are:

Congestive heart failure

Hypertension

Age > 75

Diabetes

Stroke

Vascular disease (peripheral artery disease, myocardial infarction, carotid disease, aortic aneurysm, complex aortic plaques on CT and coronary plaques with significant stenosis)

Age 65-75

Sex (female)

Two points in CHA_2DS_2-VASc are assigned for stroke and age > 75, as indicated by the "2", while one point is given for each of the other components. Hypertension, diabetes, age, and vascular disease are all strong risk factors for strokes of all causes.[62] If you search for AF post-stroke, you will find less AF in patients with diabetes and hypertension,[63] indicating that these factors are stronger risk factors for stroke not caused by AF. However, closer monitoring, which may lead to AF being detected before a stroke in these diagnoses, could also play a role.

Stroke is a strong risk factor for recurrent strokes;[64] the two points awarded for this in the score may underestimate the risk.[65] After a stroke, monitoring with ECG is recommended, and if AF is not found, the remaining stroke types are either of vascular origin or considered to be embolic strokes of undetermined source (ESUS). Undetected AF is likely the cause of some ESUS, but studies where patients with ESUS are randomized to receive anticoagulation have not shown benefit,[66-69] an indication that few strokes in ESUS patients in these studies were caused by AF.

Increasing ECG monitoring post-stroke will enhance AF detection, reducing the number of strokes caused by undiagnosed AF (detected before or after the stroke). Longer ECG monitoring will decrease the likelihood that an ESUS stroke was caused by AF. Despite recommendations of 24-hour ECG monitoring, only 30.6% of stroke patients admitted to stroke centres between 2003 and 2013 in Ontario, Canada, were screened with ECG for at least 24 hours. Short (24-48h) monitoring post-stroke is still common, but the duration of monitoring post-stroke has likely increased in many places; in 2019, a consensus document suggested increasing ECG screening post-stroke from 24-48 hours to 72 hours, motivated by a substantially higher detection rate of AF.[70]

Individuals with strokes caused by AF have a risk factor profile that predisposes them to strokes caused by AF (see causal pie model, page 28), the risk of stroke

recurrence without anticoagulation in these patients is likely very high, regardless of other risk factors. In the recent LOOP trial, AF screening in patients with a previous stroke did not reduce strokes, but strokes were significantly reduced in patients without a previous stroke, even though they had a lower rate of strokes.[71] This contrasts with the recent ARTESIA trial, where anticoagulation significantly reduced strokes in DDAF patients with a previous stroke.[72] The discrepancy may be explained by better ECG monitoring post-stroke in Denmark compared to the countries/sites participating in ARTESIA. It is unclear if previous strokes not caused by AF increase the risk of a subsequent strokes caused by AF. If not, the importance of previous strokes in informing the need for anticoagulation will decrease as AF detection increases.

Congestive heart failure differs from the other components in CHA_2DS_2-VASc, in being a "cardiac" parameter rather than vascular. However, the common causes of heart failure are hypertension and infarction and these are,[73] as previously mentioned, risk factors for stroke not caused by AF.

The latest European guidelines have removed the "female" component from the CHA_2DS_2-VASc score, sparking some debate. Previously, women needed 2 points for anticoagulation to be indicated, compared to 1 point in men. Removing sex from the score did not alter the recommendation for anticoagulation. Interestingly, women in the general population have a lower risk of stroke (Figure 1). Even if men and women with AF have the same overall stroke risk, it is possible that a larger proportions of strokes in women are caused by AF and that they benefit more from anticoagulation. This is further supported by the higher rate of thromboembolic events in women after cardioversion without anticoagulation.[74] Nevertheless, it is possible that women with a risk profile leading to the development of AF do not benefit more from anticoagulation than men with AF. Additionally, the difference in overall stroke rates between men and women could at least partially be explained by a higher prevalence of AF in men.

ABC-score

An alternative to the CHA_2DS_2-VASc score is the ABC-score.

The components of the **ABC** score are:

Age
Biomarkers (NT-proBNP and hs-troponin)
Clinical history of stroke

The ABC-score uses continuous variables, making it slightly more time-consuming – to compute the ABC score a physician needs to use an online calculator, whereas the CHA_2DS_2-VASc score can easily be tallied using simple mental math. But the ABC-score outperforms the CHA_2DS_2-VASc score and the extra minute in calculation time is likely justified considering the implications of lifelong anticoagulation treatment.

The initial ABC-score was developed using residual stroke risk in anticoagulated AF patients,[59] and this may not directly translate to the risk reduction that can be achieved from anticoagulation. But the score was recalibrated in two cohorts of AF-patients not using anticoagulation and had better stroke discrimination than CHA_2DS_2-VASc.[75]

A caveat with both the ABC and CHA_2DS_2-VASc scores is that they were created from cohorts and trials that are becoming outdated and may not reflect current patient populations. Strokes rates decreased by 25% between 2007-2010 and 2015-2018 in AF patients without anticoagulation in Finland, even though the mean CHA_2DS_2-VASc score increased from 2.5 to 3.0.[76] This may reflect better control of comorbidities and higher detection rates at lower AF burdens. Neither score includes AF burden, although it is well known to be associated with stroke risk in AF patients.[77] Given that it is unethical not to treat AF patients with anticoagulation, this may still be the best available data.

Causal Pie for Explanation of Stroke in AF

The triad of 'stasis', 'vascular or endothelial damage' and 'hypercoagulability' as causes of venous thrombosis has been attributed to Virchow, a 19th century physician. It is possible that thrombus formation in AF is also caused by the triad.

Stasis: The ineffective atrial twitches in AF causes blood to flow slowly in the atria. Spontaneous contrast is an ultrasound phenomenon in which when blood flow looks smokey and swirling instead of black. The phenomenon can be caused by reversible aggregation of red blood cells and is greater in low flow or stasis.[78] In AF patients spontaneous contrast in the left atrium is associated with presence of thrombi, increased atrial size, and low flow velocity in the left atrial appendage.[79]

Endothelial damage: Blood clots form in response to vessel damage to stop bleeding. There are no non-invasive methods to directly measure endothelial damage in the left atrium. However, factors such as atrial size/stretch, inflammation and the biomarkers included in ABC-score may be related to endothelial damage.

Hypercoagulability: The risk of thrombi is logically related to the degree of hypercoagulability, proven by the reduction of thromboembolic events through anticoagulation.

The causal pie model can explain why only some AF patients have strokes. For a stroke to occur, the pie must be complete. **Figure 2** illustrates this in three

patients: In Patient 1, the pie is not complete so no stroke will occur. In Patient 2, the pie is complete, and stroke occurs, but if anticoagulation is used, the pie will no longer be complete, preventing the stroke. Patient 3 has a different set of causes for stroke, but like Patient 2, the pie is complete, and stroke occurs.

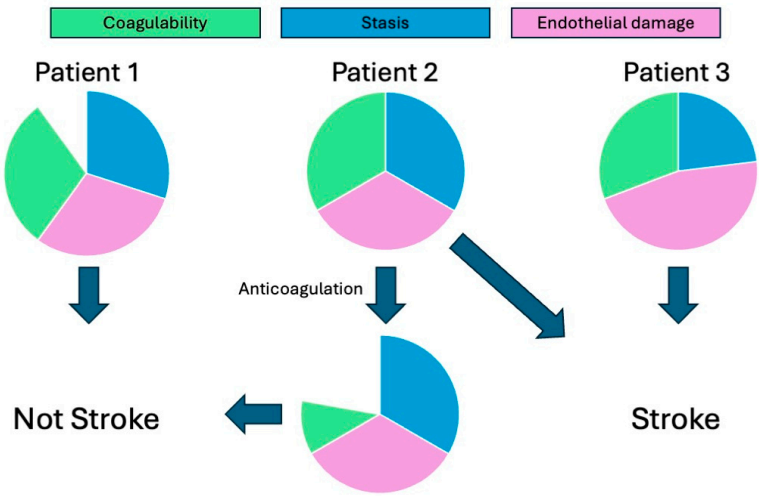

Figure 2
Causal pies for stroke in AF patients

In the causal pie model, all components are considered 100% causes. For example, if you go to work in your hybrid car, you need either fuel or a charged battery. If you run out of fuel but have charged the battery enough to reach work, you will still get there. If the battery is empty and you run out of fuel, you might still get to work by walking, but it will take longer. These are all 100% causes of you reaching work.

The time it takes for thrombi to form in AF is likely somewhat random but also dependent on components of the triad, making it difficult to establish specific cutoff for the duration of AF that causes stroke. But it is possible that stroke risk at a specific AF burden is lower in staccato AF (many short episodes) than in legato AF (few longer episodes),[80] because it might take some time for thrombi to form. The ABC score used biomarkers that are likely related to stasis and perhaps also endothelial damage, which might explain its superiority to CHA_2DS_2-VASc score. To identify new components to further improve the risk score, searching for factors affecting components of the causal pie may be the way to go.

In theory, thrombi can form in the atria even in patients on optimal anticoagulation dosing if stasis and endothelial injury is severe enough. However, it is more likely that thrombi seen in patients that were prescribed anticoagulation are due to adherence problems, which are common, especially in chronic diseases.[77,81] This

may explain why surgical removal of left atrial appendage (in patients undergoing heart surgery for other reasons) effectively reduces strokes even in anticoagulated patients.[82] Adherence problems could also explain much higher rates of left atrial thrombi in patients examined before cardioversion (often acute examinations) compared to examinations before planned ablation,[83] where patients had time to adhere. Another cause for the difference is that ablation is often performed in relatively healthy patients.

Dementia

The risk of cognitive decline and dementia is increased in AF patients.[84-86] An observational study reported small asymptomatic strokes, "silent cerebral ischemia", in 89% of patients with paroxysmal AF compared to 46% in controls with sinus rhythm.[87] The BRAIN-AF (NCT02387229) study randomized AF patients with low stroke risk to anticoagulation under the theory that silent cerebral ischemia is the cause of cognitive decline in AF and could be prevented using anticoagulation. BRAIN-AF found no difference in cognitive decline using anticoagulation (results were presented at the American Heart Association meeting 2024).

Heart Failure

Heart failure is the most common cause of death in atrial fibrillation patients.[88] But it is not as simple as AF patients develop heart failure and then die. The link between heart failure and AF is complex.[89]

Association between AF and heart failure: AF and heart failure share risk factors (such as age, hypertension, diabetes and valvular heart disease) causing them to occur simultaneously.

Heart failure as a cause of AF: In heart failure the blood pumped by the heart is decreased, this causes congestion of blood, leading to increased atrial pressure and enlargement that is likely a cause of atrial fibrillation. And the prevalence of AF increases with increasing severity of heart failure.[90,91]

AF as a cause of heart failure: Both loss of atrial contractions and irregular rhythm in AF likely contribute to decreased cardiac output. Restoration of sinus rhythm in AF patients improves cardiac output,[92] and in patients with heart failure, the presence of AF worsens symptoms.[91]

Atrial fibrillation is a cause of tachycardia induced cardiomyopathy,[93] which is a type of heart failure caused by rapid heart rhythm and considered reversible upon termination of the rapid rhythm. However, signs of diffuse ventricular fibrosis can be seen long after successful ablation for atrial tachycardia in patients with tachycardia-induced cardiomyopathy.[94] In patients with a previous tachycardia-induced

cardiomyopathy episode, recurrent episodes cause symptoms to occur faster than in the initial episode, indicating that tachycardia-induced cardiomyopathy might not be fully reversible. If a patient presents with tachycardia and heart failure (of unknown cause) that does not improve after reversal of tachycardia, it is not possible to determine if the heart failure was caused by tachycardia.

Symptoms and Decreased Quality of Life

More than 90% of clinical AF patients report at least occasional symptoms,[95] and AF patients have a reduced quality of life.[96] However, 87% of screening detected AF, in whom the median AF burden was 0.13%, in the LOOP study never reported AF symptoms during follow-up.[35]

Non-specific symptoms such as fatigue and dyspnoea are more common and have a larger impact on quality of life than cardiac-specific symptoms such as palpitations and irregular heart rhythm.[97] Comorbidities likely contribute to the non-specific symptoms. AF can reduce cardiac output and worsen heart failure and is a plausible cause of non-specific symptoms. AF ablation decrease AF burden, reduce symptoms and substantially improve quality of life.[36] The reduction of AF burden accompanied by improved quality of life points support the notion that AF causes both symptoms and reduced quality of life.

Treatment in AF

The aim of treatment in AF is to reduce morbidity, mortality and improve quality of life. In the 2024 European guideline the abbreviation “AF-CARE” is used for the different components of treatment.[56]

The components of AF-**CARE** are:

Comorbidities and risk factor management
Avoid stroke and thromboembolism
Reduce symptoms by rate and rhythm control
Evaluation and dynamic reassessment

Comorbidities and Risk Factor Management

AF patients often have comorbidities, many of which are also are risk factors for AF. For AF to occur, a causal pie must be complete (see stroke section for the causal pie model). By addressing causes of AF, it is possible to reduce AF burden. Hypertension, heart failure, obesity, physical inactivity and alcohol are examples of potential causes of AF. Optimal treatment of these factors may not only decrease the risk of their respective adverse outcomes but also reduce AF burden, AF symptoms, and the risks of adverse outcomes caused by AF.

Hypertension

Reducing blood pressure by 5 mmHg in patients with hypertension decrease hazard ratios by 9% for cardiovascular events (stroke, ischemic heart disease or heart failure) in patients both with and without AF.[98] As AF patients have higher risk of cardiovascular events, identical hazard ratios to patients with sinus rhythm means that the absolute effect of blood pressure reduction is higher in AF patients.

Heart Failure

Heart failure and AF is closely linked, with evidence suggesting that both conditions can cause the other.[89] When both are present, symptoms and the risk of death are increased,[99] highlighting the importance of heart failure treatment in AF patients. The basis for treating heart failure in AF patients is the same as for those without AF, according to European guidelines.[56,100] However, beta-blockers do not reduce mortality in AF patients with heart failure,[101,102] and results from angiotensin receptor blocker trials are conflicting.[103,104]

Obesity and Physical Inactivity

Patients with BMI at least 27 kg/m^2 in the LEGACY study cohort were offered weight counselling initially aiming at a weight loss of 10% and prescribed physical activity. All participants were screened for hypertension, glucose intolerance, sleep apnea, alcohol use, and tobacco use. If any of these factors were found, they were managed individually. The LEGACY study found that individuals with a weight loss of at least 10% was associated with a reduction in AF burden.[38] The similar CARDIO-FIT study found that improved cardiorespiratory fitness augmented the effect of weight loss.[28] Weight loss and improved fitness in these observational studies reflect adherence to the protocol. It is likely that patients who lost weight and improved fitness also had better adherence to medications, making it difficult to determine the specific impact of the intervention on weight loss and physical activity on AF burden. However, aerobic training reduced AF burden in a small, randomized trial,[105] supporting the findings in the CARDIO-FIT study.

Alcohol

Alcohol consumption is associated with increased risk of AF,[106] and adverse events in AF patients.[107,108] Individuals randomized to alcohol abstinence had lower AF burden in a trial including regular non-binge drinkers.[109]

Avoiding Stroke and Thromboembolism

Stroke and stroke risk reduction has been discussed in the "Stroke and Systemic Embolism"-section of this thesis. In brief, AF patients are at increased risk of stroke,[1] and anticoagulation reduces this risk.[2] But in some AF patients anticoagulation is not indicated, most commonly due to a very low risk of stroke.

The first-line agents for anticoagulation are DOACs, as they more efficiently reduce stroke rates and have lower risk of bleeding compared to VKA.[42,45] There are a few exceptions, however. VKA is the drug of choice for patients with mechanical heart valves and moderate to severe mitral stenosis.[56,110,111]

The FRAIL-AF trial investigated the safety of switching from VKA to DOAC in frail elderly patients with AF.[112] Patients were randomized to either continue with VKA or switch to DOACs. The study was stopped early due to an increased rate of bleeding in patients that switched to DOACs without a decrease in thromboembolic events. It is important to note that the study included individuals already using VKA, meaning that individuals who previously discontinued VKA because of bleeding were not included.

The COMBINE-AF study, which includes patient-level data from four pivotal trials comparing DOACs to VKA , showed that treatment benefit from DOACs was consistent across all age group.[42] In COMBINE 25% of patients were 77 years or older, which likely underrepresents elderly AF patients, and it is possible that a higher proportion of multimorbid frail individuals did not participate. However, there is no evidence that initiating VKA is superior to DOACs in the elderly.

In addition to anticoagulation, surgical closure of left atrial appendage in AF patients undergoing heart surgery for other causes decreases the risk of stroke.[82]

Reducing Symptoms by Rate and Rhythm Control

Treatment regimes in AF can be divided into rate and rhythm control. Rate control aims to keep the heart rate under control, whereas rhythm control aims to restore and maintain sinus rhythm.

