DEPARTMENT OF CLINICAL SCIENCES,
DANDERYD HOSPITAL
Division of Cardiovascular Medicine,
Karolinska Institutet, Stockholm, Sweden

CLINICAL ASPECTS OF DEVICE-DETECTED ARRHYTHMIAS

Emma Sandgren

Karolinska Institutet

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CLINICAL ASPECTS OF DEVICE-DETECTED ARRHYTHMIAS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Emma Sandgren

Principal Supervisor:
Associate Professor Johan Engdahl
Karolinska Institutet, Stockholm
Department of Clinical Sciences
Danderyd Hospital (KI-DS),
Division of Cardiovascular Medicine

Co-supervisors:
Associate Professor Nils Edvardsson
Sahlgrenska Academy at University of Gothenburg, Gothenburg
Department of Molecular and Clinical Medicine,
Institute of Medicine

Professor Mårten Rosenqvist
Karolinska Institutet, Stockholm
Department of Clinical Sciences
Danderyd Hospital (KI-DS),
Division of Cardiovascular Medicine

Opponent:
Associate Professor Artur Fedorowski
Lund University, Malmö
Department of Clinical Sciences
Skåne University Hospital

Examination Board:
Professor Mats Jensen-Urstad
Karolinska Institutet, Stockholm
Department of Cardiology
Karolinska University Hospital

Associate Professor Maria Eriksson
Karolinska Institutet, Stockholm
Department of Molecular Medicine and Surgery
Karolinska University Hospital

Associate Professor Fredrik Holmqvist
Lund University, Lund
Department of Clinical Sciences
Skåne University Hospital

“Η γνώση είναι η τροφή του σώματος”

Knowledge is the food of the soul

Kunskap är näring för själen

Plato, Greek philosopher, 427–347 f.Kr.

In honour of my parents, Eva Nilsson and Roger Sandgren, for teaching me what is right and wrong in life and for always believing in me and my choices.

ABSTRACT

INTRODUCTION

Cardiac implantable electronic devices (CIEDs) enable continuous monitoring of the heart rhythm. CIEDs constitute a unique opportunity for detecting arrhythmias, as the duration of cardiac monitoring is of the utmost importance for the detection rate.

The CIED population consists mostly of patients from older age categories where risk factors for atrial fibrillation (AF) are common. A dual-chamber device can detect and store episodes with a high atrial rate, i.e. atrial high-rate episodes (AHREs). AHREs confirmed to be AF, atrial flutter or focal atrial tachycardia are termed subclinical AF. Both terms refer to patients with no symptoms attributed to AF, with no previous diagnosis of clinical AF. These episodes of device-detected AF are associated with increased risk of ischaemic stroke, although the risk seems to be lower than in patients with documented clinical AF, and the benefit of oral anticoagulation (OAC) treatment in this population has not been established.

Patients presenting with syncope represent a diagnostic challenge. Initial evaluation can provide the underlying mechanism in up to half of the patients. However, the mechanism remains unexplained in many patients, and long-term electrocardiogram (ECG) monitoring with an implantable loop recorder (ILR) enables ECG recording at the time of syncope recurrence, which can reveal the underlying mechanism.

The aim of this thesis is to highlight different aspects of arrhythmias diagnosed with CIEDs, both from a diagnostic and a therapeutic point of view. More specifically, it aims to describe the incidence of subclinical AF/AHREs in a pacemaker population, along with its OAC treatment, and the incidence of ischaemic stroke and vascular dementia. In addition, it will explore the role of the baseline 12-lead ECG in predicting the syncope mechanism during ILR monitoring, and whether age and gender impact the evaluation before the implantation and subsequent diagnostic yield of the ILR. Finally, the thesis will test the hypothesis that patients with incident AF during inpatient care after coronary artery bypass graft (CABG) surgery often experience a relapse of AF within a year, with little chance of detection.

METHODS AND RESULTS

In study I, consecutive patients were enrolled who had been implanted with a dual-chamber device for the indication of sinus node disease or atrioventricular block/ bundle branch block between 2010 and 2014 in Halland County in Sweden. The incidence of subclinical AF/AHREs, ischaemic stroke, or vascular dementia, and the initiation of and/or any change of OAC treatment were recorded during follow-up. At inclusion, 271 patients had clinical/known AF, of which 80% (216/271) were on OAC treatment. Four hundred eleven patients had no history of AF, and of these 30% (125/411) were diagnosed with subclinical AF/AHREs during a mean follow-up of 38 months. 62% of these were prescribed OAC treatment. Patients with congestive heart failure ($p = .03$) and age >75 years ($p = .0002$) were more often diagnosed with subclinical AF/AHREs. The annual stroke incidence was 2.1% in

patients with clinical/known AF, 1.9% in patients with subclinical AF/AHREs, and 1.4% in patients with no AF. Corresponding values for a diagnosis of vascular dementia was 11.2%, 5.6% (p= .09), and 6.2% (p= .048).

The study population in studies II and III consisted of consecutive patients with unexplained syncope in Halland County in Sweden, who had been selected to be implanted with an ILR after an initial non-diagnostic evaluation between 2007 and 2016. In study II, baseline 12-lead ECG was compared with clinically adjudicated cause of syncope. In study III the role of age and gender in the evaluation before implantation, and in the diagnostic yield of the ILR, was reported. There is a notable difference between the two terms ILR-guided diagnosis (study II) and ECG-based diagnosis (study III). ILR-guided diagnosis refers to all patients where the ILR has informed the clinical diagnosis, i.e. where captured ECG recordings both during syncope recurrence or other times have enabled a clinical diagnosis to be made, while ECG-based diagnosis only includes patients with syncope recurrence. In total, 300 (147 women) patients were included. The mean age was 66±16 years. In study II, 49% (146/300) received an ILR-guided diagnosis. Bifascicular block was the second most common pathological baseline 12-lead ECG finding (n=33). It was most common in patients ≥60 years of age (31/33), and more common in patients who received an ILR-guided diagnosis (bifascicular block: 25/33, 76%; normal baseline 12-lead ECG: 90/205, 44%, p< .001). Among patients with bifascicular block, 96% (24/25) were clinically adjudicated to have an arrhythmia-caused syncope, and of these, 23 had ECG recordings of a bradyarrhythmia. Bifascicular block was a strong predictor of a clinically adjudicated arrhythmia-caused syncope, with an adjusted odds ratio of 5.5 (95%CI (confidence interval) 2.3-13.2), p< .001, and a positive predictive value of 73%. In the total population, bifascicular block predicted a clinically adjudicated arrhythmia-caused syncope due to bradyarrhythmia, with an adjusted odds ratio of 11.4 (95%CI 5.0-26.2), p< .001. In study III, women experienced syncope recurrence and received an ECG-based diagnosis more often than men (women: 56/147, 38%; men: 33/153, 22%; p= .001), mainly because of a higher incidence of non-arrhythmic syncope recurrence, i.e. syncope with a normal ECG recording (women: 27/147, 18%; men: 15/153, 10%; p= .045). Patients ≥60 years of age had the lowest rate of pre-implant tests (<40 years: 6.5±1.2; 40-59 years: 5.75±1.0; and ≥60 years: 5.1±1.9; p= .002) but the highest rate of arrhythmic syncope (<40 years: 3/11, 27%; 41-59 years: 7/18, 39%; and ≥60 years: 37/60, 62%; p= .045). Fifty patients with no recurrent syncope had ECG findings potentially indicative of recurrent syncope.

Study IV was a sub-study of the prospective AFAF study (Atrial Fibrillation AFter CABG and percutaneous coronary intervention). In short, the AFAF study investigates the incidence of AF after percutaneous coronary intervention or CABG surgery by non-invasive handheld ECG recordings. It is investigated three times daily during the first postoperative month, and thereafter for two weeks at three, 12 and 24 months in addition to routine care. This sub-study added continuous ECG monitoring with an ILR. The primary endpoint was the proportion of patients with incident or recurrent AF during the 12-month monitoring period. The secondary endpoints were the proportion of patients who developed persistent AF and calculated AF

burden. In total, 27/40 (68%) patients were diagnosed with incident AF, 21 in hospital and six later. Eighteen of these 27 (67%) also experienced AF recurrence, and three patients progressed into persistent AF. The incidence of AF episodes was highest during the first 30 postoperative days, as 17/40 patients had episodes of AF after discharge within this period. The rate of incident and recurrent AF after the first 30 days was low: three patients had incident AF and 10 patients recurrent AF. The CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)) score was higher in patients with AF than in patients who remained in sinus rhythm: median 4 (IQR (interquartile range) 1) and median 3 (IQR 2) respectively, p= .006. In patients with paroxysmal AF, the AF burden was low: 0.1% (IQR 0.28). Handheld ECG identified fewer patients with AF after discharge than the ILR (handheld ECG: 9/20, 45%; ILR: 20/20, 100%; p= .001).

CONCLUSIONS

CIEDs are a valuable asset in arrhythmia diagnostics, and can inform clinical decisions.

Subclinical AF/AHREs were common, and were associated with older age and congestive heart failure. The stroke incidence was low, but clinical/known AF was associated with an increased risk of vascular dementia.

In syncope patients bifascicular block at baseline 12-lead ECG predicted a clinically adjudicated arrhythmia-caused syncope, commonly due to intermittent complete heart block.

Women experienced syncope recurrence more often than men, especially for non-arrhythmic reasons. The highest rate of arrhythmic syncope and the lowest rate of pre-implant tests were found in patients ≥60 years of age.

In patients treated with CABG surgery, the recurrence rate of AF was high in patients with incident AF during hospitalisation, especially during the first postoperative month. After the first month, the rate of incident and recurrent AF was low. The ILR was more effective in detecting patients with AF than handheld ECG.

LIST OF SCIENTIFIC PAPERS

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

I. **Sandgren E**, Rorsman C, Edvardsson N, Engdahl J

Stroke incidence and anticoagulation treatment in patients with pacemaker-detected silent atrial fibrillation.

PLoS One. 2018;13(9):e0203661.

II. **Sandgren E**, Rorsman C, Edvardsson N, Engdahl J

Role of baseline 12-lead ECG in predicting syncope caused by arrhythmia in patients investigated using an implantable loop recorder.

Int J Cardiol Heart Vasc. 2019;24:100386.

III. **Sandgren E**, Rorsman C, Edvardsson N, Engdahl J

Role of age and gender in the evaluation before implantation and in the diagnostic yield of an implantable loop recorder in patients with unexplained syncope.

Submitted.

IV. **Sandgren E**, Wickbom A, Kalm T, Ahlsson A, Edvardsson N, Engdahl J

Detection of incident and recurrent atrial fibrillation after coronary artery bypass graft surgery – the contribution of intermittent handheld ECG and continuous ECG monitoring with an implantable loop recorder.

Submitted.

CONTENTS

LIST OF ABBREVIATIONS

AATS	American Association for Thoracic Surgery
ABC	Age, Biomarkers, Clinical history
ABC AF	ABC-Scores for Reduction of Stroke and Mortality in Atrial Fibrillation
ACC	American College of Cardiology
AF	Atrial fibrillation
AFAF	Atrial Fibrillation AFter CABG and percutaneous coronary intervention
AHA	American Heart Association
A-HIRATE	The Atrial High Rate Episodes
AHRE	Atrial high-rate episode
ANOVA	Analysis of variance
ARTESiA	Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-clinical Atrial Fibrillation
ASSERT	ASymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial
AV	Atrioventricular
BNP	B-type natriuretic peptide
Bpm	Beats per minute
CABG	Coronary artery bypass graft
$CHADS_2$	Congestive heart failure, Hypertension, Age >75 years, Diabetes, Stroke (2 points)
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)
CI	Confidence interval
CIED	Cardiac implantable electronic device
ECG	Electrocardiogram
EGM	Electrogram
EHRA	European Heart Rhythm Society
ESC	European Society of Cardiology

HRS	Heart Rhythm Society
ILR	Implantable loop recorder
IMPACT	Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk
IQR	Interquartile range
ISSUE	International Study on Syncope of Uncertain Etiology
LAH	Left anterior hemiblock
LBBB	Left bundle branch block
LOOP	Atrial Fibrillation Detected by Continuous ECG Monitoring
LPH	Left posterior hemiblock
MOST	The Mode Selection Trial
NOAH-AFNET 6	Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes
OAC	Oral anticoagulation
PPV	Positive predictive value
RBBB	Right bundle branch block
SD	Standard deviation
SILENT	Subclinical Atrial Fibrillation and Stroke Prevention Trial
TRENDS	A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics

1 PREFACE

My interest in cardiology and arrhythmias begun at medical school. During my residency in internal medicine and cardiology I met Cecilia, and I still remember the day she asked if I would like to join in the Arrhythmia Unit. The obvious answer was YES. Having the opportunity to spend every day with arrhythmias and devices is a dream for someone who likes mathematics and physics.

During my time as a resident, I also had the good fortune to meet Johan, who aroused my interest in undertaking research, and when he gave me the chance to be one of his Ph.D. students, I took the opportunity. It was also Johan who introduced me to Nils and Mårten, and when Nils called some months later and asked whether I was interested in conducting a study, my supervisors were appointed. Since then, I have spent even more time trying to grasp, treat and understand the nature and meaning of device-detected arrhythmias. Along the way I have learnt a lot, but luckily for me, there is infinitely more to learn!

2 GENERAL INFORMATION ON THE THESIS

2.1 FLOWCHART

This thesis consists of four studies. Two of them (studies II and III) involve the same study population as delineated in Figure 1, and described in more detail in the Patients and Methods section.