Several trials published between 2000 and 2004 showed that rate control is not inferior to rhythm control.[113-118] But the mortality rate was lower in those patients in

the rhythm control arm in whom sinus rhythm was successfully achieved, indicating a benefit of sinus rhythm that is offset by harms related to antiarrhythmic drugs.[119]

Rhythm control

Since these trials were published, antiarrhythmic therapies have improved. The ATHENA trial showed that dronedarone (an antiarrhythmic drug) reduced the composite primary endpoint of first hospitalization due to cardiovascular events or death.[120] Rhythm-control with ablation and/or antiarrhythmic was associated with a reduction in cardiovascular events compared to usual care in the EAST AFNET 4 trial, which included patients with cardiovascular conditions and newly diagnosed AF (within one year prior to enrollment).[121]

Catheter ablation has also been shown to be beneficial in the CASTLE-AF trial. This study included AF patients with heart failure (ejection fraction 35% or less), an implantable defibrillator, and with unacceptable side effects from/unwillingness to take antiarrhythmic drugs. In this population catheter ablation was found to reduce a composite endpoint of death or hospitalization for worsening of heart failure. Benefits of catheter ablation have also shown in a different patient population, using sham surgery as a control. The small but important SHAM-PVI study showed that catheter ablation decreased AF burden and improved quality of life compared to a sham procedure. This study included patients with symptomatic paroxysmal or not long-standing persistent atrial fibrillation, without previous ablation, ejection fraction at least 35%, left atrial size of less than 5.5 cm and no other arrhythmias requiring ablation.[36] Ablation also reduced the rate of persistent AF compared to antiarrhythmic drugs at three year follow up in the EARLY-AF trial, which included patients with symptomatic paroxysmal atrial fibrillation not on daily antiarrhythmic drugs.[122]

Catheter ablation may not be beneficial in all patients, however. In the CABANA trial, which included symptomatic AF patients aged 65 years or older, or younger than 65 years with one risk factor for stroke the composite primary endpoint death, disabling stroke, serious bleeding was not reduced in the catheter ablation arm. The nonsignificant result may have been influenced by a large crossover, 27.5% in the control arm received catheter ablation.

Rate control

While rhythm control strategies have improved, most AF patients will at some point require some form of rate control, either in combination with rhythm control or as the remaining option when rhythm control is not feasible. Rate control is used to decrease symptoms and potentially reduce risk of heart failure caused by an elevated heart rate in AF. The optimal goal for heart rate is not known, but lenient control (<110 beats per minute (bpm)) of resting heart rate is not inferior to strict control (<80 bpm).[123] The heart rate in AF is irregular, and is often measured using 10-second resting ECG. Since the reliability of these measurements impacts both the

results of studies of rate control and treatment choices in individual patients, we assessed the reliability of resting heart rate measurements in **Paper IV**.

Rate control treatment is usually achieved with rate controlling drugs. Beta-blockers, diltiazem, verapamil and digoxin are all considered first-line agents for rate control in AF patients.[56] Compared to digoxin, beta-blockers were associated with increased risk of AF outcomes and increased levels of the biomarker NT-pro-BNP in the RATE-AF trial.[124] NT-proBNP is associated with an increased risk of stroke in AF patients.[59]

Evaluation and Dynamic Reassessment

As comorbidities, AF burden and symptoms can change over time evaluation and dynamic reassessment is needed. Patients might for example develop indications for anticoagulation, ablation or adjustment of rate controlling drugs.

Heart Rate, Physical Activity, Atrial Fibrillation and Death

Low resting heart rate[7,125,126] and vigorous physical activity[26,27] both increase the risk of AF. Regular physical activity decreases the resting heart rate[127] so it is reasonable to think that low heart rate is a marker of physical activity and therefore related to atrial fibrillation. But the relationship between physical activity and atrial fibrillation is J-shaped, meaning that both low and high physical activity increases AF-risk compared to moderate activity.[25] Physical activity is beneficial in AF patients and decrease AF-burden.[128]

A low heart rate can have several causes, only one of which is high volume endurance training. In population-based studies that have shown increased AF risk with low heart rate high level endurance athletes can be assumed to be rare. Therefore, the association between low heart and incident AF can be assumed to be mostly independent of physical activity. It is not known why low heart rate increases AF risk; one reason could be that low heart rates increase the filling volumes of the atria in each cycle. This could increase filling pressure,[129] leading to atrial stretch/size and in long term AF. Ivabradine and betablockers decrease heart rate by different mechanisms, and both increase AF risk,[130] supporting a causal link between low heart rate and AF. It is possible that vigorous endurance training causes AF because of increased atrial size and low heart rate.

Increased frequency of PACs is another risk factor for atrial fibrillation.[29,131] The interval between heartbeats is longer with lower heart rates, so the time window where a PAC can occur is increased. It is conceivable that low heart rates are

associated with increased PAC frequency, and that heart rate and PAC occurrence interact as regards AF risk. We investigated this in **Paper II**.[132]

AF and mortality share many risk factors. But in contrast to low heart rate being a risk factor for AF, high heart rate is associated with all-cause mortality, cancer deaths and cardiovascular deaths.[133] This could be due to sympathetic nervous system activation activates in response to physiological stress resulting in increased heart rate, and the association between high heart rates and death is therefore possibly confounded by morbidity.

Heart rate is a marker for both mortality and AF-risk, but normal ranges of ambulatory heart rates have been lacking. In **Paper I** we presented reference ranges for ambulatory heart rates in a middle-aged population.

Aims

The aim of this thesis was to study heart rate at long-term ECG in relation to atrial fibrillation and whether Micro AF is related to future atrial fibrillation. This was achieved by the specific aims included in this thesis:

I. To describe the normal ranges of ambulatory heart rate and study the relationship between cardiovascular risk factors and heart rate.

II. To study if low heart rate predicts AF independently of supraventricular activity

III. To study if Micro AF predicts future clinical AF diagnosed in a hospital setting.

IV. To study the reliability of single resting heart rate measurements in atrial fibrillation.

Methods

Study Populations

The Swedish CArdioPulmonary Imaging Study

The Swedish CArdioPulmonary Imaging Study (SCAPIS) is a population-based study that included 30,154 participants aged 50-65 years. These individuals were recruited between 2013 and 2018 from the general population living near university hospitals in Gothenburg, Linköping, Malmö, Stockholm, Uppsala or Umeå. Written invitations were sent to 59,909, with a participation rate of 50,3%.[134]

Participants underwent extensive examinations, including blood sampling, anthropometric measurements, lung function testing, ECG, blood pressure measurement, and coronary artery imaging. They also completed a questionnaire covering diet, lifestyle habits (e.g., smoke status, alcohol consumption and physical activity) and health (e.g., previous diagnosed diseases and medication use).

All participants in Uppsala were asked from the start to contribute a 24-hour ECG. In Malmö 24hECGs were included in screening activities starting September 2016. A total of 6,292 24-hour ECG registrations were performed, and these form the basis for **Paper I,** where we establish reference values for heart rate.

The Malmö Diet and Cancer Study

The Malmö Diet and Cancer study (MDCS) is a population-based cohort with baseline examinations conducted between 1991 and 1996. All women born between 1923 and 1950, and men born between 1923 and 1945, residing in Malmö were invited to participate. The study enrolled 30,446 individuals, achieving a participation rate of 41%.

A cardiovascular sub-study was conducted within MDCS, where the homeostatic model assessment of insulin resistance (HOMA-IR) was available for 5,533 out of 6,103 participants. Between 1998 and 2000, a subgroup of the cardiovascular substudy was invited based on their HOMA-IR levels. Higher sex-specific levels of HOMA-IR were oversampled: 40% from the highest quartile, 30% from the third quartile, and 15% from each of the first and second quartiles.

A random sample of 389 individuals from this HOMA-IR subgroup underwent 24-hour ECG examinations. The study population in **Paper II and III** consists of 377 individuals who were examined with 24-hour ECG, after excluding those with AF (n=7) and inadequate recordings (n=5). A flow chart of the Study population for **Paper II and III** is shown in **Figure 3**.

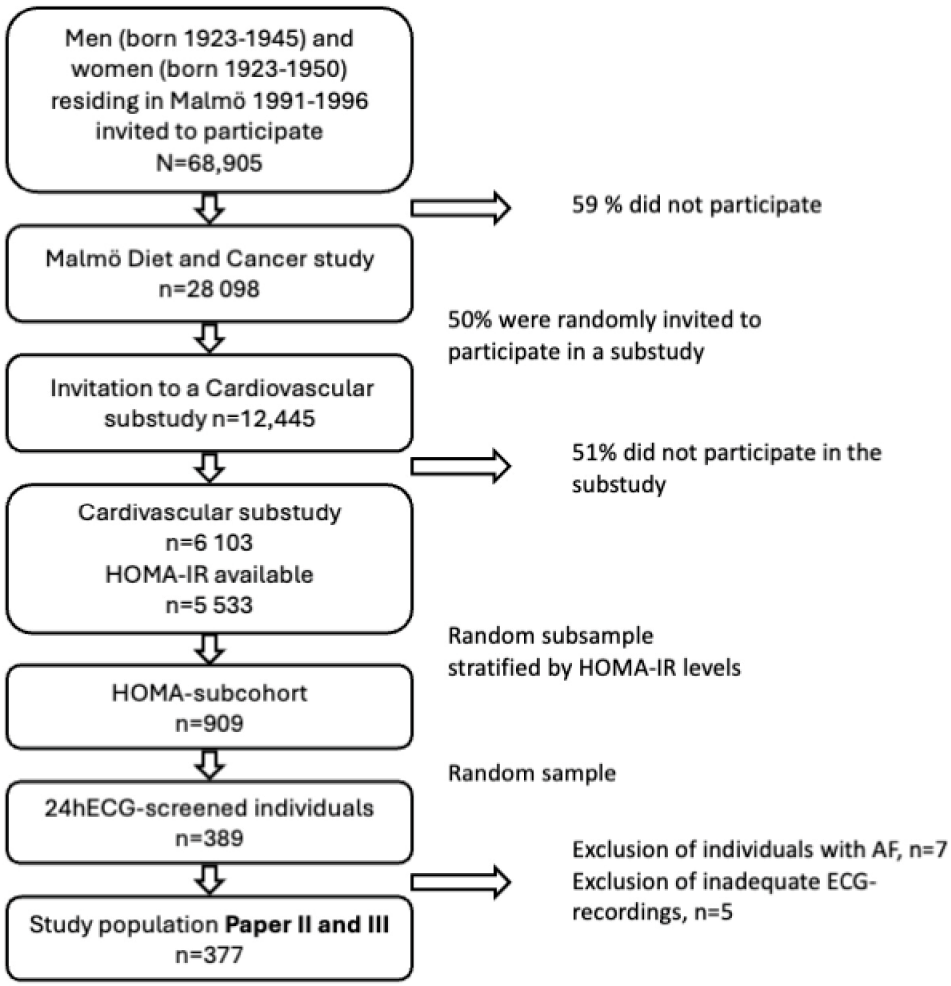

Figure 3
Derivation of study population for Paper II and III

The PocketECG Database

The study population in **Paper IV** consists of clinical patients examined using PocketECG (MEDICALgorithmics, Warsaw, Poland). PocketECG is long-term ambulatory ECG device equipped with a built-in accelerometer. We included examinations performed with PocketECG in United States in 2021, which had more than 95% AF-beats and at least two full registration days, resulting in a sample size of 832.

Consent and Ethical Approval

Participants in the SCAPIS and MDCS studies provided written informed consent, and the studies were approved by regional ethical boards. The data in the clinical long-term ECG population used in **Paper IV** is anonymized, and the ethics review board waived the need for approval for using this data. All papers included in this thesis has been conducted in accordance with the Declaration of Helsinki.

Variables in SCAPIS

The variables of interest in SCAPIS were heart rate measurements derived from the CardioSpy ECG analysis software, based on a 24-hour ECG recording with CardioSpy equipment (Labtech, Debrecen, Hungary), featuring X, Y, Z coupling and 256 Hz sampling rate. We defined mean heart rate as the average during the recording and the minimum heart rate as the lowest heart rate for 1 minute. The average day (06:00-22:00) and night-time (22:00-06:00) heart rates were measured, and the nightly dip calculated as the difference between day and night-time heart rates. Reference ranges of heart rate were derived from a subset of healthy individuals, defined as those without known prevalent cardiovascular disease, hypertension, heart failure, anemia, diabetes, obstructive sleep apnea, chronic obstructive pulmonary disease, or use of beta-blockers. A flow chart of the study populations in SCAPIS is shown in **Figure 4**.

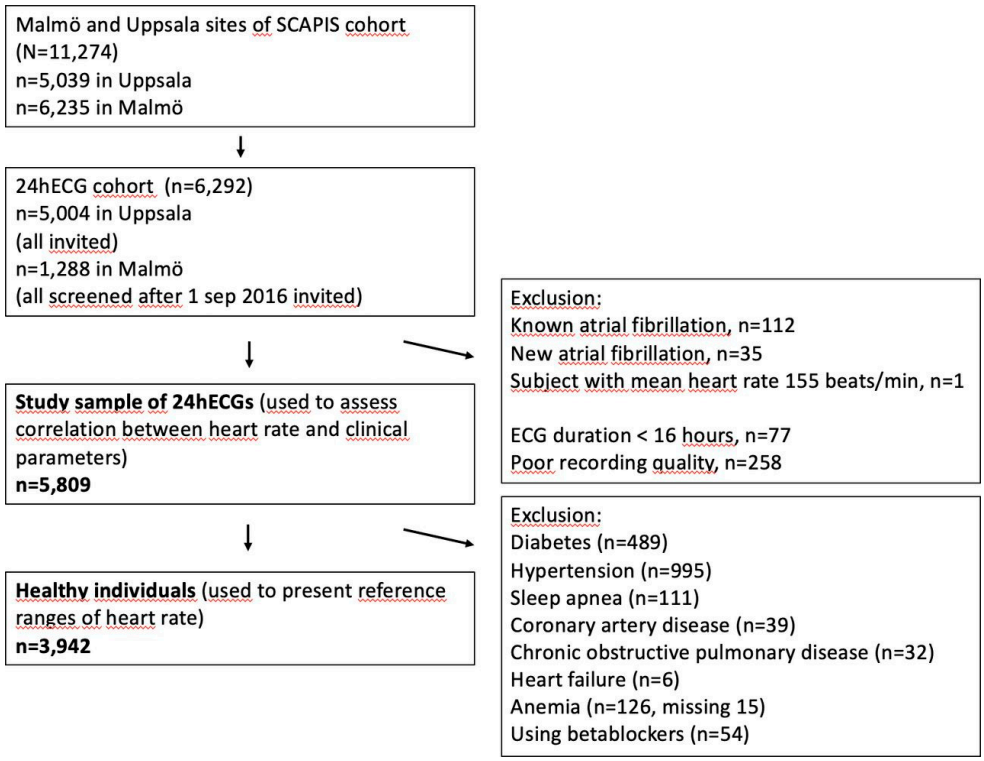

Figure 4
Derivation of study population. Reprinted from Paper I,[135] Heart, open access under CC BY 4.0.

We assessed the correlation between heart rate and various factors, including age, sex, height, body mass index (BMI), smoking status, physical activity, alcohol use, diabetes, hypertension, use of beta-blockers, percent of expected forced expiratory volume in one second (FEV1), coronary artery calcium score, estimated glomerular filtration rate (eGFR) and haemoglobin levels. Height was measured to the nearest centimeter, and weight was measured in light clothing on a digital scale. BMI calculated as weight in kilograms divided by the height in meters squared. Physical activity, alcohol use and previous diagnosis of diabetes or hypertension were obtained from a questionnaire. If fasting blood glucose was elevated (≥7 mmol/L), sampling was repeated on another day, and diabetes diagnosed if levels remained elevated. Blood samples were also taken to measure haemoglobin and creatinine levels. We calculated eGFR using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration formula.[136] Computed tomography (CT) was performed using Siemens Definition Flash 2 × 128 slice, stellar detector, 4D-Care dose, Care-kV and sinogram-affirmed iterative reconstruction (Forchheim, Germany). Coronary artery calcium was assessed by calculating the Agatston

score.[137] Spirometry was performed 15 minutes after bronchodilatation, and FEV1 in percent of expected was calculated using Hedenström formula.[138,139]

Exposure Variables and Co-variables in MDCS-cohort

The exposure variables in **Paper II and III** were collected using a 24-hour ECG with X,Y,Z coupling, recorded on a Spacelabs Healthcare Lifecard CF 12 bits Digital ECG recorder with 256 Hz sampling rate and a mean recording duration of 23.5 hours (SD 1.2 hours).

Paper II Exposures

Heart rate: Mean heart rate was defined as the average during the recording, and minimum heart rate as the lowest heart rate for 1 minute.

Increased supraventricular activity: PACs were defined as premature beats with RR intervals less than 80% of the preceding RR interval, with a presumed atrial origin (based on beat morphology or timing in relation to surrounding beats). Three or more consecutive PACs were classified as supraventricular tachycardia (SVT). Increased supraventricular activity was defined as having PAC and/or SVTs in the top quartile of the population distribution.

Paper III Exposures

Types of SVTs: Four types of SVTs were categorized based on the presence of P-waves and irregularity: regular with P wave (n=151), regular without P wave (n=24), irregular with P wave (n=15) and Micro AF (irregular without P wave, n=19). Patients with AF with a duration over 30 seconds were excluded.

Assessment: Two reviewers individually assessed all 136 SVTs with at least 5 beats for P-waves and irregularity, with discrepancies resolved by a third reviewer. SVTs with a 3-4 beat duration were included in the regular SVT with P-waves group due to insufficient length for irregularity analysis.

Covariates

Covariates included age, sex, height, BMI, HOMA-IR, systolic blood pressure, hypertensive medication, smoking status, and physical activity. Height and weight were measured in light clothing without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. HOMA-IR was calculated by multiplying fasting glucose by fasting insulin and dividing by a constant. Blood pressure was measured manually after 10 minutes of supine rest using a modifiable sphygmomanometer cuff. Information on the use of hypertensive medication, smoking status and leisure time physical activity was obtained from a questionnaire.