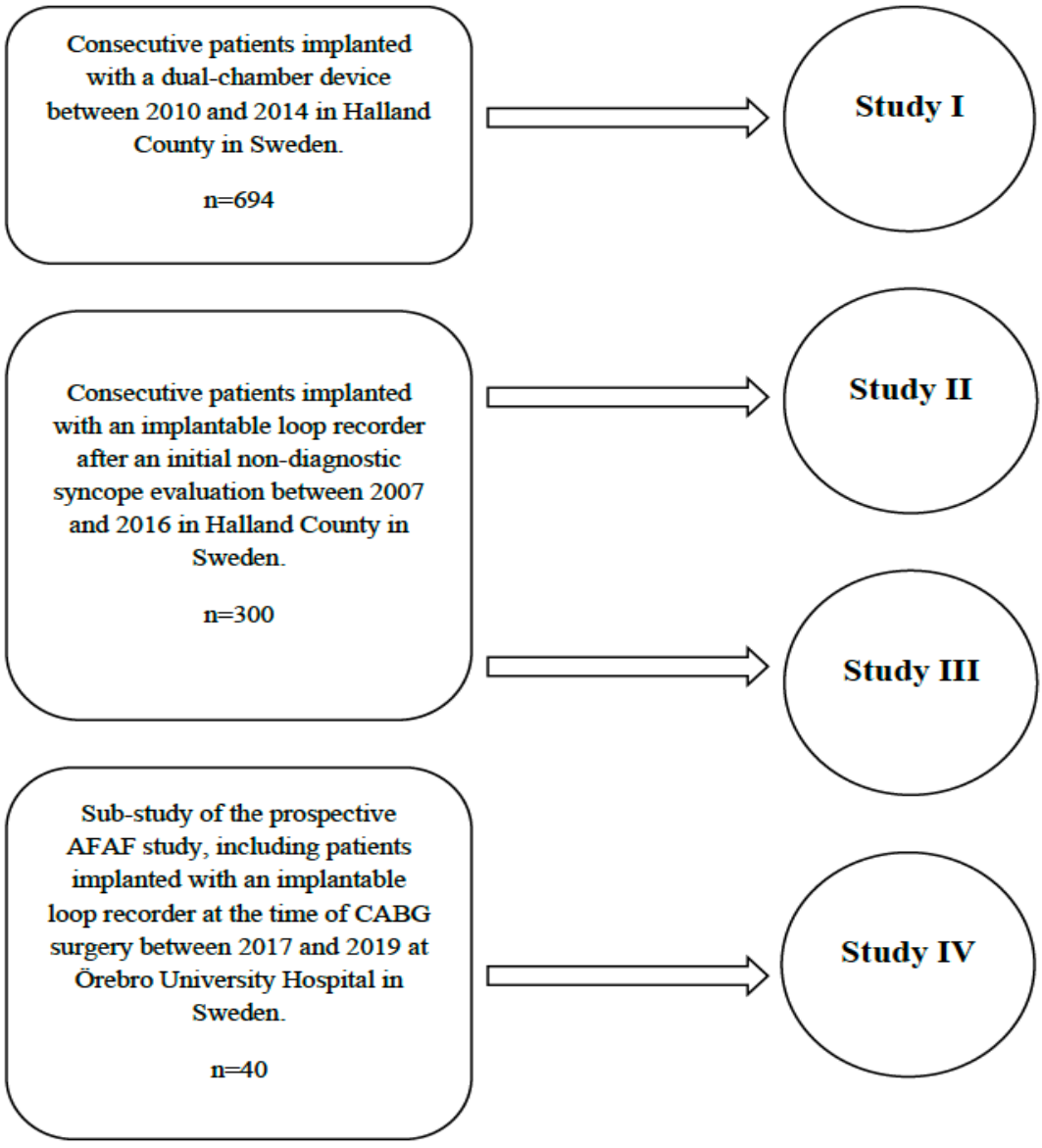

Figure 1. Flowchart of the thesis. AFAF, Atrial Fibrillation AFter CABG and percutaneous coronary intervention; CABG, coronary artery bypass graft.

3 INTRODUCTION

3.1 THE PACEMAKER

3.1.1 History and development of modern pacing

Modern cardiac electrophysiology is based on two important discoveries involving organic tissue. First, the fact that electricity is an inherent part of organic tissue was described by Luigi Galvani in 1791 (Figure 2) (1). Second, the fact that the success of electrical stimuli to the heart depends on applying pulsed stimuli established at the end of the nineteenth century by J A McWilliam. The latter also forms the basic concept of modern pacing (2).

These two important discoveries paved the way for the development of the first pacemaker. In 1928, the Australian anaesthesiologist Mark C Lidwell developed the first pacemaker (1), followed closely by the construction of an electro-mechanical device in 1932 by the American cardiologist Albert S Hyman, who was the first to use and popularise the term "artificial pacemaker" (3). The next advancement came in 1952, when Doctor Wilfred Bigelow, Doctor Johan Callaghan and engineer Jack Hopps succeeded in stimulating endocardial tissue using a bipolar electrode on the distal tip of a small catheter. They were credited with the first endocardial electrode placement, as well as the first pacemaker circuit (4, 5). Another pioneer in the evolution of artificial pacemakers was cardiologist Paul Zoll. At the beginning of the 1950s, he reported the successful use of a complete external artificial pacemaker system with skin electrodes, to treat cardiac standstill (6). Zoll was also one of the first to use rechargeable batteries as a power source (5).

The widespread use of pacemakers was limited by the large, bulky external energy sources required, but the advent of the transistor in 1948 enabled the development of smaller implantable sources of energy (1). First came a wearable, external, battery-operated, transistorised artificial pacemaker constructed by the American engineer Earl Bakken (founder of Medtronic) at the beginning of 1958 (7). In the autumn of the same year, the Swedish cardiac surgeon Åke Senning and the Swedish physician and inventor Rune Elmqvist succeeded in incorporating these new transistors into a pulse generator small enough to implant under the skin in the epigastrium. In October 1958, this made the first implantation of a fully implantable system possible at Karolinska Hospital in Solna (Figure 3). The electrodes were attached to the myocardium of the heart by thoracotomy. In the 1960s, transvenous leads replaced epicardial leads (1), and the pulse generators were placed in the prepectoral region (8).