Endpoint Retrieval in MDCS

Survival analysis was performed in **Paper II and III**. The endpoints AF and stroke were retrieved from the Swedish National Hospital Discharge Register which has covered inpatient diagnosis since 1987 and hospital outpatient diagnosis since 2000. The endpoint death was retrieved from the National Cause of Death Register. Patients were followed until the first event or censoring due to death (n=117 in **Paper II**) or emigration (n=2 in **Paper II**). The mean follow-up time was 17 years in **Paper II** and 13 years in **Paper III**. The AF diagnosis in MDCS has been validated with an accuracy of 95%.[140]

Variables in the PocketECG Database

In the clinical PocketECG population used in **Paper IV,** the data is anonymized, the only data available was age, sex and data from ECG-recordings and the accelerometer. We defined mean heart rate as the average during the entire recording and daily mean as 24-hour averages. The minimum and maximum daily (24-hour period) heart rates were defined as the lowest and highest heart rates for one minute. The overall lowest and highest heart rates were defined as the mean of daily minimum and maximum heart rates, respectively.

Rest was assessed using data from the accelerometer, with resting heart rates sampled as 10-second averages between 08:00 and 20:00 after at least 10 minutes of rest. The overall resting heart rate was calculated as the average heart rate during periods of rest between 08:00 and 20:00 following at least 10 minutes of rest.

Statistical Methods

The statistical analyses were performed using Stata for Mac, V15.1. in **Paper I and II**, Stata for Mac v18.0 and Python 3.10.12 in **Paper IV** and Stata for Mac in **Paper III**.

Cross-sectional and Cohort Studies

In a cross-sectional study, a group of individuals is examined at a single point in time. The examination results can be used to create reference intervals and identify correlations between different parameters, as demonstrated in **Paper I**. When parameters are measured repeatedly, the reliability or precision of a single measure can be calculated, as we did in **Paper IV**.

Cohort studies differ from cross-sectional studies in that they follow a group of individuals over time. There are two types of cohorts: prospective and retrospective. In prospective cohorts, a group of individuals is examined, measurements (exposures) are gathered, and the follow until event of interest (outcome) occurs. In retrospective cohorts, a group of individuals is sampled, and information of their past exposures is gathered. The knowledge of the outcome status leads to a risk of bias in the ascertainment of the exposure data, and for this reason prospective cohorts are considered to be superior. The purpose of both retrospective and prospective cohorts is to identify exposures related to later outcomes. In **Paper II and III** we used prospective cohorts to identify risk factors for future AF.

Normal Distribution and Variability

A normal distribution has a bell-shaped curve with many observations close to the mean, see **Figure 5**.

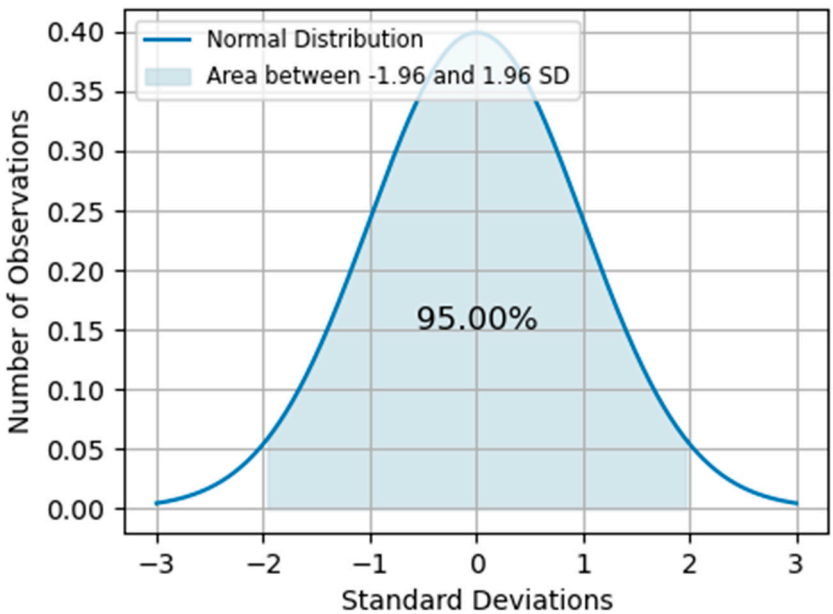

Figure 5
Normal distrubution, standard deviation, and area under the curve between -1.96 and 1.96 standard deviations. The figure was created with the assistance of Microsoft Copilot.

There are different methods to assess the variability of measurements, with standard deviations being the are most commonly used:

$$Standard\ deviation = \sqrt{\frac{\sum(X - \bar{x})^2}{n - 1}}$$

The standard deviation is the square root of the sum of the squared differences between observations and the mean, divided by the number of observations minus 1. It is similar to the mean absolute deviation:

$$Mean\ absolute\ deviation = \frac{\sum|X - \bar{x}|}{n}$$

The mean absolute deviation is the average absolute difference between a measurement and the mean of all measurements. The standard deviation is slightly more complex, as it involves taking the square root of the average of squared differences. The mean absolute deviation, or average distance from the mean, is easier to understand and was therefore used in **Paper IV**. Squaring differences also makes the standard deviation sensitive to outliers. Standard deviations are often used to describe reference ranges; for example, ±1.96 standard deviations include 95% of the population if the distribution is normal.

A third option to describe variability is percentiles. Percentiles are easy to understand and can be used even if the parameter has a skewed (non-normal) distribution.

Bootstrap

The term 'bootstrap' comes from the expression "pull yourself up by your bootstraps", meaning to improve your situation without external help. This is precisely what bootstrapping does in statistical analysis. In bootstrap analyses, one uses the actual study population to sample other study populations that could also have been drawn from the same source population. This is done by using so called sampling with replacement. From the study population an equal number of individuals is drawn, but each individual can be drawn several times, or not at all. Using bootstrapping one can obtain and study thousands of slightly different, but possible, study populations at once, and the confidence intervals derived using bootstrap reflect the differences between these different populations. Bootstrapping can, for example, be used to calculated confidence intervals around percentiles as we did in **Paper IV**.

C statistic and ROC Curve

Harrell's C statistic is used to assess if a method can discriminate with patients with a disease from those without. It is not a measure of calibration, which refers to how well the predicted risk correlate with observed risk. The C statistic ranges from 0.5-1, where 1 is perfect discrimination (the values of the method are higher or lower for everyone with disease than for those without), and 0.5 means that the method is as good as flipping a coin. The C statistic is the probability that the value of the method is higher for those with disease than those without.[141] The C statistic is calculated as the area under the receiver operating characteristic (ROC) curve. The ROC curve is a function of sensitivity vs false positive rate (1-specificity).

Linear Regression

In simple linear regression, a correlation between two parameters is analysed. The difference between an observed value and the predicted value is known as a residual. The regression line is positioned such that the sum of the squared residuals is minimized. An example equation for a simple linear regression is (Y=0.5+2X) and an example of a regression line is shown in **Figure 6**.

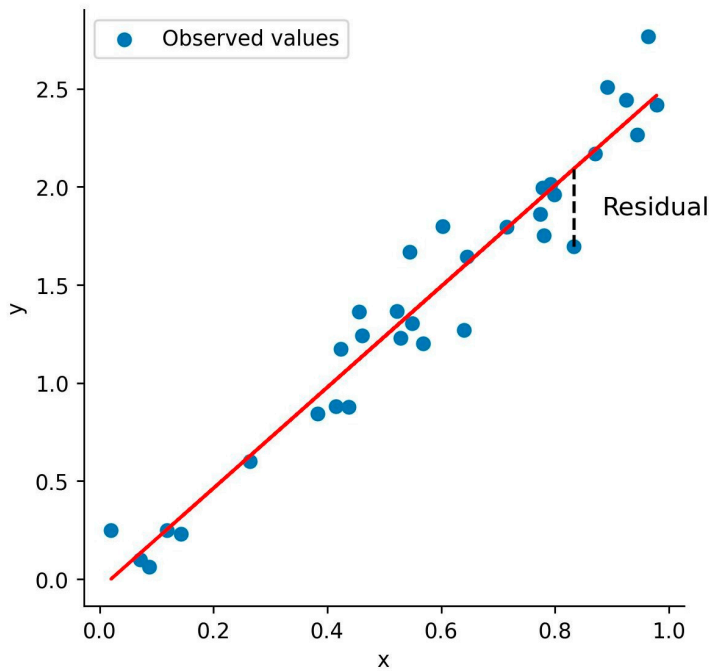

Figure 6
Example of a regression line fitted by least squares, where the sum of squared residuals is minimized. The figure was created with the assistance of Microsoft Copilot.

In multivariable linear regression, more than one parameter is used to estimate (Y). For example the equation (Y = 0.5 + 2X + 1.5Z) uses both (X) and (Z) to estimate (Y). This can be illustrated graphically as a plane, as shown in **Figure 7**, instead of a simple line. It is possible include more variables in a multivariable linear regression, such as (Y = 0.5 + 2X + 1Z + …) , but not possible to graphically illustrate as it would require a multidimensional graph.

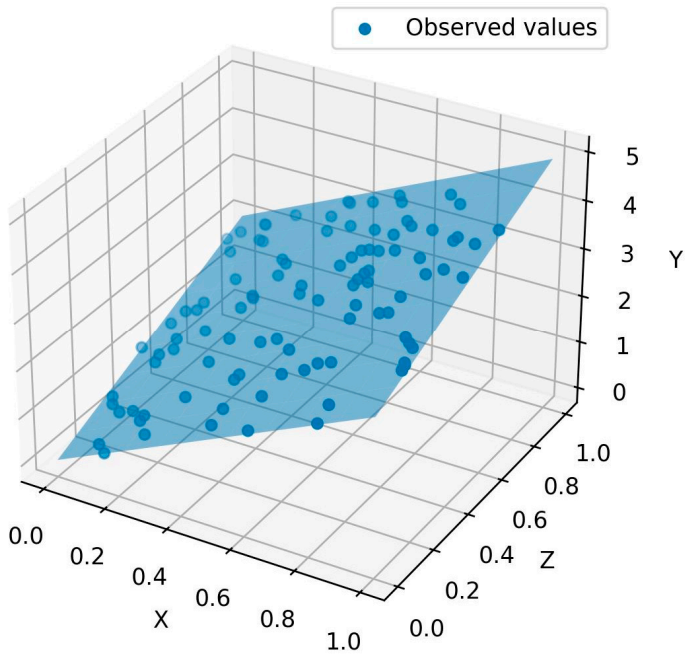

Figure 7
Multivariable linear regression: Using two indepependent variables (X and Z), the fitted "line" is actually a plane. The figure was created with the assistance of Microsoft Copilot.

There are several assumptions to consider when using linear regression:

1. **Linear Relationship:** The fitted line is straight, so a linear relationship should be present. Non-linear relationship, such as for U-shaped or exponential patterns, are not suitable for linear regression.
2. **Normally Distributed Residuals:** The residuals should be normally distributed. Outliers will also be squared and can have a large impact on the regression line.
3. **Homoscedasticity:** Residuals should be evenly distributed around all values of the dependent variable. If not, the p-value/statistical significance is unreliable.

4. **No Collinearity:** For reliable estimates between the independent and dependent variables, there should not be any collinearity. Collinearity means that two or more independent variables are correlated, which might result in strange estimates and wide confidence intervals. The variance inflation factor (VIF) can be used to identify collinearity. A VIF > 5 is generally taken to indicate a problem with collinearity and at VIF < 2.5 or 3, there is likely not any substantial collinearity.

R^2

The slope of the line in a simple linear regression tells us something about the relationship between two variables. However, if we want to know how well our line estimates (Y) from (X), we can calculate R^2. For example, if we want to estimate weight from height, we plot weight and height and fit a line using least squares.

To calculate R^2, we first calculate the variance for weight:

$$Variance_{weight} = \frac{(Measured\ weight - \ Mean\ weight)^2}{Number\ of\ individuals}$$

We then calculate the variance for residuals:

$$Variance_{residuals} = \frac{(Residuals)^2}{Number\ of\ individuals}$$

We can then calculate R^2:

$$R^2 = \frac{Variance_{weight} - Variance_{residuals}}{Variance_{weight}}$$

or, in other words:

$$R^2 = \frac{Variation\ in\ weight\ explained\ by\ height}{Variation\ in\ weight}$$

R^2 is the percentage of variation explained by the variables included in the model and ranges from 0 to 1. If ($R^2 = 1$) there is a perfect fit (variance of residuals is 0, meaning the fitted line goes through all measured values). An R^2 of 0.3 would mean that 30% of the difference in weight can be explained by differences in height. Including more variables in a multilinear regression will never decrease R^2. However, by adding variables, there is risk that R^2 is increased just by chance. Adjusted R^2 can be used to adjust for number of included variables.

Survival Analysis

Kaplan-Meier curves

Kaplan-Meier survival curves illustrate the percentage of event-free survival over time. The x-axis represents the follow-up period, while the y-axis shows the probability of remaining event-free. The curve starts at 100 %.

For example, if we track 10 individuals for AF and one develops AF after one month, the curve will drop to 90%. If we lose track of two individuals after two months, and after three months one of the remaining seven develops AF, the curve will then drop by 1/7th of 90%, resulting in a new probability of event-free survival of 77.1% after three months.

It is not possible to adjust for confounding in Kaplan-Meier curves, which is often needed in observational studies. However, Kaplan-Meier curves are often used in randomized control trials where randomization implies that one can assume no confounding. In such cases, one curve is plotted for treatment group and the other curve for control. Kaplan-Meier curves can also be useful in observational studies. If the unadjusted hazard ratio is similar to the adjusted hazard ratio, the curves illustrate the rate of events over time. If curves are drawn for exposed and non-exposed and separate at a relatively constant rate the proportional hazard assumption in Cox-regression can be assumed to be fulfilled.

Cox Regression

The Cox proportional hazard model,[142] introduced in 1972 and has become a standard method in survival analysis. The regression model calculates hazard ratios:

$$Hazard\ ratio = \frac{Hazard\ rate\ in\ exposed}{Hazard\ rate\ in\ unexposed}$$

These are very similar to relative risks:

$$Relative\ risk = \frac{Risk\ in\ exposed}{Risk\ in\ unexposed}$$

Relative risks are calculated by dividing the number of cases in the exposed group with the number in the unexposed group. But this does not adequately account for time to event.

> "On a long enough timeline, the survival rate for everyone drops to zero"
> -Chuck Palaniuk, Fight Club

In Cox regression, hazard ratios are calculated each time an event occur by comparing the characteristics (exposure/included covariates) of the individual with

the event to others still at risk. The hazard ratios can be viewed as relative risks in each instant, and thus Cox regression assumes that the hazards are proportional over time, meaning that the hazard ratio is constant during the study period. In a sense, Cox regression reduces a survival analysis to a case-control analysis, with the controls being the other individuals at risk at the same time as each case.

There are several ways to test if the hazards are proportional. In **Paper II**, we used Kaplan-Meier curves and log-log plots, and in **Paper III**, we used and Kaplan-Meier curves and Schoenfeld residuals. But it is unlikely that hazards are perfectly proportional over time, so the hazard ratios can be interpreted as weighted averages during the follow-up period.[143]

Competing Risks

If being exposed (or not) causes an increased risk of death (or censoring from other causes), this might influence the hazard ratios. It is not possible to develop AF if you have already died. There are a few methods to adjust for competing risks. In **Paper III**, we used competing risks regression as described by Fine and Gray[144] to adjust for competing risk of mortality. Competing risk analysis provides sub-hazard ratios, which can be interpreted as hazard ratios independent of the competing risk.

Lexis Expansion

In Cox regression age is usually measured at baseline and does not account for changing age or calendar time. Lexis expansion addresses this by calculating rate ratios for strata (bands) of time, such as acquired age or calendar time. If the rate ratios are similar in different strata, it indicates that there is no interaction with changing age or calendar time.[145] The bands can also be incorporated into the Cox regression model by using an interaction term between the covariate and the bands to assess if the covariate is time-dependent.[146] We used Lexis expansion in **Paper II**.

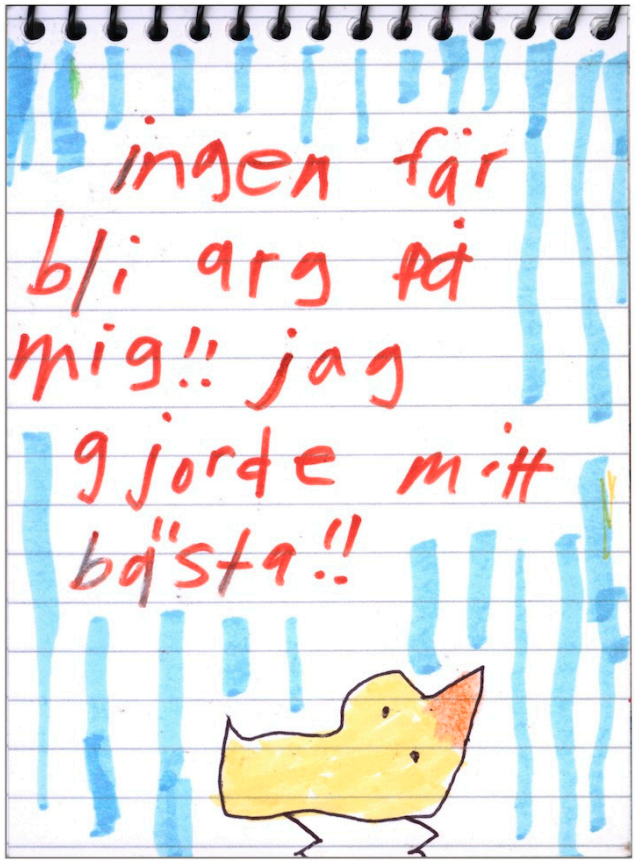

Image reproduced with permission from the artist,
© Magda Lundberg

Utilization of Artificial Intelligence in this Thesis

Artificial intelligence, specifically Copilot, was utilized for language review and figure generation in preparation of this thesis.

Results

Study population characteristics in the subgroups of SCAPIS, MDCS and PocketECG.

The characteristics of the AF-free sample of 5,809 individuals from SCAPIS used in **Paper I** are reported in **Table 1**. Age was evenly distributed between 50 and 65 years, with 52% being women.

Baseline characteristics of the 377 individuals without AF included in from MDCS in **Paper II** and **III** are shown in **Table 2**. The mean age was 65 years (range 53-74), and 55% were women. Baseline examinations were performed in 1998 and 2000, with 23% being current smokers, compared to 11% in the more recent SCAPIS subgroup used in **Paper I**.

The characteristics of the study population in **Paper IV** is presented in **Table 3**. This population consists of 832 individuals with AF with a median age of 77 years (IQR 69-83), and 42% being women.

Table 1
Sample characteristics in SCAPIS

	All (N=5,809)	Women	Men	Healthy reference sample (n=3,942)
Age, mean (range)	58 (50-65)	58 (50-65)	58 (50-65)	57 (50-65)
Women, %	53	100	0	54
Height, cm, mean (SD)	172 (9.7)	166 (6.5)	179 (7.0)	172 (9.7)
BMI, %				
<25	35	42	27	40
25-30	44	38	51	44
>30	21	20	22	16
Smoking, %				
-never	56	53	59	58
-former	34	37	30	32
-current	11	11	11	10
Alcohol intake units/week, median (IQR)	2.6 (1.1-4.1)	1.1 (0.4-3.8)	2.6 (1.1-6.0)	2.6 (1.1-4.1)
Physical activity, %				
-low	57	60	54	54
-high	43	40	46	46
Diabetes, %	25	7	11	-
Hypertension, %	21	20	22	-
Use of oral beta-blockers, %	5.8	6.1	5.5	-
FEV1%predicted (SD)	109 (15)	109 (15)	108 (14)	110 (14)
Coronary artery calcium score, %				
0	61	74	46	67
1-99	27	21	35	25
≥100	11	5	19	8
eGFR, mL/min/1.73m^2 (IQR)	88 (79-96)	88 (78-96)	89 (80-96)	88 (79-96)
Hemoglobin, g/L, mean (SD)	142 (12)	135 (9.1)	149 (9.4)	142 (11)
Sleep apnea, %	3.7	2.6	4.9	-
Coronary artery disease, %	2.0	1.1	3.0	-
Heart failure, %	0.3	0.3	0.4	-

Table 2
Baseline characteristics in MDCS

	All	Men	Women
Number, n	377	170	207
Women	55		
Age (years), median (range)	65 (53-74)	65 (53-74)	65 (53-74)
Height (cm)	169 (9)	176 (7)	163 (6)
Weight (kg)	77 (13)	84 (12)	72 (11)
Body mass index (kg/m^2)	27 (4)	27 (3)	27 (4)
HOMA-IR*, median (interquartile range)	2.1 (1.4-3.2)	2.2 (1.5-3.3)	1.9 (1.3-3.0)
Systolic blood pressure	144 (18)	145 (19)	142 (18)
Current smokers	23	26	19
Mean heart rate, bpm	78 (9)	75 (9)	80 (9)
Minimum heart rate, bpm	56 (8)	54 (7)	58 (8)
Premature atrial contractions/hour, median (IQR)	1.6 (0.6-5.5)	1.6 (0.7-5.9)	1.4 (0.5-4.6)
Supraventricular tachycardia/hour, median (IQR)	0.04 (0-0.13)	0.04 (0-0.13)	0.04 (0-0.13)

Values are % or mean±SD unless otherwise indicated.
*HOMA-IR is the homeostasis model assessment of insulin resistance

Table 3
Sample characteristics in the PocketECG study

	All
Number, n	832
Women, %	42
Age in years, median (interquartile range)	77 (69-83)
Duration of ECG registration in days, median (interquartile range)	13 (7-22)
Mean heart rate in bpm, mean (SD)	86 (16)
Minimum heart rate in bpm, mean (SD)	63 (14)

Paper I

Heart Rate Reference Ranges at Ambulatory ECG

Heart rate reference ranges at ambulatory ECG were determined in a healthy subset of the study population, as reported in **Table 4.** The average mean heart rate was 73 bpm for men and 76 bpm in men and women, respectively, and 2.5th to 97.5th percentiles of mean heart rate were 57-90 bpm for men and 61-92 bpm for women. Percentiles for mean and minimum heart rates are reported in more detail in **Table 4. Figure 8** presents histograms of heart rate and sex-specific cumulative distribution curves.

Table 4
Reference ranges for measures of ambulatory heart rate

	Mean heart rate (bpm)		**Minimum heart rate*** **(bpm)**	
	Men	Women	Men	Women
Healthy individuals$^{\Psi}$ (1,825 men and 2,117 women)				
Mean (SD)	73 (9)	76 (8)	48 (7)	51 (7)
Percentiles				
2.5	**57**	**61**	**36**	**39**
5	59	63	38	40
25	67	71	44	46
50	**73**	**76**	**48**	**51**
75	79	81	53	55
95	87	89	60	62
97.5	**90**	**92**	**63**	**65**

Ψ defined as those without known prevalent cardiovascular disease, hypertension, heart failure, anemia, diabetes, obstructive sleep apnea, chronic obstructive pulmonary disease, or use of beta-blockers
*Lowest average heart rate for one minute.

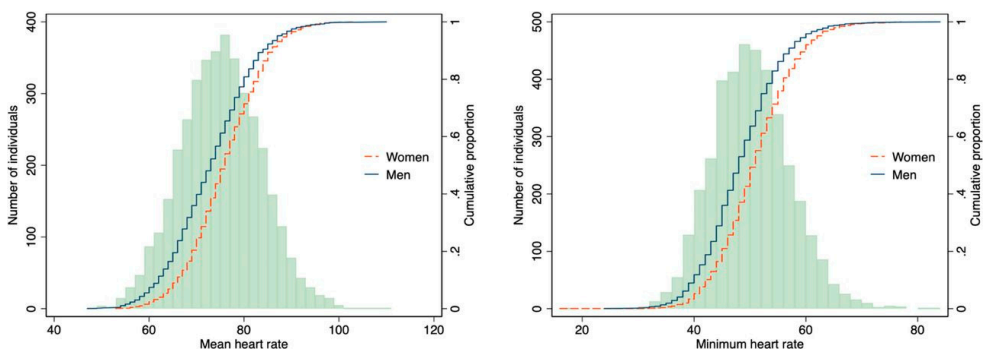

Figure 8
Heart rates in healthy reference sample, histogram and sex-specific cumulative distribution curves. Reprinted from Paper I,[135] Heart, open access CC BY 4.0.

Predictors of Heart Rate

The correlation between heart rate and various co-variables in the full study sample was calculated using multivariable linear regression, as presented in **Table 5**. Out of the 14 included variables, 11 were significantly associated with heart rate. However, these associations were relatively weak, with less than 15% of differences in mean and minimum heart rate explained by all included variables ($R^2 < 0.15$).

Table 5
Multivariable linear regression models for ambulatory heart rate measures.

N=5021	Mean heart rate, bpm (95%CI)		Minimum heart rate, bpm (95%CI)	
	Beta (95%CI)	**t ratio$^{\Psi}$**	**Beta (95%CI)**	**t ratio$^{\Psi}$**
Age (per 1 year)	-0.0 (-0.1,0.0)	-1.4	0.1 (0.0,0.1)	3.3
Men (vs women)	**-2.8 (-3.5,-2.0)**	-7.3	**-2.2 (-2.9,-1.6)**	-7.1
Height (per 10 cm)	**-0.8 (-1.2,-0.5)**	-4.9	**-0.8 (-1.0,-0.5)**	-5.2
Body mass index, kg/m^2				
<25	ref.	ref.	ref.	ref.
25-30	**0.9 (0.4,1.4)**	3.5	**0.8 (0.4,1.3)**	3.8
>30	**1.9 (1.2,2.6)**	5.6	**1.4 (0.9,2.0)**	5.1
Smoking				
-never	ref.	ref.	ref.	ref.
-former	**1.2 (0.7,1.7)**	4.9	**0.9 (0.5,1.3)**	4.3
-current	**2.7 (1.9,3.4)**	6.7	**2.2 (1.6,2.9)**	6.8
High physical activity (vs low)	**-3.6 (-4.1,-3.1)**	-15.1	**-2.7 (-3.1,-2.3)**	-13.5
Alcohol intake, above median (vs below median)	**0.7 (0.2,1.1)**	3.0	**0.8 (0.4,1.2)**	4.1
Diabetes (yes vs no)	**2.0 (1.1,2.8)**	4.5	**2.1 (1.4,2.8)**	5.8
Hypertension (yes vs no)	0.4 (-0.1,1.0)	1.5	0.1 (-0.4,0.6)	0.4
Using oral beta-blockers (yes vs no)	**-4.5 (-5.5,-3.4)**	-8.5	**-0.9 (-1.8,-0.1)**	-2.2
FEV1%predicted, per 10 % increase	**-0.3 (-0.4,-0.1)**	-3.6	**-0.3 (-0.5,-0.2)**	-4.8
Coronary artery calcium score				
0	ref.	ref.	ref.	ref.
1-99	0.4 (-0.1,1.0)	1.6	0.4 (-0.1,0.8)	1.6
≥100	0.6 (-0.2,1.4)	1.5	0.5 (-0.1,1.2)	1.6
eGFR (per 10 mL/min/1.73m^2)	**0.6 (0.4,0.8)**	6.1	**0.4 (0.3,0.6)**	5.0
Hemoglobin (per 10 g/L increase)	**0.7 (0.5,1.0)**	5.7	**0.3 (0.1,0.5)**	2.5
Constant*	76.1 (75.4,76.8)		49.9 (49.3,50.5)	
Unadjusted R^2	0.149		0.143	
Adjusted R^2	0.146		0.140	

Bold numbers indicate statistical significance (P<0.05).

Ψ larger t-ratios (both positive and negative) imply larger impacts on heart rate

Paper II

During a mean follow-up time of 17 years, 80 (21%) were diagnosed with AF. Low mean heart rate predicts incident AF both as a continuous variable and when dichotomised into groups below and above the median. The results from the Cox regression are reported in **Table 6**. The hazard ratios for groups of mean heart rate dichotomized by the median and SVA indicate additive effects between the two variables. Additionally, non-significant multiplicative interaction suggests that low heart rate and SVA are independent predictors of AF. Kaplan-Meier curves for AF-free survival by groups of heart rate dichotomized by median and SVA are shown in **Figure 9**.

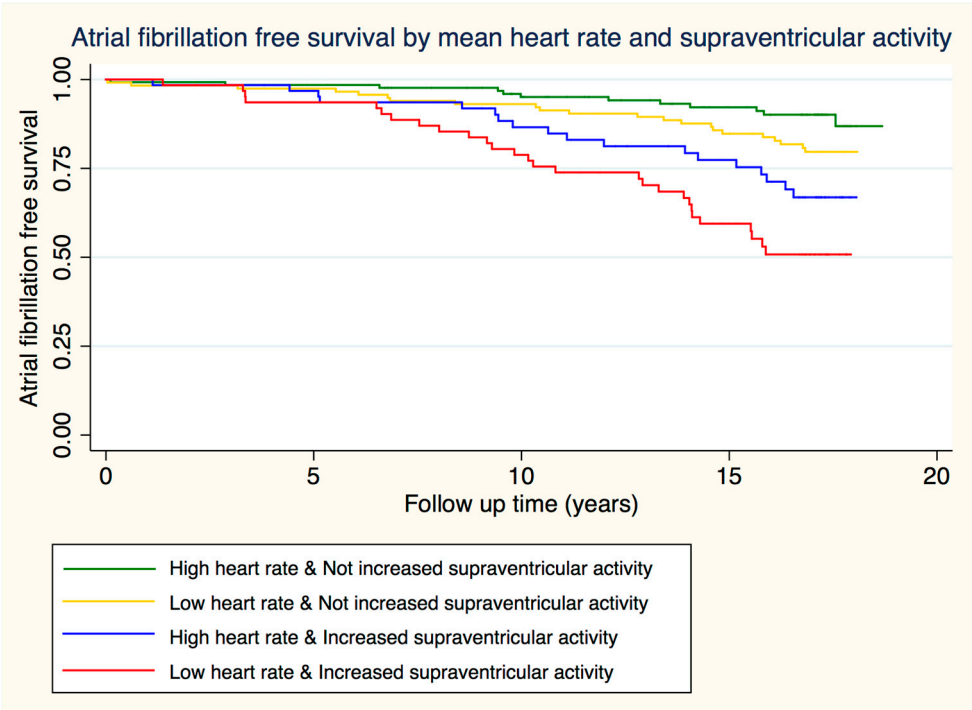

Figure 9
Kaplan-Meier survival curves for incident AF by groups of mean heart rate above and below median (high and low respectively) and increased supraventricular activity (top quartile of either premature atrial contractions or supraventricular tachycardias. The figure is adapted from the original figure in Paper II, "Heart rate and premature atrial contractions at 24hECG independently predict atrial fibrillation in a population-based study", by AP Persson, 2020, Heart;106(4), 287-291, © Author(s) (or their employer(s)) 2020, with permission from The BMJ.

Table 6
Cox regression analysis of heart rate at 24-hour ECG and indcidence of atrial fibrillation

	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
Mean heart rate (mHR)						
Per 1 beat decrease	1.034	1.006-1.063	1.033	1.005-1.061	1.036	1.008-1.065
Quartile 4	ref		ref		ref	
Quartile 3	0.84	0.41-1.73	0.77	0.37-1.59	0.82	0.39-1.72
Quartile 2	1.44	0.76-2.71	1.65	0.87-3.13	1.82	0.94-3.51
Quartile 1	1.72	0.89-3.33	1.63	0.83-3.22	1.76	0.88-3.53
High heart rate†	ref		ref		ref	
Low heart rate‡	1.69	1.07-2.66	1.89	1.18-3.02	2.00	1.24-3.22
Minimum heart rate§, per 1 beat decrease	1.024	0.99-1.06	1.027	0.99-1.06	1.030	1.00-1.07
Increased supraventricular activity (SVA)¶	2.39	1.51-3.77	2.36	1.49-3.77	2.49	1.56-3.97
Groups based on mHR and SVA						
High heart rate and not SVA (N=132)	ref		ref		Ref	
Low heart rate and not SVA (N=118)	1.81	0.89-3.65	2.14	1.03-4.46	2.43	1.14-5.21
High heart rate and SVA (N=63)	2.54	1.21-5.31	2.74	1.30-5.80	3.12	1.44-6.75
Low heart rate and SVA (N=64)	4.31	2.16-8.58	4.51	2.24-9.05	5.16	2.50-10.63

Model 1: adjusted for age and sex (377 cases and 80 events).
Model 2: adjusted for Model 1 plus height, BMI, systolic blood pressure, hypertensive medication, smoking and natural log of HOMA-IR (369 cases and 79 events).
Model 3: adjusted for Model 2 and low physical activity (367 cases and 78 events)
† Above median of mean heart rate (≥ 75 bpm in men and 80 bpm in women)
‡ Below median of mean heart rate (<75 bpm in men and 80 bpm in women)
§ Lowest average heart rate during 1 minute
¶ Increased supraventricular activity (SVA) is defined as the 4th quartile of PAC/h or SVT/h

Paper III

During a mean follow-up time of 13 years, 64 participants (17%) were diagnosed with AF, 29 (8%) experienced an ischemic stroke and 91 (24%) died.

SVT Types and Incident Atrial Fibrillation

The incidence rates for AF for different types of SVTs are reported in **Table 7**, and hazard ratios (HR) from Cox regression models are presented in **Table 8**. Micro AF (irregular without p-waves) had an adjusted hazard ratio for AF of 4.95 (95% CI 2.06-11.0). The subhazard ratios (SHR) for SVT types in a competing risks analysis by mortality, as described by Fine and Gray,[144] using co-variables in model 3, did not differ substantially from the hazard ratios of the Cox regression: SHR 2.11 (95% CI 1.05-4.24) for regular SVT with P waves; SHR 2.57 (95% CI 0.78-8.48) for irregular with P waves; SHR 2.95 (95% CI 1.14-7.60) for regular SVT without P waves; and SHR 4.45 (95% CI 1.70-11.6) for Micro AF.

The HR for Micro AF was 2.66 (95% CI 1.24-5.71) compared to regular SVTs with P-waves adjusted for co-variables in model 3. Kaplan-Meier curves for AF-free survival by SVT types are shown in **Figure 10**.

SVT Types and Incident Stroke

The incidence rates for ischemic stroke for different types of SVTs are given in **Table 7**, and HR from Cox regression models are presented in **Table 8**. The highest hazard ratio 14.2 (95% CI 3.76-57.6) was found in regular SVTs without P-waves adjusted for age and sex. However, there were only 28 strokes in total during follow-up (7 strokes in this SVT type), making all HRs susceptible to chance findings. Kaplan-Meier curves for stroke-free survival are shown in **Figure 11**.

Table 7
Incident atrial fibrillation and stroke by SVT classification and baseline characteristics.