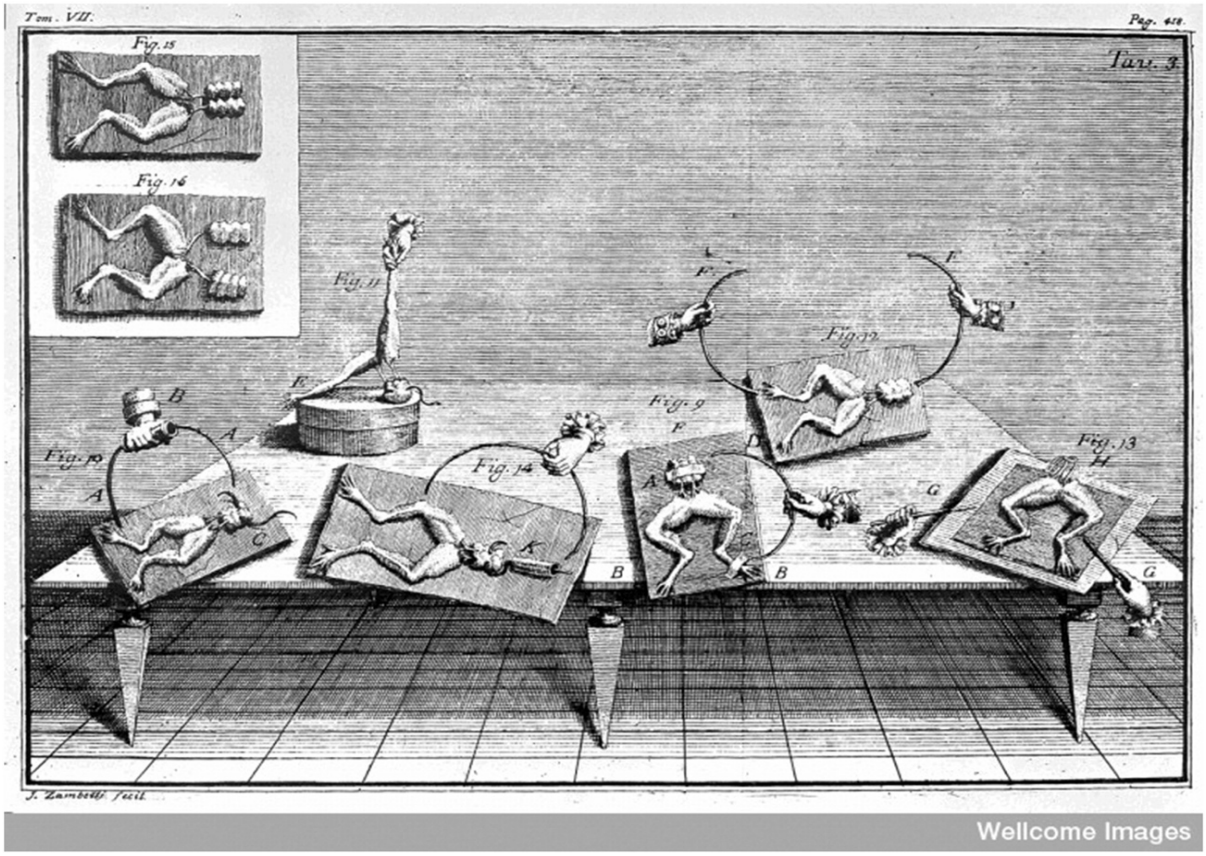

Figure 2. A drawing from Luigi Galvani's De Viribus Electricitatis in Motu Musculari Commentarius, showing his experiments in electrophysiology. The Wellcome Collection (https://wellcomecollection.org). Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

In the following decades new features were developed, improving the technical performance of pacemakers. In the 1960s, "demand" pacemakers were introduced to sense underlying cardiac activity, which ensured the pacemaker only provided pacing when needed. In the mid-1970s pacemakers were made programmable in a non-invasive way, through radio-frequency telemetry links. In 1978, the dual-chamber pacemaker was developed to pace and sense in both atria and ventricles. Late in the 1980s, rate-responsive pacemakers were introduced so that the pacing rate could change according to the patient's activity level. In the 1990s, microprocessors were incorporated into pacemakers, enabling features which allowed events to be detected and stored, and pacing functions to be changed automatically (5).

Parallel to this technological development, knowledge of the hemodynamic effects of pacing improved, as did awareness of the risk of infection associated with implantable leads and generators. This resulted in the development of alternative pacing strategies. In the 1990s, understanding of the hemodynamic benefits of bi-ventricular pacing for heart failure was

evolving, as was the technology associated with it. This made widespread introduction of cardiac resynchronisation therapy possible in the beginning of the 21st century (9). In the mid-2010s, the concept of leadless pacing was introduced (10, 11). At the same time, conduction system pacing emerged as an alternative to right-ventricular and bi-ventricular pacing. Conduction system pacing maintains a physiological pattern of ventricular electrical activation via the native His-Purkinje system (12-15).

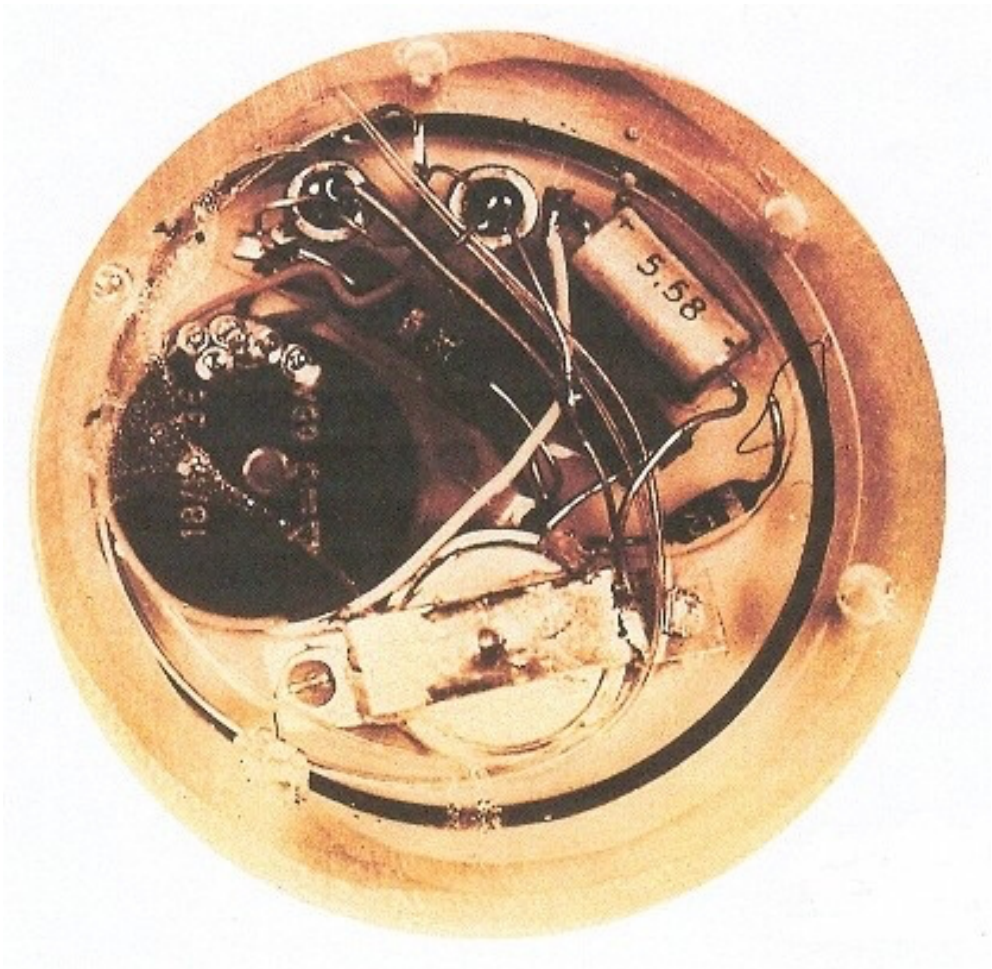

Figure 3. First implanted pacemaker, constructed by Rune Elmqvist and implanted at Karolinska Hospital in 1958 by the surgeon Åke Senning. Dimensions of the pacemaker: diameter: 55 millimetres, and thickness: 16 millimetres. Picture from "A brief history of cardiac pacing" by O Aquilina, 2006. Images in Paediatric Cardiology, 8, 17-81 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232561/). Copyright © 2006 Images in Paediatric Cardiology. Licensed under CC BY-NC-SA 3.0 (https://creativecommons.org/licenses/by-nc-sa/3.0/).

3.2 ATRIAL FIBRILLATION

3.2.1 Prevalence of atrial fibrillation

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia, and prevalence increases with advancing age. Prevalence is reported to be approximately 3% in the adult population (16), and reaches 8-10% at the age of 80 years (17). As AF is often asymptomatic, there are large numbers of undetected cases (18). Moreover, with stable prevalence, a large increase in the number of adults with AF is predicted in the coming decades, due to an ageing population (19).