	No SVT	Regular with p-waves or shorter than 5 beats	Irregular with p-waves	Regular without p-waves	Micro AF (irregular without p-waves)
Number (%)	168 (44.6)	151 (40.0)	15 (4.0)	24 (6.4)	19 (5.0)
Mean duration of longest SVT, beats	0	40	17	36	13
No. of SVT, median (IQR)		1 (3)	2 (11)	4 (4)	6 (12)
Age, years	63.3 (5.7)	64.8 (6.01)	66.6 (4.2)	67.4 (4.7)	68.2 (4.8)
Cumulative AF incidence, n (%)	13 (7.7)	31 (20.5)	4 (26.7)	7 (29.7)	9 (47.4)
AF incidence per 1000 person-years (95%CI)	5.7 (3.3-9.9)	15.2 (10.7-21.6)	21.5 (8.1-57.2)	23.6 (11.2-49.5)	46.2 (24.0-88.7)
Cumulative stroke incidence, n (%)	25 (6.6)	13 (8.6)	1 (6.7)	7 (29.2)	2 (10.5)
Stroke incidence per 1000 person-years (95%CI)	1.3 (0.4-4.0)	5.7 (3.2-10.0)	5.0 (0.7-35.7)	23.9 (11.4-50.2)	8.2 (2.1-32.9)
CHA_2DS_2-Vasc Score	1.7 (1.0)	1.9 (1.0)	2.0 (0.8)	2.1 (0.9)	2.3 (0.9)
Heart failure	0	1.3	0	0	0
History of coronary event, PCI or CABG	3.6	2.0	6.7	0	5.3
Hypertension	64.3	72.9	80.0	75.0	79.0
History of stroke	1.2	0.7	0	0	5.3
Prevalent diabetes	7.1	10.6	0	8.3	10.5
Female	56	54	47	58	58

Values are reported as mean (standard deviations) or % unless states otherwise.
AF = atrial fibrillation; CABG = coronary artery bypass surgery; PCI = percutaneous coronary intervention; SVT = supraventricular tachycardia

Table 8
Cox regression models for incident atrial fibrillation and stroke by supraventricular tachycardia classification.

Atrial fibrillation models	No SVT	Regular with p-waves or shorter than 5 beats		Irregular with p-waves		Regular without p-waves		Irregular without p-waves	
		HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Model 1[†]	Ref.	2.61	1.36-4.99	3.84	1.25-11.8	4.37	1.74-11.0	9.03	3.84-21.2
Model 2[‡]	Ref.	2.12	1.10-4.08	2.95	0.96-9.08	3.15	1.24-7.98	5.48	2.28-13.2
Model 3[§]	Ref.	1.93	1.00-3.77	2.58	0.82-8.07	2.90	1.14-7.41	4.95	2.06-11.9
Stroke models									
Model 1[†]	Ref.	4.40	1.24-15.6	4.05	0.42-38.9	18.8	4.86-72.7	6.46	1.08-38.7
Model 2[‡]	Ref.	3.14	1.00-12.8	3.01	0.32-29.9	14.2	3.76-57.6	4.10	0.69-26.8

[†] Adjusted for other SVT classifications. Includes 377 subjects, 64 atrial fibrillation events and 25 stroke events
[‡] Adjusted for Model 1 + age and sex. Includes 377 subjects, 64 atrial fibrillation events and 25 stroke events
[§] Adjusted for Model 2 + body mass index, systolic blood pressure, current smoking status and ln-HOMA-IR. Includes 369 subjects and 64 atrial fibrillation events

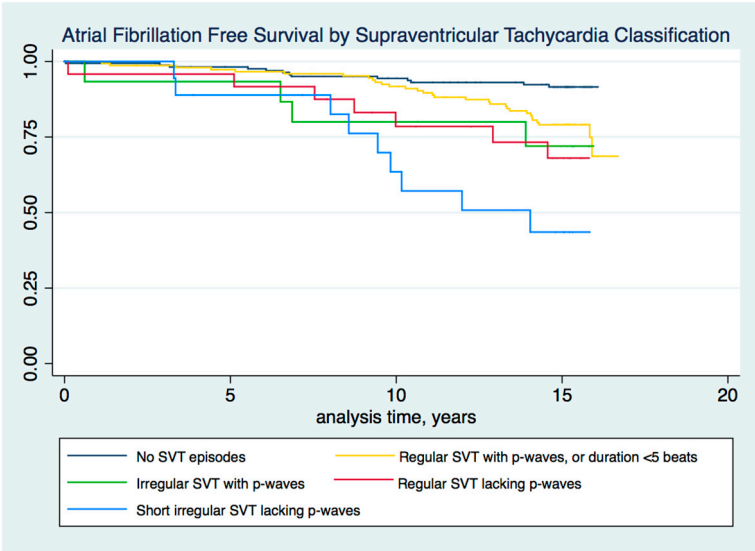

Figure 10
Kaplan-Meier survival curves for incident AF, by SVT classifications. Reprinted from Paper III, "Irregularity and lack of p waves in short tachycardia episodes predict atrial fibrillaion and ischemic stroke", by L.S.B. Johnson, 2018, Heart Rhythm, 15(6), 805-811, Copyright: © 2018 Heart Rhythm Society, with permission from Elsevier.

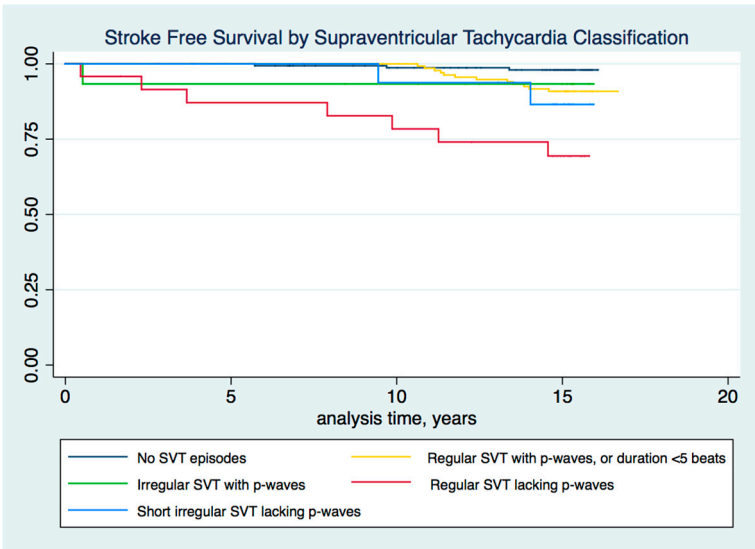

Figure 11
Kaplan-Meier survival curves for incident ischemic stroke, by SVT classifications. Reprinted from Paper III, "Irregularity and lack of p waves in short tachycardia episodes predict atrial fibrillaion and ischemic stroke", by L.S.B. Johnson, 2018, Heart Rhythm, 15(6), 805-811, Copyright: © 2018 Heart Rhythm Society, with permission from Elsevier.

Paper IV

The primary finding in **Paper IV** is that a single resting heart rate measurement differ by an average of 10% from the overall resting heart rate in AF patients. **Table 9** presents the overall heart rates and the average differences from the overall heart rate for single measurements of minimum, mean, maximum and resting heart rates.

Table 9
Heart rates and the average deviation from overall heart rate for a single measurement

N=832	Overall heart rate[α], mean (SD), bpm	Difference between overall heart rate and a random sample, mean absolute deviation	
		bpm	%
Minimum heart rate			
All	63 (14)	4.7	7.4
Female	65 (13)	4.6	7.0
Male	62 (15)	4.8	7.6
Age < 70 years	68 (14)	6.1	9.0
Age ≥ 70 years	62 (14)	4.2	6.8
Mean heart rate,			
All	86 (16)	4.9	5.7
Female	87 (15)	4.8	5.4
Male	85 (18)	5.0	5.9
Age < 70 years	93 (16)	5.8	6.2
Age ≥ 70 years	83 (16)	4.6	5.5
Maximum heart rate			
All	128 (24)	9.6	7.5
Female	128 (20)	9.6	7.5
Male	128 (26)	9.6	7.6
Age < 70 years	141 (23)	10.5	7.5
Age ≥ 70 years	123 (22)	9.3	7.5
Resting heart rate			
All	85 (17)	8.9	10.4
Female	86 (15)	9.3	10.7
Male	84 (18)	8.5	10.2
Age < 70 years	92 (17)	10.0	10.9
Age ≥70 years	83 (17)	8.5	10.2

Resting heart rate was categorized into three groups: <80 bpm, 80-109 bpm and ≥110 bpm. Single resting heart rate measurements were often found in a group different from the individual's overall resting heart rate. Misclassifications according to these groups are reported in **Table 10**.

Table 10
Number of missclassified resting ECGs according to overall resting heart rate

		Number of resting-ECG measurements (mean of intra-individual percentage), %		
		<80 bpm	**80-109 bpm**	**≥110 bpm**
Overall resting heart rate	<80 bpm	83	17	0
	80-109 bpm	21	67	11
	≥110 bpm	1	28	71

The ranges within which overall resting heart rate can be found with 90% confidence, given a single resting heart rate measurement, are presented in **Table 11**.

Table 11
Reference intervals for overall resting heart rate according to a single random heart rate measurement.

	Overall resting heart rate (bpm)*	
Measured resting heart rate (bpm) (N=832)	5th percentile, bpm (95% CI)	95th percentile, bpm (95% CI)
34-59 (n=61)	40 (34-46)	80 (64-96)
60-69 (n=132)	58 (56-60)	85 (79-90)
70-79 (n=147)	67 (62-71)	91 (89-94)
80-89 (n=164)	71 (68-73)	100 (96-104)
90-99 (n=127)	77 (73-82)	105 (102-109)
100-109 (n=96)	82 (78-86)	116 (109-123)
110-119 (n=55)	80 (74-87)	119 (115-122)
120-161 (n=50)	87 (76-97)	143 (133-153)

The overall resting heart rate is the mean resting heart rate 08:00-20:00 after at least 10 minutes rest. The percentiles and confidence intervals are calculated using bootstrap with 10,000 iterations.

Figure 12 illustrates the difference between the overall resting heart rate and the mean of increasing number of resting heart rate samples. **Figure 13** shows the difference between overall resting heart rate and increasing duration of a single resting heart rate sample.

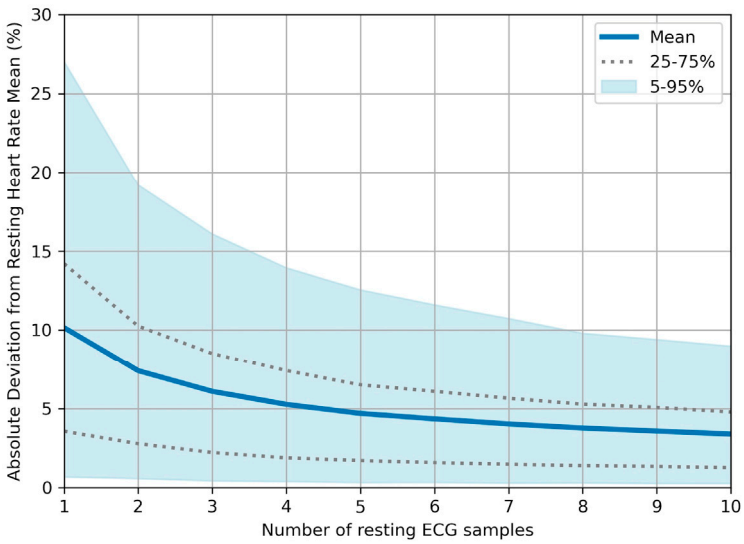

Figure 12
Deviation between randomly chosen resting ECGs and overall resting heart rate as a function of resting ECG-samples. Mean and percentiles were calculated using bootstrap with 10,000 iterations

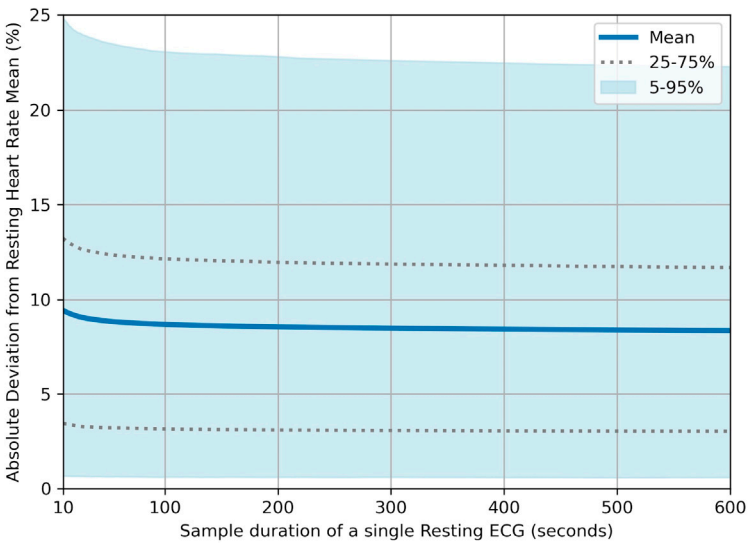

Figure 13
Deviation between randomly chosen resting ECGs and overall resting heart rate as a function of recording duration.

Discussion

Main Findings and Clinical Implications

Low heart rates have been shown to predict AF incidence,[25] while high heart rate has been linked to mortality.[133] A feeling of inappropriately high heart rate is a common indication for ambulatory ECG. Normal ranges for heart rates at ambulatory ECG have been lacking. The reference values for heart rates at 24-hour ECG that we present in **Paper I** can be directly implemented in clinical practice.

Low heart rate increases AF incidence, independent of PACs (**Paper II**). It is mechanistically plausible that low heart rate causes AF via increased atrial size and filling pressure. This potentially causal association between low heart rates and AF risk is also supported by the data showing that the use beta-blockers and ivabradine,[130] which reduce heart rate through different mechanisms, are associated with increased AF incidence. The results in **Paper II** imply that it is reasonable to consider that there may be a risk of inducing AF associated with heart rate lowering interventions. However, there is no conclusive evidence that low heart rate is the cause of AF, and interventions to increase heart rate in asymptomatic individuals should not be performed outside of clinical trials.

We demonstrated in **Paper IV** that a single resting heart rate measurement differs by 10% on average from the overall resting heart rate in AF patients. This could lead to misclassification of heart rate and incorrect dosage of rate-controlling drugs. Over-dosing of rate reduction will increase the risk of symptomatic bradyarrhythmia and may accelerate AF progression if low heart rate is a cause of AF. Under-dosing rate reduction may result in suboptimal symptom control and potentially increase risk of tachycardia-induced heart failure. To reliably assess heart rate, repeated resting measurements, or perhaps even better, ambulatory measurement should be considered. Since information bias can reduce statistical power, these results may also have implications for the interpretation of studies testing strict or lenient rate control, or studies of the association between resting heart rates and AF.

Micro AF is associated with a substantially increased risk of future clinical AF (**Paper III**). This finding has been confirmed in studies by Fredriksson et al, who have used data from STROKESTOP and STROKESTOP II to show that Micro AF is also associated with increased detection of concurrent AF if monitoring duration is prolonged.[147,148] The 30-second cutoff for when Micro AF turns into clinical AF

is completely arbitrary. With reservation for the difficulty in separating Micro AF from other short SVT types, Micro AF can be viewed as an ultra short AF, rather than just a risk factor for AF. In that sense, Micro AF could be treated according to European guidelines "AF-CARE" (**C**omorbidities and risk factor management, **A**void stroke, **R**educe symptoms, **E**valuation and dynamic assessment)[56] with some adaptations considering the short duration:

- **Comorbidities** and risk factor management: Handling comorbidities and risk factor management could prevent progression of Micro AF to higher burden with higher risks.
- **Avoid stroke**: DDAF (≥6 minutes) only causes a small increase in stroke risk.[50-52] Anticoagulation for the even shorter Micro AF is not indicated.
- **Reduce symptoms**: Short AF rarely gives any symptoms,[35] and if it does, Micro AF is very short-lasting, and the potential benefit of rate or rhythm control can be questioned.
- **Evaluation and dynamic assessment**: The duration of AF episodes varies, and presence of Micro AF is associated with increased AF detection if monitoring duration is prolonged.[148] If Micro AF is found at a short ECG recording post-stroke or in patients with palpitations that were not present during the recording, prolonged ECG monitoring should be considered. Since AF often progresses, and Micro AF is associated with future AF ,[147,149] a follow-up ECG monitoring can be considered.

Methodological considerations

The studies in this thesis include cross-sectional analyses (**Papers I** and **IV**) and cohort studies (**Papers II** and **III**). Below is a brief introduction to some key considerations in observational cross-sectional and cohort studies.

Selection Bias and External Validity

Selection Bias

Selection bias occurs when individuals participating in a study do not reflect the target population. In studies assessing the effect of an exposure on an outcome, selection bias occurs when the underlying risk of the outcome of interest is different in the exposed and the unexposed groups, in a manner unrelated to the exposure. Participation rates in cohort studies tend to be higher for healthier individuals with high socioeconomic status,[150] and this pattern was seen in both the SCAPIS and MDCS populations.

- The participation rate in the full SCAPIS study (a subpopulation was used in **Paper I**) was 50.3%, with a lower participation rate for individuals with lower income.[134]
- In MDCS, 41% participated, and the mortality rate was higher in non-participants.[151] A few years later, a substudy with a 49% participation rate was conducted, from which the study population in **Paper II** and **Paper III** was drawn. Only two participants were lost to follow-up.
- In the PocketECG study, we included all individuals in the United States in 2021 with at least 2 full recording days using a specific ambulatory ECG device with 95% AF beats.

Selection bias due to selective inclusion of healthier individuals in SCAPIS could have influenced reference values in **Paper I**. We create reference values from a healthy subset so the impact of selection bias is likely relatively small, but "healthy" non-participants might differ from "healthy" participants. This healthy selection bias likely had larger impact on how much of the differences in heart rates were explained by clinical factors in the multivariable linear regression model. We showed that clinical factors were associated with heart rate but the difference in heart rate was rather small. If diseases were more prevalent and severe, they would have a larger impact on heart rate, and a larger proportion of the differences in heart rates would have been explained by clinical factors.

A healthy selection bias could perhaps have influenced the association between low heart rate and future AF in **Paper II**, although the net effect of bias is difficult to determine. As indicated in **Paper I**, higher heart rate is associated with morbidity, and morbidity is associated with future AF. We sought to estimate the association between heart rate and future AF independent of morbidity. A healthy selection bias would reduce AF incidence, likely with little impact on the hazard ratios (in **Papers II** and **III**) but which may have reduced the probability of finding a statistically significant effect.

External Validity

External validity describes whether the findings in studies can be applied outside the study population. Selection bias has implications for external validity. The time at which cohorts are recruited is important when considering external validity, as prevalence and risks of diseases can change over time. The baseline examinations in MDCS were performed between 1998 and 2000 and much has happened since. Stroke rates has fallen (and likely also AF rates). The prevalence of current smoking was 23% in MDCS compared to 11% in SCAPIS (2013-2018). However, these secular trends likely had little impact on the hazard ratios for AF in **Paper II** and **Paper III**. It is important to note, however, that both SCAPIS and MDCS included middle-aged individuals, and findings might not be transportable to individuals of different ages.

Selection Bias and External Validity in Clinical Trials

Selection bias and external validity can also occur in randomized control trials, not only in observational science. The reasons why not all eligible patients are included in trials might be even more complex than in cohort studies. For example, inclusion might depend on physicians' predilection for the intervention in certain patients, and these patients would therefore not be included in the study. Like in cohort studies, selection bias causes a problem with external validity. Another issue with trials is that inclusions criteria are often set to find patients likely to have an effect of the intervention. Results are then often also used clinically to guide treatment in patients with characteristics that were not included in trials, but it is not known if results are valid for these patients.

Information Bias

Information bias is caused by the misclassification of exposures and/or outcomes.

Misclassification of Exposures

Heart rates were only measured using a 24-hour ECG in **Paper I** and **Paper II**. It is possible that day-to-day variations in heart rates could cause misclassification. These day-to-day differences likely had little impact on heart rate reference ranges in **Paper I**; some individuals would by chance have had for them unusually high heart rates on the test day, but considering the size of the population this would likely have be balanced by other individuals who had a for them unusually low heart rate on the test day, and these differences would cancel out for the purpose of reference ranges. However, any measurement error (either for heart rate or for any other variable) would have led to a towards null effect on the association between heart rate and the clinical variables in **Paper I**.

Misclassification of Micro AF in **Paper II** would have occurred for two reasons: first, SVTs (including Micro AF) could have been missed completely, and second, SVTs could have been classified to the wrong category of SVT type. Misclassification of Micro AF would have reduced the effect measure (hazard ratios), because increased prevalence of Micro AF in the non-Micro AF groups would have increased their AF risk, and wrongly classifying an SVT as Micro AF would decrease the average risk in the Micro AF group. The effect estimates in **Paper III** are therefore likely to be conservative estimations.

In **Paper IV**, daytime resting heart rate was assessed using an accelerometer. Factors not measured by the accelerometer, such as emotional agitation and daytime napping, could have had some impact on heart rates, and this would increase the variability of resting heart rate. It is, however, possible that emotional agitation cause even larger differences in heart rate when measured by health care professionals, similar to the rise in blood pressure caused by the white coat effect.[152]

Misclassification of Outcomes

The endpoint AF in **Papers II** and **III** was retrieved from Swedish Hospital Discharge Register. This endpoint has been validated in a subset and shown to be of good quality (95% definitive AF, 3% no AF, 2% unavailable ECG) .[140] AF patients only treated in primary care would been misclassified as not having the outcome, but since most patients eventually seek hospital care for some reason the number of such cases is likely to be relatively small. Any missed AF diagnoses would likely have had a toward-null effect on the association between the exposure and outcome. Another possible source of bias is that since high heart rate is associated with comorbidities, it is possible that this would lead to earlier detection and diagnosis of AF in patients with high heart rate, which would have a toward-null effect on the association between low heart rates and AF. But, as stated above, given the long follow-up time in this study, it is likely that most patients with AF were diagnosed during a hospital visit at some point, limiting the effect of this bias.

Confounding and Collider Bias

We aimed to assess the risk of incident AF for low heart rate (**Paper II**) and Micro AF (**Paper III**) independent of other risk factors.

A confounder is a factor that causes both the exposure and the outcome. For example, being a man might cause both low heart rate and AF (see **Figure 14**). An association between low heart rate and AF can be found as a result of lower heart rate and higher AF risk in men. Male sex, in this case, is a confounder, and can cause a false association between low heart rate and AF if not adjusted for.

There are different ways to handle confounders. We used prespecified models including factors we thought could be important confounders. Some studies adjust for factors that are statistically significantly associated with both the exposure and outcome. We opted not to use this approach for two reasons:

1. Statistical significance tells us nothing about the size of the difference (or if it is meaningful).
2. Adjusting for all statistically significant variables might introduce collider bias. A collider is the cause of both the exposure and the outcome (in contrast to a confounder that causes both). Adjusting for a collider can cause false positive associations between the exposure and the outcome.

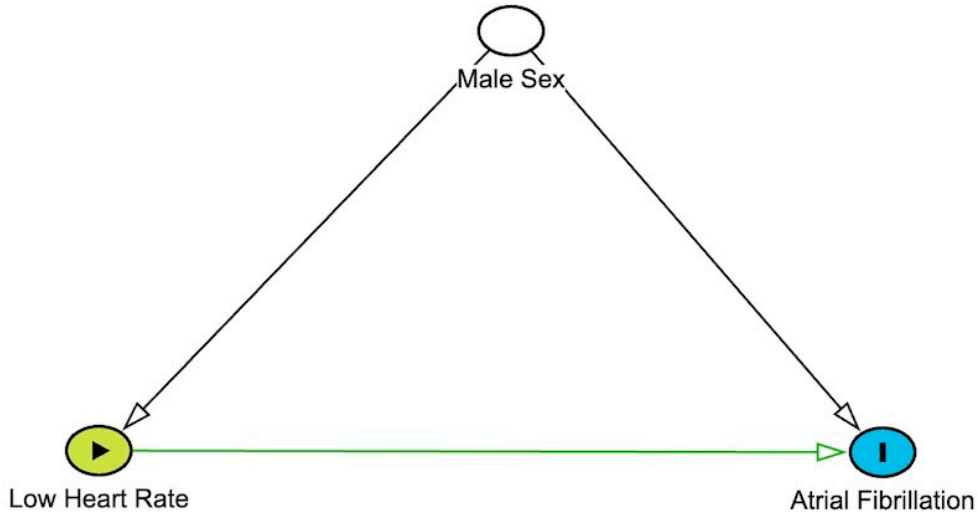

Figure 14
Directed acyclic graph illustrating how association between low heart rate and atrial fibrillation can be confounded by male sex. Figure created using DAGitty v3.1.

Power

No power calculations were performed in the studies included in this thesis as data was already gathered. Lack of power likely had some effect in our studies. In **Paper II,** we dichotomized mean heart rate at median based on the hazard ratios in quartiles. It is in retrospect hard to see any other reason than chance for the similar hazard ratios in the two upper and in the two lower quartiles. This could have caused an overestimation of effect size for heart rate dichotomized at median. If the sample size was larger, it would be possible to find more reliable hazard ratios. In **Paper III,** there were very few strokes, and chance likely played a large part in the unreasonably high hazard ratios (much higher than for clinical AF) for stroke for certain types of SVTs. The small number of Micro AF episodes also made the finding of association with incident clinical AF prone to chance to some degree. However, the importance of Micro AF as a marker of risk for AF has later been confirmed.[147,148]

Conclusions

I. There is a wide range of heart rate in healthy middle-aged individuals, and only a small portion of the inter-individual differences are explained by clinical correlates. The reference ranges of heart rate obtained in this study can be used for interpretation of ambulatory ECG-recordings.

II. Low mean heart rate at 24-hour ECG predicts AF, and it does so independent of increased supraventricular activity (top quartile PAC or SVT).

III. Micro AF increases the risk of future clinical AF diagnosed in a hospital setting.

IV. A single resting heart rate measurement in AF patients is on average 10% higher or lower than the overall resting heart rate. The uncertainty of a single measurement might lead to over- or undertreatment with rate-controlling drugs. Repeated resting ECG-sampling or ambulatory ECG monitoring could be used to increase the reliability of heart rate assessments.

Future Perspectives

The detection and treatment of AF are continuously evolving. These advancements will lead to better patient care in the future, but also present new challenges.

The proliferation ECG monitoring devices, some capable of long-term monitoring, has undoubtedly increased the detection rate of AF in Western populations. A recent study by our group showed that artificial intelligence (AI) detects more critical arrythmias and misses fewer AF diagnoses on ambulatory ECG recordings compared to ECG technicians.[153] With continuing technological advancements the AF detection rate will only rise, and more patients with low-burden AF, that have lower stroke risk than patients with permanent AF that formed a large part of the pivotal trials of anticoagulation drugs, will be detected. More studies that address the needs of these populations are needed.

Another factor that affects the future of AF research is the ageing of the population in the Western world. Age is a major risk factor for AF, and as life-expectancy increases, elderly individuals will constitute a larger proportion of patients with AF. Elderly, frail individuals have likely been underrepresented in anticoagulation trials. These patients have higher risks of stroke, but it does not necessarily translate to a greater net benefit from treatment. An example of this from a different field of cardiology can be found for statin therapy. In the CORONA trial, which included elderly patients with heart failure, statin therapy did not significantly reduce the risk of cardiovascular outcomes, but in the JUPITER trial, which included lower-risk healthy individuals with increased high-sensitivity C-reactive protein, outcomes were significantly reduced in the statin treatment arm.[154,155]

Age also affects the risk of harm due to treatment. The risk of bleeding is higher in elderly patients using anticoagulation.[156] In the future we can expect to see more frail elderly patients with low AF burdens, and the benefit of anticoagulation in these patients is not clear-cut.

In the LOOP study,[39] screening to detect AF was not sufficient to significantly reduce stroke rates, but STROKESTOP did find a significant effect with screening.[40] The potential benefit of systematic AF-screening may be lower today and continue to decrease due to increased AF detection without screening. It is possible that AF screening in individuals at high AF risk due to for example low heart rate (**Paper II**) or Micro AF (**Paper III**) would be more effective. However, for screening to be truly useful, it must identify individuals at high risk of AF who

also benefit from treatment. This implies that even though much has been done in the field of stroke prevention in AF there is still a need for further studies.

Treatment options for AF are increasing. It was only ~35 years ago that anticoagulation (VKA) in AF was introduced, and DOACs came on the market ~15 years ago. Current advances in the field of stroke prevention could include surgical interventions. The removal of the left atrial appendage in AF patients undergoing heart surgery for other reasons reduces stroke-risk.[82] Endovascular devices for left atrial appendage closure have been developed and are used to reduce stroke risk, despite a lack of conclusive evidence. The ongoing LAAOS 4 trial (NCT05963698) will provide more guidance regarding this use.

Treatment guidelines regarding the importance of maintaining sinus rhythm may also change. Rate control was shown to be non-inferior to rhythm control in trials conducted over 20 years ago,[113,114,117,118] but studies using catheter ablation have shown rhythm control to be beneficial in selected patients, likely due to higher success rate in maintaining sinus rhythm and fewer adverse effects compared to oral antiarrhythmic drugs.[119,122] Rate control remains common, but the optimal heart rate goal is not known. Lenient (<110 bpm) resting heart rate control is non-inferior to strict (<80 bpm).[123] However, a single heart rate measurement might misclassify the resting heart rate, as shown in **Paper IV,** possibly contributing to the non-significant difference between strict and lenient control through reduced statistical power.

The risk of outcomes in AF are changing, and treatment options are increasing, posing challenges for both primary care physicians and researchers. Adherence to guidelines is poor, before education intervention only 21% received rhythm control and 63% stroke prevention according to guidelines in the STEER AF trial (results presented at European Society of Cardiology meeting 2024). Nurse led AF care is potentially beneficial,[157,158] and would also facilitate the conduction of registry-based randomised clinical trials to improve AF-care in the long run.

Sweden and a few other countries have registries that allow cheap and effective follow-up, which makes it possible to conduct registry-based randomized clinical trials.[159] The ABC-AF Study (NCT03753490) used this approach: AF patients filled in an internet based form using the national AF registry AURICULA and were randomized to treatment guided by ABC score or standard care. Recruitment of participants was stopped in 2023; results will undoubtedly contribute to the knowledge of stroke reduction in AF. A similar approach using information from patients and nurses in AURICULA would allow randomization into multiple randomization registry-based trials.

A few suggestions for trials could be:

1. **Randomizing anticoagulation** in patients where treatment effect is uncertain. This would allow contemporary assessment of the results from the now much awaited ABC-AF Study, evaluate treatment effects for components of CHA_2DS_2-VAsc or ABC-score, as well as other variables such as atrial size, AF-type and CRP.
2. **Randomizing to different types of DOAC**. The DOAC trials were funded by pharmaceutical companies. Individual pharmaceutical companies likely do not have an interest in funding trials that compare the different types of DOACs. Investigator-driven research may be needed to address this gap.
3. **Randomizing to different types of rate controlling drugs**.
4. **Randomizing different heart rate goals** according to different ways to measure heart rate (resting office, resting home, ambulatory, during physical activity etc).
5. **Randomizing ablation** in patients who potentially benefit but the effect is uncertain.

Creating a system in Sweden that allow all AF patients to be included in randomized registry-based trials would enable studies with a large number participants, ensuring that elderly individuals are not underrepresented, and at a low cost. Such a database would also facilitate for observational studies to identify novel markers for stroke risk, which could then be investigated in trials.

A limitation of trials is their relatively blunt nature. For example, the ARTESIA trial showed that DOAC reduced strokes rate in patients with DDAF lasting from 6 minutes to 24 hours. However, we do not know if 6 minutes of DDAF is the correct cutoff for anticoagulation. A system allowing repeated trial could help refine this cutoff. AF care could also adapt to secular changes by continuously randomizing all uncertain areas (such as when to anticoagulate, use rate or rhythm control etc).

The large sample sizes would not only allow treatment effect to be studied but also help identify previously unknown adverse effects and provide better estimates of know adverse effects. This would have an impact of AF treatment not only in Sweden but worldwide.

Acknowledgements

I have received tremendous support from many people throughout my journey as a PhD student. I would particularly like to thank:

My main supervisor **Linda Johnson**: I am incredibly grateful for the opportunity you gave me! You are probably the smartest person I know and always open to new ideas. You have been very generous with your time, knowledge and support! Thank you for your patience, feedback and advice, both regarding my career and life. “If you are allowed to think big, what do you really want to do?” is a mindset I will carry with me always.

My co-supervisor, **Gunnar Engström**: Thank you for generously sharing your vast knowledge in epidemiologic methodology! The feedback you have given me over the years never made me feel stupid, even though I sometimes was. Somehow, your direct and important feedback just increased my interest.

My co-supervisor, **Artur Fedorowski**: Thank you for being enthusiastic and never being more than an email away (even late evenings).

My partner, **Li**: Your encouragement means the world to me. Thank you for being my best friend! And to our two little sweethearts, **Snöbjörn and Pärla**, thank you for bringing me back to real life after disappearing in the land of stroke and AF. Being squeezed between you like a sleeping meerkat when putting you to bed is the best way to recover.

My mother, **Kerstin**: Thank you for your support, not only as a loving mother to me but as a great grandmother to my kids. My late **father**, I can imagine the proud look of your face if you were here. To my older siblings, my sister **Frida**, for showing me how fun research can be, and my brother **Fredrik**, thank you for not pursuing an academic career, and putting pressure on your younger siblings.

My parents-in-law, **Elisabeth and Sture**: Thank you for the cute paiting on the cover of this thesis, for the lunch boxes, and for your incredible hospitality in opening your door to my vomiting kids when the deadline for this thesis was close (so I for once stayed healthy) – truly amazing!

My fellow PhD-students, **Alexandra Måneheim**, **Johan Lundeberg** and **Magdalena Okrajni**: Thank you for the opportunity of having a small role in your projects, our discussions and meetings. I learned a lot!

Everyone at the Clinical Physiology department in Malmö: I am lucky to have coworkers who really help each other out, regardless of profession. And perhaps even more important, it is so much fun working with you!

My boss **Jonas Jögi, Elin Trägårdh, Morten Kraen, Ola Thorsson**, **Per Wollmer,** and all others who contribute, and have contributed, to a research-friendly environment at the Clinical Physiology department in Malmö.

Finally, I want to express my gratitude by thanking participants of MDCS and SCAPIS and everyone involved in planning, carrying out, and contributing to these important studies. I also want to acknowledge MEDICALgoritmics for giving access to their large database of clinical long-term ECG examinations.