AF is associated with increased morbidity and mortality. For instance, AF predisposes for congestive heart failure (20). It is associated with a twofold increased risk of all-cause mortality (21) and a fivefold increased risk of ischaemic stroke (22). Furthermore, AF is associated with increased risk of developing dementia (23, 24).

3.2.2 Diagnosis and classification of atrial fibrillation

An electrocardiogram (ECG) recording showing irregularly irregular RR intervals and no discernible, distinct P-waves is required to diagnose AF. By convention, a single-lead ECG recording lasting at least 30 seconds or an entire 12-lead ECG is diagnostic of clinical AF (20). The atrial cycle length is usually less than 200 milliseconds, i.e. an atrial rate greater than 300 beats per minute (bpm) (25).

AF is by convention classified into five different types based on the presentation, the duration and whether the episodes with AF terminate spontaneously (20).

- *First diagnosed AF* – first AF episode in a patient without prior history of AF.
- *Paroxysmal AF* – AF terminates within seven days (spontaneously or with intervention).
- *Persistent AF* – an AF episode lasting for more than seven days, or where cardioversion is needed to restore sinus rhythm after seven or more days.
- *Long-standing persistent AF* – an AF episode lasting for more than one year, where the aim is to restore sinus rhythm.
- *Permanent AF* – continuous AF, where the arrhythmia is accepted by the physician and patient, and no rhythm control interventions are applicable.

3.2.3 Pathophysiology and risk factors for atrial fibrillation

AF is defined as a supraventricular arrhythmia which is characterised by chaotic and irregular atrial activity, resulting in ineffective atrial contractions (20). Initiation of AF requires a focal

trigger, and it is maintained through an appropriate anatomic substrate (26). In 1998, Haissaguerre et al. showed that the pulmonary veins were an important source of ectopic beats, and that this was where 94% of all focal triggers responsible for initiating AF were situated (Figure 4) (27). Advancing age and underlying heart disease, such as coronary artery disease, valvar heart disease, cardiomyopathies, heart failure and AF itself, induce a slow but progressive process of structural remodeling of the atrial architecture. This remodeling is enhanced by external stressors such as hypertension, obesity, diabetes, sleep apnoea and alcohol or drugs. The structural remodeling with areas of fibrosis results in electrical dissociation between muscle bundles and local conduction heterogeneities, favouring re-entry and maintaining of AF (26).

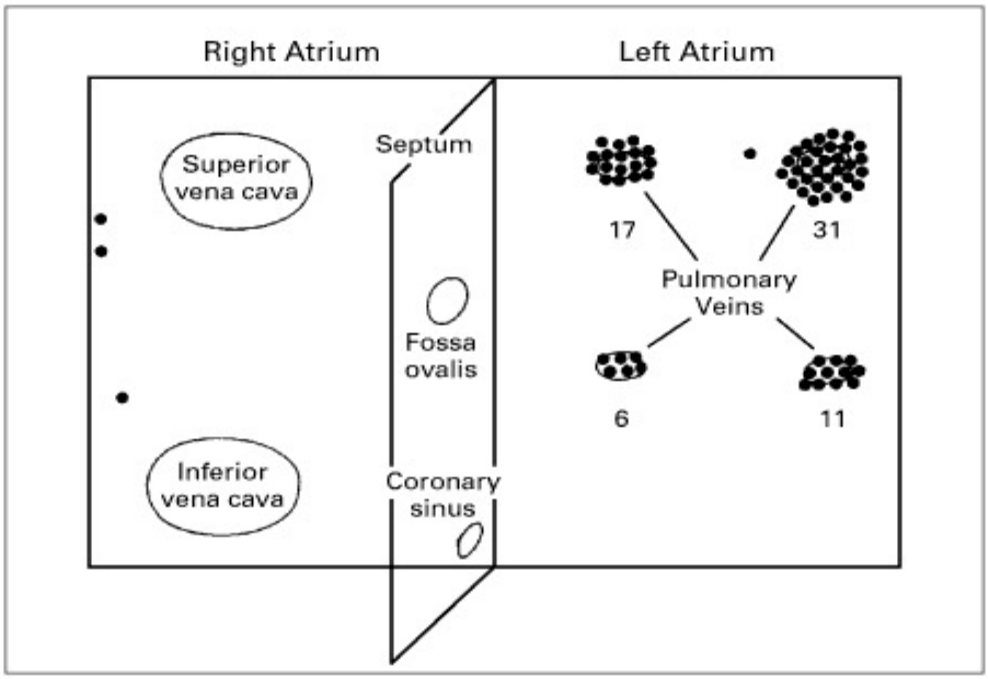

Figure 4. Diagram of the distribution of 69 foci triggering AF in 45 patients. AF, atrial fibrillation. Reprinted with permission from "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins" by Haïssaguerre M, Jaïs P, Shah DC, et al., 1998. New England Journal of Medicine, 339, 659-666. Copyright © 1998 Massachusetts Medical Society.

These above-mentioned structural changes and electrophysiological disturbances in the atrial myocardium are different manifestations of atrial cardiomyopathy, which is defined as any complex of structural, architectural, contractile or electrophysiological changes affecting the atria, with the potential to produce clinically relevant manifestations (28). The atrial myocardial damage associated with atrial cardiomyopathy causes the expression of prothrombotic factors

on the endothelia surface, and activation of platelets and inflammatory cells which, in combination with stasis of blood, generate a prothrombotic milieu (Figure 5) (29-31). This activation of the coagulation system partially explains why short episodes of AF imply a long-term risk of stroke. It should also be emphasised that atrial cardiomyopathy has a strong impact on atrial arrhythmogenesis, e.g. the occurrence of AF.

In addition to the contribution from atrial cardiomyopathy, AF itself gives rise to structural changes which favour its own maintenance (32). AF, with its high-frequency atrial excitations, leads to ion-channel remodeling, abbreviating the duration and refractory period of the action potential which enhance its stabilisation. In the short term (minutes, hours, days), AF-induced electrical remodeling is reversible, but becomes less so with longer duration (months, years) (28).

3.2.4 Risk of stroke, and anticoagulation treatment in atrial fibrillation

The structural changes in the atrial myocardium, in combination with the stasis in blood flow due to loss of atrial contraction, generate a prothrombotic milieu, especially in the left atrial appendage. Consequently, there is a manifold increased risk of ischaemic stroke in patients with AF. This increased risk is independent of AF symptoms (33). Therefore, all patients with AF, with or without symptoms, should be evaluated in terms of thromboembolic risk. The European Society of Cardiology (ESC) and the Swedish healthcare authorities recommend using the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)) score. Oral anticoagulation (OAC) treatment should be considered for men and women with a CHA_2DS_2-VASc score of one and two points respectively. For men with CHA_2DS_2-VASc scores of two or more, and for women with three or more, OAC treatment is recommended to prevent thromboembolism (20, 34). In individuals with increased risk of embolic stroke, OAC treatment reduces the ischaemic stroke risk by 60-70% (35). The advances in stroke prevention and potential areas for further improvements were recently highlighted in a systematic review (36).

Alternative systems for risk prediction are currently being evaluated, such as the ABC AF study (ABC-Scores for Reduction of Stroke and Mortality in Atrial Fibrillation, NCT03753490), which randomise patients to specific OAC treatment based on ABC (age, biomarkers, clinical history) stroke and bleeding risk scores, or standard treatment. In addition to clinical characteristics, the ABC risk score is based on biomarkers, to improve the prognostication of stroke and bleeding in patients with AF (37). The biomarker-based risk score is validated for stroke risk (38), bleeding risk (39) and mortality (40).

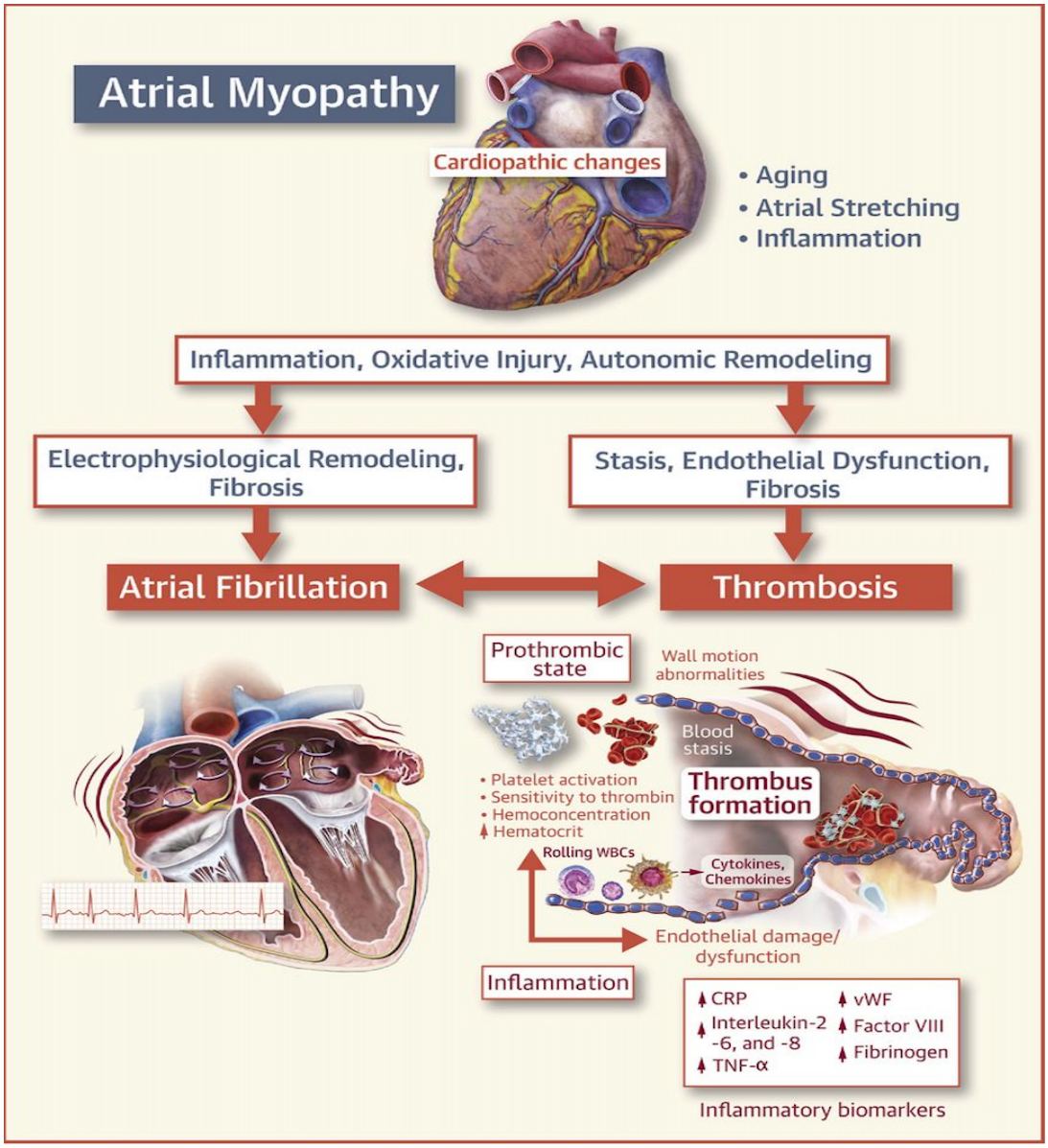

Figure 5. The relationship between atrial myopathy, AF and ischaemic stroke. Atrial myopathy is induced by ageing, inflammation, oxidative stress and stretching of the atria. Atrial myopathy leads to electrophysiological and architectural changes in the atrial myocardium, alters the properties of the cardiac autonomic nervous system and results in endothelial dysfunction and stasis, thereby contributing to a prothrombotic state. The electrophysiological and architectural changes facilitate the development of AF, which in turn causes more inflammation, fibrosis and autonomic remodeling. All these changes lead to a prothrombotic milieu mediated by circulating inflammatory molecules. CRP, C-reactive protein; TNF, tumour necrosis factor; vWF, von Willebrand factor. Reprinted with permission from "Atrial Myopathy" by Shen MJ, Arora R, Jalife J, 2019. Journal of the American College of Cardiology: Basic to Translational Science, 4, 640-654 (https://www.jacc.org/doi/full/10.1016/j.jacbts.2019.05.005). Copyright © 2019 The Authors. Licensed under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

3.3 DEVICE-DETECTED ATRIAL FIBRILLATION

3.3.1 Definition of an atrial high-rate episode and subclinical atrial fibrillation

Implantable devices with an atrial lead can detect and store episodes with a high atrial rate, i.e. atrial high-rate episodes (AHREs). Most modern dual-chamber pacemakers have specific AF-detection algorithms, while others have "atrial high-rate episode" detection algorithms which provide an opportunity to collect information about the number of episodes, the date and time of the onset of episodes, the duration of episodes and AF burden over time. Most devices can store intra-atrial electrograms (EGMs) for detected episodes, to allow the captured arrhythmia to be visually adjudicated (Figure 6). The definition of an atrial high-rate episode is an atrial tachyarrhythmia episode with a rate >175-190 bpm, lasting at least five minutes and detected by implantable cardiac devices (20, 41). Accordingly, atrial tachyarrhythmias other than AF, such as atrial flutter and focal atrial tachycardia might be detected as AHREs. However, only a minority of AHREs are not AF or atrial flutter (42, 43). Importantly, EGMs must be visually inspected to identify false positives due to electrical artefacts or oversensing. The term subclinical AF includes AHREs confirmed to be AF, atrial flutter or focal atrial tachycardia, as well as AF episodes detected by an implantable loop recorder (ILR) or a wearable monitor and confirmed by visual inspection of EGMs or ECG recordings. There is no specific rate limit for subclinical AF. Note in particular that these two terms refer to patients with no symptoms attributed to AF, with no previous diagnosis of clinical AF, i.e. no 12-lead ECG or rhythm strip documenting AF. Asymptomatic AF in patients with AF verified by a 12-lead ECG or a rhythm strip is called silent AF (20, 41).