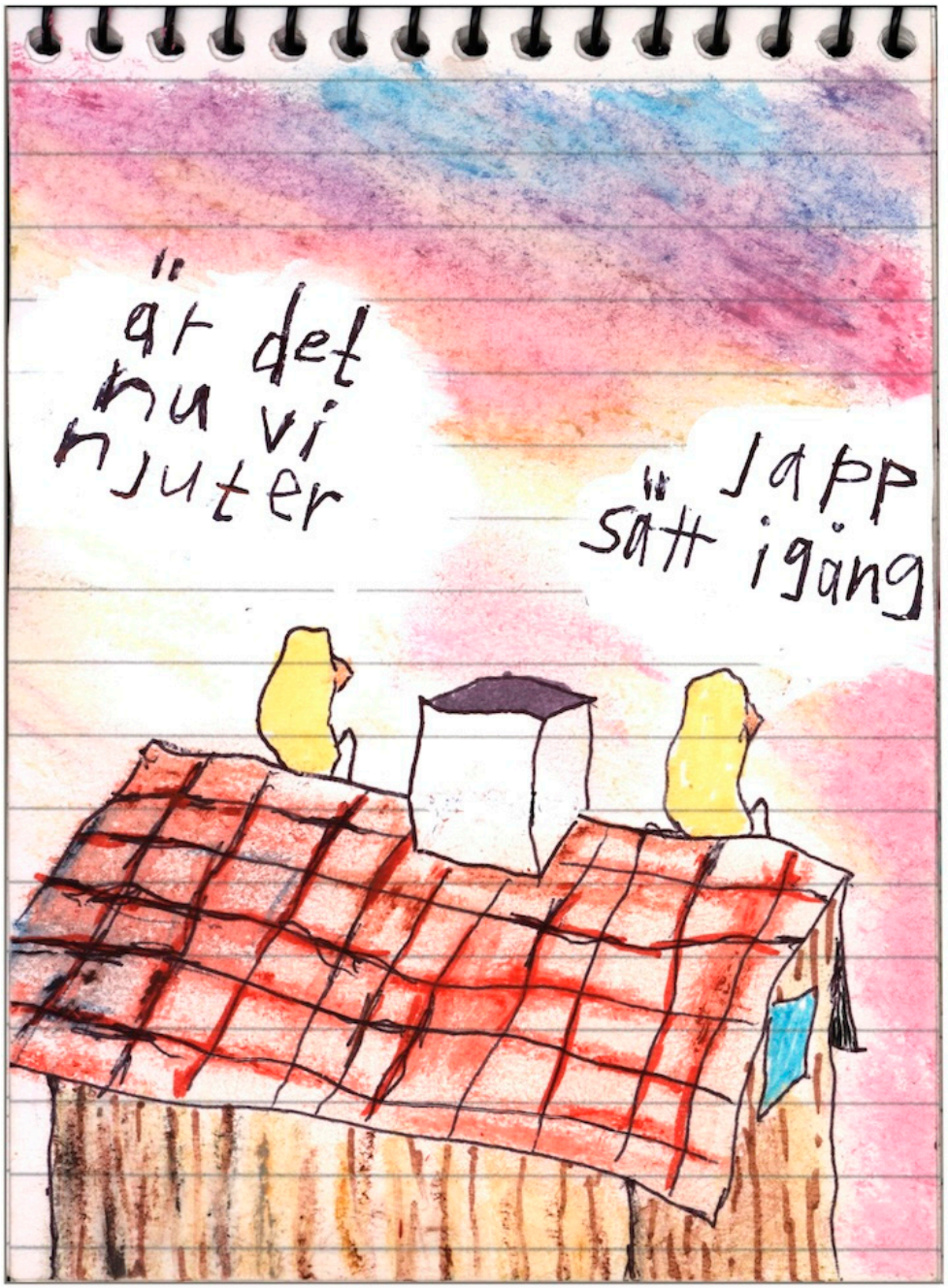

Image reproduced with permission from the artist, © Magda Lundberg

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22(8):983-8. (In eng). DOI: 10.1161/01.str.22.8.983.
2. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131(7):492-501. (In eng). DOI: 10.7326/0003-4819-131-7-199910050-00003.
3. Monfredi O, Dobrzynski H, Mondal T, Boyett MR, Morris GM. The anatomy and physiology of the sinoatrial node--a contemporary review. Pacing Clin Electrophysiol 2010;33(11):1392-406. (In eng). DOI: 10.1111/j.1540-8159.2010.02838.x.
4. Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E. Braunwald's heart disease : a textbook of cardiovascular medicine. Tenth edition. ed: Elsevier/Saunders, 2015.
5. Samet P, Bernstein W, Levine S. Significance of the atrial contribution to ventricular filling. The American Journal of Cardiology 1965;15(2):195-202. DOI: https://doi.org/10.1016/0002-9149(65)90454-6.
6. LANGENDORF R, PICK A, KATZ LN. Ventricular Response in Atrial Fibrillation. Circulation 1965;32(1):69-75. DOI: doi:10.1161/01.CIR.32.1.69.
7. Toivonen L, Kadish A, Kou W, Morady F. Determinants of the ventricular rate during atrial fibrillation. Journal of the American College of Cardiology 1990;16(5):1194-1200. DOI: https://doi.org/10.1016/0735-1097(90)90552-Z.
8. Wasmund SL, Li J-M, Page RL, et al. Effect of Atrial Fibrillation and an Irregular Ventricular Response on Sympathetic Nerve Activity in Human Subjects. Circulation 2003;107(15):2011-2015. DOI: doi:10.1161/01.CIR.0000064900.76674.CC.
9. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92(7):1954-68. (In eng). DOI: 10.1161/01.cir.92.7.1954.
10. Vinter N, Cordsen P, Johnsen SP, et al. Temporal trends in lifetime risks of atrial fibrillation and its complications between 2000 and 2022: Danish, nationwide, population based cohort study. Bmj 2024;385:e077209. (In eng). DOI: 10.1136/bmj-2023-077209.
11. Magnussen C, Niiranen TJ, Ojeda FM, et al. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). Circulation 2017;136(17):1588-1597. (In eng). DOI: 10.1161/circulationaha.117.028981.

12. Staerk L, Wang B, Preis SR, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. Bmj 2018;361:k1453. (In eng). DOI: 10.1136/bmj.k1453.
13. Andrade J, Khairy P, Dobrev D, Nattel S. The Clinical Profile and Pathophysiology of Atrial Fibrillation. Circulation Research 2014;114(9):1453-1468. DOI: doi:10.1161/CIRCRESAHA.114.303211.
14. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol 2020;76(25):2982-3021. (In eng). DOI: 10.1016/j.jacc.2020.11.010.
15. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J 2013;34(35):2746-51. (In eng). DOI: 10.1093/eurheartj/eht280.
16. Petersen P, Godtfredsen J, Boysen G, Andersen E, Andersen Bor. PLACEBO-CONTROLLED, RANDOMISED TRIAL OF WARFARIN AND ASPIRIN FOR PREVENTION OF THROMBOEMBOLIC COMPLICATIONS IN CHRONIC ATRIAL FIBRILLATION: The Copenhagen AFASAK Study. The Lancet 1989;333(8631):175-179. DOI: 10.1016/S0140-6736(89)91200-2.
17. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. Eur Heart J 2010;31(8):967-75. (In eng). DOI: 10.1093/eurheartj/ehn599.
18. Chamberlain AM, Agarwal SK, Folsom AR, et al. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol 2011;107(1):85-91. (In eng). DOI: 10.1016/j.amjcard.2010.08.049.
19. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc 2013;2(2):e000102. DOI: 10.1161/JAHA.112.000102.
20. Weng L-C, Preis SR, Hulme OL, et al. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation. Circulation 2018;137(10):1027-1038. DOI: doi:10.1161/CIRCULATIONAHA.117.031431.
21. Segan L, Canovas R, Nanayakkara S, et al. New-onset atrial fibrillation prediction: the HARMS2-AF risk score. European Heart Journal 2023;44(36):3443-3452. DOI: 10.1093/eurheartj/ehad375.
22. Johnson LS, Juhlin T, Engström G, Nilsson PM. Reduced forced expiratory volume is associated with increased incidence of atrial fibrillation: the Malmo Preventive Project. Europace 2014;16(2):182-8. (In eng). DOI: 10.1093/europace/eut255.
23. Grymonprez M, Vakaet V, Kavousi M, et al. Chronic obstructive pulmonary disease and the development of atrial fibrillation. Int J Cardiol 2019;276:118-124. (In eng). DOI: 10.1016/j.ijcard.2018.09.056.

24. Xiao J, Persson AP, Engström G, Johnson LSB. Supraventricular arrhythmia, N-terminal pro-brain natriuretic peptide and troponin T concentration in relation to incidence of atrial fibrillation: a prospective cohort study. BMC Cardiovascular Disorders 2021;21(1):134. DOI: 10.1186/s12872-021-01942-6.
25. Morseth B, Graff-Iversen S, Jacobsen BK, et al. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study. European heart journal 2016;37(29):2307-2313.
26. Johansen KR, Ranhoff AH, Sørensen E, et al. Risk of atrial fibrillation and stroke among older men exposed to prolonged endurance sport practice: a 10-year follow-up. The Birkebeiner Ageing Study and the Tromsø Study. Open Heart 2022;9(2) (In eng). DOI: 10.1136/openhrt-2022-002154.
27. Drca N, Larsson SC, Grannas D, Jensen-Urstad M. Elite female endurance athletes are at increased risk of atrial fibrillation compared to the general population: a matched cohort study. Br J Sports Med 2023;57(18):1175-1179. (In eng). DOI: 10.1136/bjsports-2022-106035.
28. Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol 2015;66(9):985-96. (In eng). DOI: 10.1016/j.jacc.2015.06.488.
29. Johnson LS, Juhlin T, Juul-Möller S, Hedblad B, Nilsson PM, Engström G. A prospective study of supraventricular activity and incidence of atrial fibrillation. Heart Rhythm 2015;12(9):1898-904. (In eng). DOI: 10.1016/j.hrthm.2015.04.042.
30. Bruyne BD, Pijls NHJ, Kalesan B, et al. Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease. New England Journal of Medicine 2012;367(11):991-1001. DOI: doi:10.1056/NEJMoa1205361.
31. De With RR, Erküner Ö, Rienstra M, et al. Temporal patterns and short-term progression of paroxysmal atrial fibrillation: data from RACE V. Europace 2020;22(8):1162-1172. (In eng). DOI: 10.1093/europace/euaa123.
32. Padfield GJ, Steinberg C, Swampillai J, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. Heart Rhythm 2017;14(6):801-807. (In eng). DOI: 10.1016/j.hrthm.2017.01.038.
33. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. Eur Heart J 2016;37(20):1591-602. (In eng). DOI: 10.1093/eurheartj/ehw007.
34. de Vos CB, Pisters R, Nieuwlaat R, et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol 2010;55(8):725-31. (In eng). DOI: 10.1016/j.jacc.2009.11.040.
35. Diederichsen SZ, Haugan KJ, Brandes A, et al. Natural History of Subclinical Atrial Fibrillation Detected by Implanted Loop Recorders. JACC 2019;74(22):2771-2781. DOI: doi:10.1016/j.jacc.2019.09.050.
36. Dulai R, Sulke N, Freemantle N, et al. Pulmonary Vein Isolation vs Sham Intervention in Symptomatic Atrial Fibrillation: The SHAM-PVI Randomized Clinical Trial. JAMA 2024;332(14):1165-1173. DOI: 10.1001/jama.2024.17921.

37. Elliott AD, Verdicchio CV, Mahajan R, et al. An Exercise and Physical Activity Program in Patients With Atrial Fibrillation. JACC: Clinical Electrophysiology 2023;9(4):455-465. DOI: doi:10.1016/j.jacep.2022.12.002.
38. Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol 2015;65(20):2159-69. (In eng). DOI: 10.1016/j.jacc.2015.03.002.
39. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. The Lancet 2021;398(10310):1507-1516. DOI: https://doi.org/10.1016/S0140-6736(21)01698-6.
40. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. The Lancet 2021;398(10310):1498-1506. DOI: 10.1016/S0140-6736(21)01637-8.
41. Kemp Gudmundsdottir K, Svennberg E, Friberg L, et al. Randomized Invitation to Systematic NT-proBNP and ECG Screening in 75-Year-Olds to Detect Atrial Fibrillation: STROKESTOP II. Circulation 2024;150(23):1837-1846. DOI: doi:10.1161/CIRCULATIONAHA.124.071176.
42. Carnicelli AP, Hong H, Connolly SJ, et al. Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. Circulation 2022;145(4):242-255. (In eng). DOI: 10.1161/circulationaha.121.056355.
43. Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. New England Journal of Medicine 2020;382(15):1395-1407. DOI: doi:10.1056/NEJMoa1915922.
44. Dai H, Zhang Q, Much AA, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes 2021;7(6):574-582. (In eng). DOI: 10.1093/ehjqcco/qcaa061.
45. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92. (In eng). DOI: 10.1056/NEJMoa1107039.
46. Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. Heart Rhythm 2011;8(9):1416-23. (In eng). DOI: 10.1016/j.hrthm.2011.04.022.
47. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation 2014;129(21):2094-9. (In eng). DOI: 10.1161/circulationaha.113.007825.
48. Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. Circulation Research 2017;120(3):472-495. DOI: doi:10.1161/CIRCRESAHA.116.308398.

49. Glotzer TV, Daoud EG, Wyse DG, et al. The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk. Circulation: Arrhythmia and Electrophysiology 2009;2(5):474-480. DOI: doi:10.1161/CIRCEP.109.849638.
50. Healey JS, Lopes RD, Granger CB, et al. Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation. New England Journal of Medicine 2024;390(2):107-117. DOI: doi:10.1056/NEJMoa2310234.
51. Kirchhof P, Toennis T, Goette A, et al. Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes. New England Journal of Medicine 2023;389(13):1167-1179. DOI: doi:10.1056/NEJMoa2303062.
52. McIntyre WF, Benz AP, Becher N, et al. Direct Oral Anticoagulants for Stroke Prevention in Patients With Device-Detected Atrial Fibrillation: A Study-Level Meta-Analysis of the NOAH-AFNET 6 and ARTESiA Trials. Circulation 2024;149(13):981-988. DOI: doi:10.1161/CIRCULATIONAHA.123.067512.
53. Göldi T, Krisai P, Knecht S, et al. Prevalence and Management of Atrial Thrombi in Patients With Atrial Fibrillation Before Pulmonary Vein Isolation. JACC Clin Electrophysiol 2019;5(12):1406-1414. (In eng). DOI: 10.1016/j.jacep.2019.09.003.
54. Mannewald C, Roijer A, Platonov PG, Holmqvist F. Prevalence of left atrial appendage thrombus and spontaneous echo contrast on transesophageal echocardiography in patients scheduled for pulmonary vein isolation. Ann Noninvasive Electrocardiol 2024;29(3):e13119. (In eng). DOI: 10.1111/anec.13119.
55. Turakhia MP, Ziegler PD, Schmitt SK, et al. Atrial Fibrillation Burden and Short-Term Risk of Stroke. Circulation: Arrhythmia and Electrophysiology 2015;8(5):1040-1047. DOI: doi:10.1161/CIRCEP.114.003057.
56. Van Gelder IC, Rienstra M, Bunting KV, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): Developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO). European Heart Journal 2024;45(36):3314-3414. DOI: 10.1093/eurheartj/ehae176.
57. Nuotio I, Hartikainen JEK, Grönberg T, Biancari F, Airaksinen KEJ. Time to Cardioversion for Acute Atrial Fibrillation and Thromboembolic Complications. JAMA 2014;312(6):647-649. DOI: 10.1001/jama.2014.3824.
58. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72. (In eng). DOI: 10.1378/chest.09-1584.
59. Hijazi Z, Lindbäck J, Alexander JH, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J 2016;37(20):1582-90. (In eng). DOI: 10.1093/eurheartj/ehw054.

60. Wallentin L, Lindbäck J, Hijazi Z, et al. Biomarker-Based Model for Prediction of Ischemic Stroke in Patients With Atrial Fibrillation. Journal of the American College of Cardiology 2025;85(11):1173-1185. DOI: https://doi.org/10.1016/j.jacc.2024.11.052.
61. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. Bmj 2011;342:d124. (In eng). DOI: 10.1136/bmj.d124.
62. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22(3):312-8. (In eng). DOI: 10.1161/01.str.22.3.312.
63. Bisson A, Bodin A, Clementy N, Babuty D, Lip GYH, Fauchier L. Prediction of Incident Atrial Fibrillation According to Gender in Patients With Ischemic Stroke From a Nationwide Cohort. American Journal of Cardiology 2018;121(4):437-444. DOI: 10.1016/j.amjcard.2017.11.016.
64. Benz AP, Hohnloser SH, Eikelboom JW, et al. Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation. Eur Heart J 2023;44(20):1807-1814. (In eng). DOI: 10.1093/eurheartj/ehad200.
65. Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol 2012;11(3):225-31. (In eng). DOI: 10.1016/s1474-4422(12)70017-0.
66. Geisler T, Keller T, Martus P, et al. Apixaban versus Aspirin for Embolic Stroke of Undetermined Source. NEJM Evidence 2023;3(1):EVIDoa2300235. DOI: doi:10.1056/EVIDoa2300235.
67. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. New England Journal of Medicine 2018;378(23):2191-2201. DOI: doi:10.1056/NEJMoa1802686.
68. Diener H-C, Sacco RL, Easton JD, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. New England Journal of Medicine 2019;380(20):1906-1917. DOI: doi:10.1056/NEJMoa1813959.
69. Kamel H, Longstreth WT, Jr, Tirschwell DL, et al. Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy: The ARCADIA Randomized Clinical Trial. JAMA 2024;331(7):573-581. DOI: 10.1001/jama.2023.27188.
70. Schnabel RB, Haeusler KG, Healey JS, et al. Searching for Atrial Fibrillation Poststroke. Circulation 2019;140(22):1834-1850. DOI: doi:10.1161/CIRCULATIONAHA.119.040267.
71. Diederichsen SZ, Frederiksen KS, Xing LY, et al. Severity and Etiology of Incident Stroke in Patients Screened for Atrial Fibrillation vs Usual Care and the Impact of Prior Stroke: A Post Hoc Analysis of the LOOP Randomized Clinical Trial. JAMA Neurology 2022;79(10):997-1004. DOI: 10.1001/jamaneurol.2022.3031.

72. Shoamanesh A, Field TS, Coutts SB, et al. Apixaban versus aspirin for stroke prevention in people with subclinical atrial fibrillation and a history of stroke or transient ischaemic attack: subgroup analysis of the ARTESiA randomised controlled trial. The Lancet Neurology 2025;24(2):140-151. DOI: 10.1016/S1474-4422(24)00475-7.
73. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal 2021;42(36):3599-3726. DOI: 10.1093/eurheartj/ehab368.
74. Airaksinen KE, Grönberg T, Nuotio I, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. J Am Coll Cardiol 2013;62(13):1187-92. (In eng). DOI: 10.1016/j.jacc.2013.04.089.
75. Benz AP, Hijazi Z, Lindbäck J, et al. Biomarker-Based Risk Prediction With the ABC-AF Scores in Patients With Atrial Fibrillation Not Receiving Oral Anticoagulation. Circulation 2021;143(19):1863-1873. DOI: doi:10.1161/CIRCULATIONAHA.120.053100.
76. Teppo K, Airaksinen KEJ, Halminen O, et al. Temporal Trends of Ischemic Stroke Risk in Patients With Incident Atrial Fibrillation Before Anticoagulation. JACC: Clinical Electrophysiology 2024. DOI: https://doi.org/10.1016/j.jacep.2024.10.029.
77. Johnson LS, Benz AP, Shoamanesh A, et al. Residual Stroke Risk Among Patients With Atrial Fibrillation Prescribed Oral Anticoagulants: A Patient‐Level Meta‐Analysis From COMBINE AF. Journal of the American Heart Association 2024;13(17):e034758. DOI: doi:10.1161/JAHA.123.034758.
78. Reeder GS, Charlesworth JE, Moore SB. Cause of Spontaneous Echocardiographic Contrast as Assessed by Scanning Electron Microscopy. Journal of the American Society of Echocardiography 1994;7(2):169-173. DOI: 10.1016/S0894-7317(14)80123-5.
79. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 1994;23(4):961-9. (In eng). DOI: 10.1016/0735-1097(94)90644-0.
80. Wineinger NE, Barrett PM, Zhang Y, et al. Identification of paroxysmal atrial fibrillation subtypes in over 13,000 individuals. Heart Rhythm 2019;16(1):26-30. (In eng). DOI: 10.1016/j.hrthm.2018.08.012.
81. Osterberg L, Blaschke T. Adherence to Medication. New England Journal of Medicine 2005;353(5):487-497. DOI: doi:10.1056/NEJMra050100.
82. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. N Engl J Med 2021;384(22):2081-2091. (In eng). DOI: 10.1056/NEJMoa2101897.
83. Alqarawi W, Grose E, Ramirez FD, et al. Prevalence of Left Atrial Appendage Thrombus in Patients Anticoagulated With Direct Oral Anticoagulants: Systematic Review and Meta-analysis. CJC Open 2021;3(5):658-665. (In eng). DOI: 10.1016/j.cjco.2020.12.012.

84. Bunch TJ, Weiss JP, Crandall BG, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm 2010;7(4):433-437. DOI: https://doi.org/10.1016/j.hrthm.2009.12.004.

85. Kwok CS, Loke YK, Hale R, Potter JF, Myint PK. Atrial fibrillation and incidence of dementia. Neurology 2011;76(10):914-922. DOI: doi:10.1212/WNL.0b013e31820f2e38.

86. Miyasaka Y, Barnes ME, Petersen RC, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort. Eur Heart J 2007;28(16):1962-7. DOI: 10.1093/eurheartj/ehm012.

87. Gaita F, Corsinovi L, Anselmino M, et al. Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and Correlation With Cognitive Function. JACC 2013;62(21):1990-1997. DOI: doi:10.1016/j.jacc.2013.05.074.

88. Healey JS, Oldgren J, Ezekowitz M, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. The Lancet 2016;388(10050):1161-1169. DOI: 10.1016/S0140-6736(16)30968-0.

89. Anter E, Jessup M, Callans DJ. Atrial Fibrillation and Heart Failure. Circulation 2009;119(18):2516-2525. DOI: doi:10.1161/CIRCULATIONAHA.108.821306.

90. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(6a):2d-8d. (In eng). DOI: 10.1016/s0002-9149(02)03373-8.

91. Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. J Am Coll Cardiol 1998;32(1):197-204. (In eng). DOI: 10.1016/s0735-1097(98)00221-6.

92. Gosselink AT, Crijns HJ, van den Berg MP, et al. Functional capacity before and after cardioversion of atrial fibrillation: a controlled study. Br Heart J 1994;72(2):161-6. (In eng). DOI: 10.1136/hrt.72.2.161.

93. Nerheim P, Birger-Botkin S, Piracha L, Olshansky B. Heart Failure and Sudden Death in Patients With Tachycardia-Induced Cardiomyopathy and Recurrent Tachycardia. Circulation 2004;110(3):247-252. DOI: doi:10.1161/01.CIR.0000135472.28234.CC.

94. Ling LH, Kalman JM, Ellims AH, et al. Diffuse ventricular fibrosis is a late outcome of tachycardia-mediated cardiomyopathy after successful ablation. Circ Arrhythm Electrophysiol 2013;6(4):697-704. (In eng). DOI: 10.1161/circep.113.000681.

95. Schnabel RB, Pecen L, Ojeda FM, et al. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. Heart 2017;103(13):1024-1030. (In eng). DOI: 10.1136/heartjnl-2016-310406.

96. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med 2006;119(5):448.e1-19. (In eng). DOI: 10.1016/j.amjmed.2005.10.057.

97. Abu HO, Wang W, Otabil EM, et al. Perception of atrial fibrillation symptoms: Impact on quality of life and treatment in older adults. J Am Geriatr Soc 2022;70(10):2805-2817. (In eng). DOI: 10.1111/jgs.17954.

98. Pinho-Gomes AC, Azevedo L, Copland E, et al. Blood pressure-lowering treatment for the prevention of cardiovascular events in patients with atrial fibrillation: An individual participant data meta-analysis. PLoS Med 2021;18(6):e1003599. (In eng). DOI: 10.1371/journal.pmed.1003599.
99. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa. Circulation 2016;133(5):484-492. DOI: doi:10.1161/CIRCULATIONAHA.115.018614.
100. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2023;44(37):3627-3639. (In eng). DOI: 10.1093/eurheartj/ehad195.
101. Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384(9961):2235-43. (In eng). DOI: 10.1016/s0140-6736(14)61373-8.
102. Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJ, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis. JACC Heart Fail 2013;1(1):21-8. (In eng). DOI: 10.1016/j.jchf.2012.09.002.
103. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol 2006;47(10):1997-2004. (In eng). DOI: 10.1016/j.jacc.2006.01.060.
104. Yusuf S, Healey JS, Pogue J, et al. Irbesartan in patients with atrial fibrillation. N Engl J Med 2011;364(10):928-38. (In eng). DOI: 10.1056/NEJMoa1008816.
105. Malmo V, Nes BM, Amundsen BH, et al. Aerobic Interval Training Reduces the Burden of Atrial Fibrillation in the Short Term: A Randomized Trial. Circulation 2016;133(5):466-73. (In eng). DOI: 10.1161/circulationaha.115.018220.
106. Csengeri D, Sprünker N-A, Di Castelnuovo A, et al. Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. European Heart Journal 2021;42(12):1170-1177. DOI: 10.1093/eurheartj/ehaa953.
107. Overvad TF, Rasmussen LH, Skjøth F, et al. Alcohol intake and prognosis of atrial fibrillation. Heart 2013;99(15):1093-1099. DOI: 10.1136/heartjnl-2013-304036.
108. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100. (In eng). DOI: 10.1378/chest.10-0134.
109. Voskoboinik A, Kalman JM, Silva AD, et al. Alcohol Abstinence in Drinkers with Atrial Fibrillation. New England Journal of Medicine 2020;382(1):20-28. DOI: doi:10.1056/NEJMoa1817591.
110. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369(13):1206-14. (In eng). DOI: 10.1056/NEJMoa1300615.
111. Connolly SJ, Karthikeyan G, Ntsekhe M, et al. Rivaroxaban in Rheumatic Heart Disease-Associated Atrial Fibrillation. N Engl J Med 2022;387(11):978-988. (In eng). DOI: 10.1056/NEJMoa2209051.

112. Joosten LPT, van Doorn S, van de Ven PM, et al. Safety of Switching From a Vitamin K Antagonist to a Non–Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients With Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial. Circulation 2024;149(4):279-289. DOI: doi:10.1161/CIRCULATIONAHA.123.066485.
113. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347(23):1825-33. (In eng). DOI: 10.1056/NEJMoa021328.
114. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347(23):1834-40. (In eng). DOI: 10.1056/NEJMoa021375.
115. Opolski G, Torbicki A, Kosior DA, et al. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. Chest 2004;126(2):476-86. (In eng). DOI: 10.1378/chest.126.2.476.
116. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol 2003;41(10):1690-6. (In eng). DOI: 10.1016/s0735-1097(03)00332-2.
117. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation--Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. Lancet 2000;356(9244):1789-94. (In eng). DOI: 10.1016/s0140-6736(00)03230-x.
118. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358(25):2667-77. (In eng). DOI: 10.1056/NEJMoa0708789.
119. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation 2004;109(12):1509-13. (In eng). DOI: 10.1161/01.Cir.0000121736.16643.11.
120. Hohnloser SH, Crijns HJGM, Eickels Mv, et al. Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation. New England Journal of Medicine 2009;360(7):668-678. DOI: doi:10.1056/NEJMoa0803778.
121. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. N Engl J Med 2020;383(14):1305-1316. (In eng). DOI: 10.1056/NEJMoa2019422.
122. Andrade JG, Deyell MW, Macle L, et al. Progression of Atrial Fibrillation after Cryoablation or Drug Therapy. New England Journal of Medicine 2023;388(2):105-116. DOI: doi:10.1056/NEJMoa2212540.
123. Gelder ICV, Groenveld HF, Crijns HJGM, et al. Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. New England Journal of Medicine 2010;362(15):1363-1373. DOI: doi:10.1056/NEJMoa1001337.

124. Kotecha D, Bunting KV, Gill SK, et al. Effect of Digoxin vs Bisoprolol for Heart Rate Control in Atrial Fibrillation on Patient-Reported Quality of Life: The RATE-AF Randomized Clinical Trial. JAMA 2020;324(24):2497-2508. DOI: 10.1001/jama.2020.23138.
125. O'Neal WT, Almahmoud MF, Soliman EZ. Resting heart rate and incident atrial fibrillation in the elderly. Pacing Clin Electrophysiol 2015;38(5):591-7. (In eng). DOI: 10.1111/pace.12591.
126. Thelle DS, Selmer R, Gjesdal K, et al. Resting heart rate and physical activity as risk factors for lone atrial fibrillation: a prospective study of 309 540 men and women. Heart 2013;99(23):1755-1760.
127. Reimers AK, Knapp G, Reimers CD. Effects of Exercise on the Resting Heart Rate: A Systematic Review and Meta-Analysis of Interventional Studies. J Clin Med 2018;7(12) (In eng). DOI: 10.3390/jcm7120503.
128. Oesterle A, Giancaterino S, Van Noord MG, et al. Effects of Supervised Exercise Training on Atrial Fibrillation: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. Journal of Cardiopulmonary Rehabilitation and Prevention 2022;42(4) (https://journals.lww.com/jcrjournal/fulltext/2022/07000/effects_of_supervised_exercise_training_on_atrial.6.aspx).
129. Coltart J, Alderman EL, Robison SC, Harrison DC. Effect of propranolol on left ventricular function, segmental wall motion, and diastolic pressure-volume relation in man. Br Heart J 1975;37(4):357-64. (In eng). DOI: 10.1136/hrt.37.4.357.
130. Meyer M, Lustgarten D. Beta-blockers in atrial fibrillation—trying to make sense of unsettling results. EP Europace 2023;25(2):260-262. DOI: 10.1093/europace/euad010.
131. Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation 2010;121(17):1904-11. DOI: 10.1161/CIRCULATIONAHA.109.874982.
132. Persson AP, Fedorowski A, Hedblad B, et al. Heart rate and premature atrial contractions at 24hECG independently predict atrial fibrillation in a population-based study. Heart 2020;106(4):287-291. (In eng). DOI: 10.1136/heartjnl-2019-315119.
133. Aune D, Sen A, ó'Hartaigh B, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality - A systematic review and dose-response meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis 2017;27(6):504-517. (In eng). DOI: 10.1016/j.numecd.2017.04.004.
134. Bonander C, Nilsson A, Björk J, et al. The value of combining individual and small area sociodemographic data for assessing and handling selective participation in cohort studies: Evidence from the Swedish CardioPulmonary bioImage Study. PLOS ONE 2022;17(3):e0265088. DOI: 10.1371/journal.pone.0265088.
135. Persson AP, Måneheim A, Economou Lundeberg J, et al. Reference ranges for ambulatory heart rate measurements in a middle-aged population. Heart 2024 (In eng). DOI: 10.1136/heartjnl-2023-323681.

136. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-12. (In eng). DOI: 10.7326/0003-4819-150-9-200905050-00006.
137. Blaha MJ, Mortensen MB, Kianoush S, Tota-Maharaj R, Cainzos-Achirica M. Coronary Artery Calcium Scoring: Is It Time for a Change in Methodology? JACC: Cardiovascular Imaging 2017;10(8):923-937. DOI: https://doi.org/10.1016/j.jcmg.2017.05.007.
138. Hedenstrom H, Malmberg P, Fridriksson HV. Reference values for lung function tests in men: regression equations with smoking variables. Ups J Med Sci 1986;91(3):299-310. DOI: 10.3109/03009738609178670.
139. Hedenström H, Malmberg P, Agarwal K. Reference values for lung function tests in females. Regression equations with smoking variables. Bull Eur Physiopathol Respir 1985;21(6):551-7. (In eng).
140. Smith JG, Platonov PG, Hedblad B, Engström G, Melander O. Atrial fibrillation in the Malmö Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. Eur J Epidemiol 2010;25(2):95-102. (In eng). DOI: 10.1007/s10654-009-9404-1.
141. Cook NR. Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction. Circulation 2007;115(7):928-935. DOI: doi:10.1161/CIRCULATIONAHA.106.672402.
142. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society: Series B (Methodological) 1972;34(2):187-202. DOI: https://doi.org/10.1111/j.2517-6161.1972.tb00899.x.
143. Stensrud MJ, Hernán MA. Why Test for Proportional Hazards? JAMA 2020;323(14):1401-1402. DOI: 10.1001/jama.2020.1267.
144. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 1999;94(446):496-509. DOI: 10.2307/2670170.
145. Nitika, Mishra SS, Lohani P. Lexis Expansion: a prerequisite for analyzing time changing variables in a cohort study. Nepal J Epidemiol 2017;7(2):681-684. (In eng). DOI: 10.3126/nje.v7i2.17974.
146. Lewington S. Lexis Expansion- Age-at-Risk Adjustment for Survival Analysis. 2013.
147. Fredriksson T, Frykman V, Friberg L, Al-Khalili F, Engdahl J, Svennberg E. Usefulness of Short-Lasting Episodes of Supraventricular Arrhythmia (Micro-Atrial Fibrillation) as a Risk Factor for Atrial Fibrillation. Am J Cardiol 2018;122(7):1179-1184. (In eng). DOI: 10.1016/j.amjcard.2018.06.030.
148. Fredriksson T, Gudmundsdottir KK, Frykman V, et al. Brief episodes of rapid irregular atrial activity (micro-AF) are a risk marker for atrial fibrillation: a prospective cohort study. BMC Cardiovasc Disord 2020;20(1):167. (In eng). DOI: 10.1186/s12872-020-01453-w.
149. Johnson LSB, Persson AP, Wollmer P, Juul-Moller S, Juhlin T, Engstrom G. Irregularity and lack of p waves in short tachycardia episodes predict atrial fibrillation and ischemic stroke. Heart Rhythm 2018 (In eng). DOI: 10.1016/j.hrthm.2018.02.011.

150. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007;17(9):643-53. (In eng). DOI: 10.1016/j.annepidem.2007.03.013.
151. Manjer J, Carlsson S, Elmståhl S, et al. The Malmö Diet and Cancer Study: representativity, cancer incidence and mortality in participants and non-participants. Eur J Cancer Prev 2001;10(6):489-99. (In eng). DOI: 10.1097/00008469-200112000-00003.
152. Franklin SS, Thijs L, Hansen TW, O'Brien E, Staessen JA. White-Coat Hypertension. Hypertension 2013;62(6):982-987. DOI: 10.1161/HYPERTENSIONAHA.113.01275.
153. Johnson LS, Zadrozniak P, Jasina G, et al. Artificial intelligence for direct-to-physician reporting of ambulatory electrocardiography. Nature Medicine 2025. DOI: 10.1038/s41591-025-03516-x.
154. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in Older Patients with Systolic Heart Failure. New England Journal of Medicine 2007;357(22):2248-2261. DOI: doi:10.1056/NEJMoa0706201.
155. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. New England Journal of Medicine 2008;359(21):2195-2207. DOI: doi:10.1056/NEJMoa0807646.
156. Hijazi Z, Oldgren J, Lindbäck J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. The Lancet 2016;387(10035):2302-2311. DOI: 10.1016/S0140-6736(16)00741-8.
157. Wijtvliet E, Tieleman RG, van Gelder IC, et al. Nurse-led vs. usual-care for atrial fibrillation. Eur Heart J 2020;41(5):634-641. (In eng). DOI: 10.1093/eurheartj/ehz666.
158. Hendriks JM, de Wit R, Crijns HJ, et al. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. Eur Heart J 2012;33(21):2692-9. (In eng). DOI: 10.1093/eurheartj/ehs071.
159. Yndigegn T, Hofmann R, Jernberg T, Gale CP. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. Heart 2018;104(19):1562-1567. (In eng). DOI: 10.1136/heartjnl-2017-312322.

Printed by Media-Tryck, Lund 2025 NORDIC SWAN ECOLABEL 3041 0903

ATRIAL FIBRILLATION is a common arrhythmia with potentially severe consequences, but we still don't fully know why some people develop this condition or who will benefit most from treatment. This thesis examines different aspects of heart rate related to atrial fibrillation.

ANDERS PERSSON received his medical degree from Gdansk University in 2011 and finished his specialist training in Clinical Physiology (diagnostics) at Skåne University Hospital in Malmö in 2021.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2025:61
ISBN 978-91-8021-714-9
ISSN 1652-8220