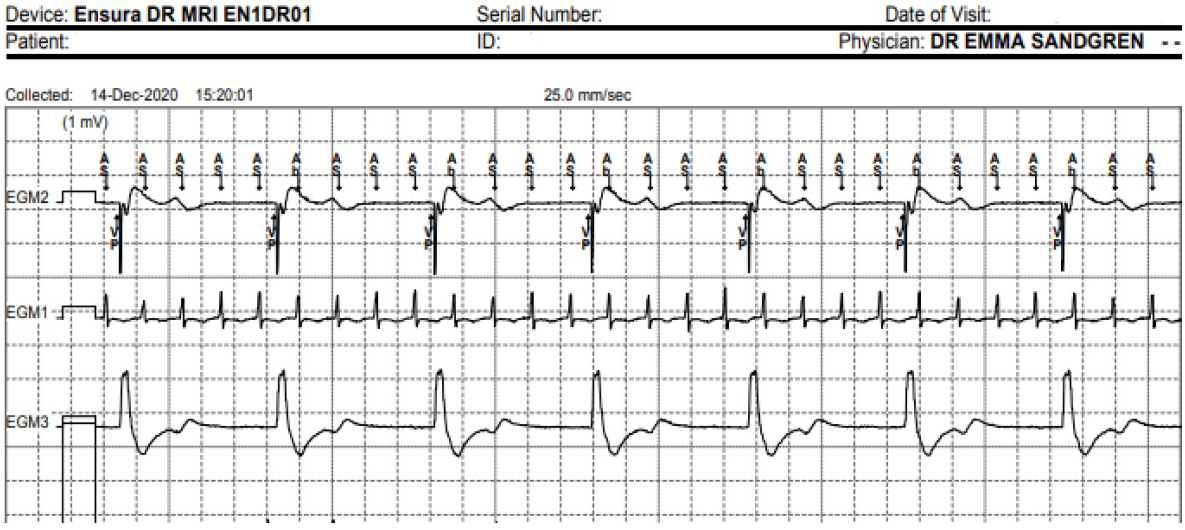

Figure 6. Episode stored as an atrial high-rate episode in a dual-chamber pacemaker. EGM 1 – atrial EGM. EGM 2 – ventricular EGM and marker channel. EGM 3 – far-field EGM. AS, atrial sense; Ab, atrial blanking; EGM, electrogram; VP, ventricular pacing.

3.3.2 Atrial high-rate episodes as a proxy for atrial fibrillation

AF-detection algorithms nevertheless have their limitations, and all cardiac rhythm recordings obtained from implantable devices require adjudication or review to verify diagnostic accuracy. For reliable AF detection by devices, a bipolar atrial lead is required to minimise the risk of inappropriate detection, as unipolar leads are more prone to oversensing issues due to their longer inter-electrode distance (tip to can for unipolar versus tip to ring for bipolar leads). Preferably, high atrial sensitivity is programmed to avoid intermittent atrial undersensing of AF, which can result in inappropriate detection of persistent AF as multiple short episodes. High atrial sensitivity may increase the risk of far-field R-wave oversensing, and this can be avoided by adjusting the post-ventricular atrial blanking interval (44, 45).

The programmed cut-off values for AHRE detection rate and duration are also important, as these influence the number of automatic mode switch episodes. A higher detection rate and duration reduce the risk of false positive recordings. In terms of cut-off values, Pollak et al. reported that only 18% of AHREs with a rate of <250 bpm were true atrial arrhythmias (confirmed by atrial EGMs), compared to 57% of episodes with a rate of >250 bpm ($p< .001$). In the same study, 91% of all EGMs verified as AF episodes had an atrial rate of >250 bpm (46). In term of duration, a good correlation has been reported between AHREs and ECG-documented AF, particularly when the episode lasts over five minutes (46-48). Shorter episodes often represent oversensing due to e.g. far-field R- or T-wave oversensing, or non-sustained atrial premature contractions (48, 49). For example, Pollak et al. reported that 18% of all AHREs shorter than 10 seconds represented true atrial arrhythmias (verified by atrial EGMs), compared to 89% of all episodes with a duration of five minutes or more ($p< .001$) (46). On the other hand, Kaufman et al. showed that the rate of false positive AHRE recordings was 17.3% with a cut-off of six minutes and >190 bpm, while the percentage decreased to 3.3% when the AHRE duration was extended to at least six hours (50). Both studies illustrate the importance of reviewing stored recordings, especially those with a short duration.

A majority of all subclinical AF/AHREs are asymptomatic. A-HIRATE (The Atrial High Rate Episodes) investigators have reported first that, out of all the days where a patient reported symptoms, no subclinical AF/AHRE was recorded on 92.4% of the days. Second, they reported that just one percentage of subclinical AF/AHREs in patients with newly implanted pacemakers and no history of clinical AF were symptomatic (49, 51).

3.3.3 Incidence of device-detected atrial fibrillation

Episodes of device-detected AF are common, and are associated with increased morbidity and mortality in patients with implantable devices. A review by Nielsen et al. reported an annual incidence of 5% after pacemaker implantation, with a mean lifetime cumulative incidence of 30-40%. Important predictors of device-detected AF were tachycardia-bradycardia syndrome, sick sinus syndrome and VVI pacing (52). In two studies, one including patients implanted with a pacemaker due to sick sinus syndrome and one including all patients with pacemakers capable of detecting AF, the incidence of device-detected AF was reported to be 51.3% for 27 months and 55.3% for six months of follow-up respectively (53, 54). Predictors of device-detected AF were older age group, history of clinical AF and larger left atrial volume (54). In turn, the presence of device-detected AF was an independent predictor of total mortality, death or non-fatal stroke and development of clinical AF (53). When patients with a history of clinical AF are excluded, the incidence is reported to be 30-34.7% during 1-2.5 years of follow-up (55-57). The occurrence of device-detected AF was associated with increased risk of ischaemic stroke and systemic embolism (56), and even if the incidence of device-detected AF was independent of the $CHADS_2$ (Congestive heart failure, Hypertension, Age >75 years, Diabetes, Stroke (2 points)) score, a higher $CHADS_2$ score was associated with increased risk of device-detected AF with a duration of more than six hours (55). A summary of the major studies in the field of AHRE incidence are seen in Figure 7 (58).

3.3.4 Device-detected atrial fibrillation and the risk of ischaemic stroke

Several observational and randomised studies have documented that subclinical AF/AHREs detected by implantable devices are associated with increased risk of subsequent ischaemic stroke and systemic embolism. In the MOST (The Mode Selection Trial) trial in 2003, subclinical AF/AHREs with a duration of at least five minutes were associated with a 2.79-fold (95%CI (confidence interval) 1.51-5.15) increased risk of thromboembolic events (53), while the TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) study in 2009 showed a doubled risk of thromboembolic events for an AF burden of more than 5.5 hours on any single day during a 30-day period (59). The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) trial in 2012 reported that subclinical AF/AHREs of at least six minutes' duration were associated with a 2.49-fold (95%CI 1.28-4.85) increased risk of ischaemic stroke or systemic embolism,

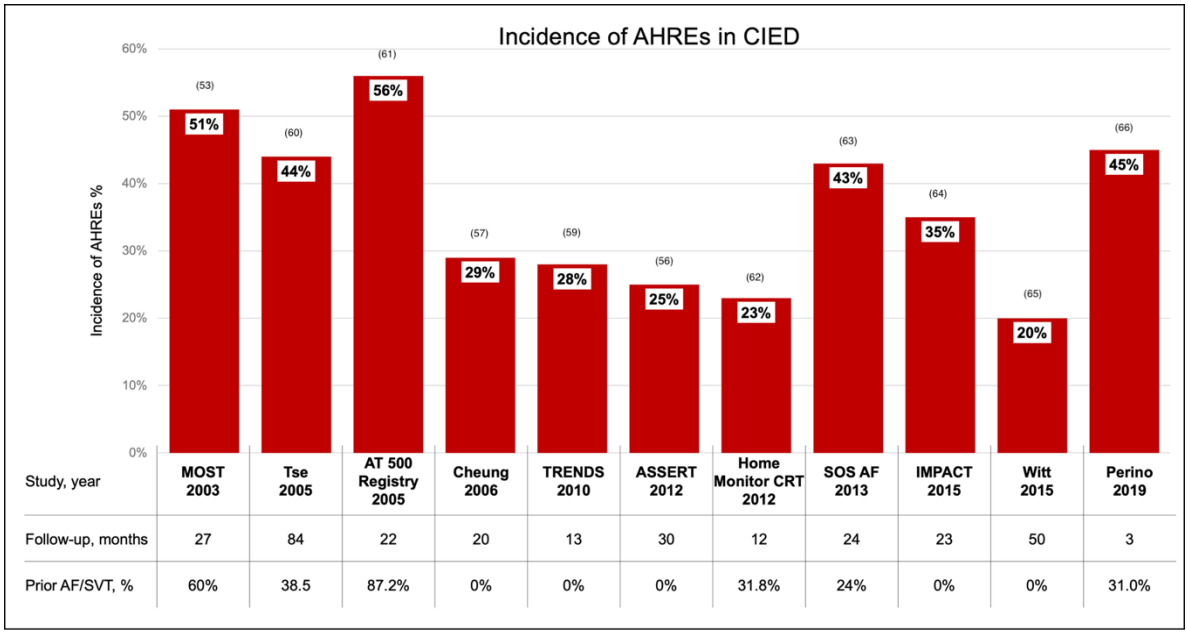

Figure 7. Incidence of device-detected AF, i.e. subclinical AF/AHREs on the basis of data from literature (53, 56, 57, 59-66). AF, atrial fibrillation; AHRE, atrial high-rate episode; CIED, cardiac implantable electronic device; SVT, supraventricular tachycardia. Reprinted with permission from "What do we do about atrial high-rate episodes?" by Boriani G, Vitolo M, Imberti JF, et al., 2020. European Heart Journal Supplements, 22, O42-O52 (https://academic.oup.com/eurheartjsupp/article/22/Supplement_O/O42/6043870). Copyright © 2020 The Authors. Licensed under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

during 2.5 years of follow-up in patients with an age of 65 years or more, in combination with hypertension, but with no history of clinical AF (56). In this vein, the SOS AF (Stroke PreventiOn Strategies based on Atrial Fibrillation information from implanted devices) study in 2014 continued to demonstrate increased risk of ischaemic stroke or transient ischaemic attack with AF burden of at least five minutes respective one hour per day, with hazard ratios of 1.76 and 2.11 respectively (63). Although these studies have different thresholds for subclinical AF/AHRE duration, often arbitrarily chosen, they all have in common that they indicate an increased risk of thromboembolic events for subclinical AF/AHREs, even if the risk seems to be lower than for clinical documented AF (20, 43). Two systematic reviews have been published on this topic, both including some of the above-mentioned studies. The first focused on the importance of subclinical AF/AHRE duration for stroke risk, and two meta-analyses were conducted, the first indicating increased risk of thromboembolic events in patients with a subclinical AF/AHRE burden of over six minutes, compared to those with no subclinical AF/AHREs. The second showed an increased risk of stroke only for those with a subclinical AF/AHRE burden of more than 24 hours (67). The second review aimed to

determine the stroke risk for patients with subclinical AF/AHREs. It showed that subclinical AF/AHREs strongly predict clinical AF with an odds ratio of 5.7, and are associated with a 2.4-fold increased risk of stroke (Figure 8) (68). A recent article summarises the evidence in terms of subclinical AF/AHREs and their impact on the risk of stroke. The article concludes that the presence of subclinical AF/AHREs increases the risk of stroke by 0.8-1.0% per year, and that subclinical AF/AHREs of longer duration (>24 hours) may be associated with higher risk of stroke (69).

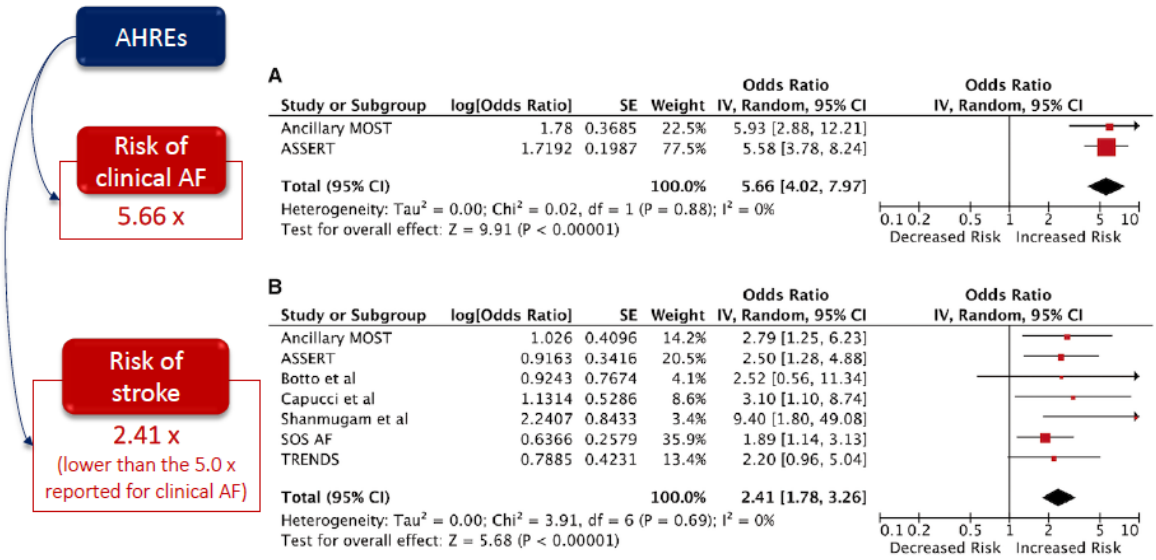

Figure 8. Forest plots demonstrating: A: Association between subclinical AF/AHREs and clinical AF. B: Association between subclinical AF/AHREs and stroke risk. AF, atrial fibrillation; AHRE, atrial high-rate episode; CI, confidence interval; SE, standard error. Reprinted with permission from "Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis" by Mahajan R, Perera T, Elliott AD, et al., 2018. European Heart Journal, 39, 1407-1415. Copyright © 2018 Oxford University Press.

Despite the fact that the occurrence of device-detected AF is associated with increased risk of thromboembolic events, no temporal relationship has been shown between subclinical AF/AHREs and ischaemic stroke. Analyses from the TRENDS trial and ASSERT trial report that 73% and 92% of patients had no AF burden within 30 days prior to an ischaemic stroke or systemic embolism (70, 71). Most likely, the stroke risk depends on an interplay between traditional stroke risk factors and AF burden, and the above-mentioned observation about no temporal relationship, has led to the argument that AF should be seen as a risk marker rather than a direct cause of stroke (Figure 9) (72).

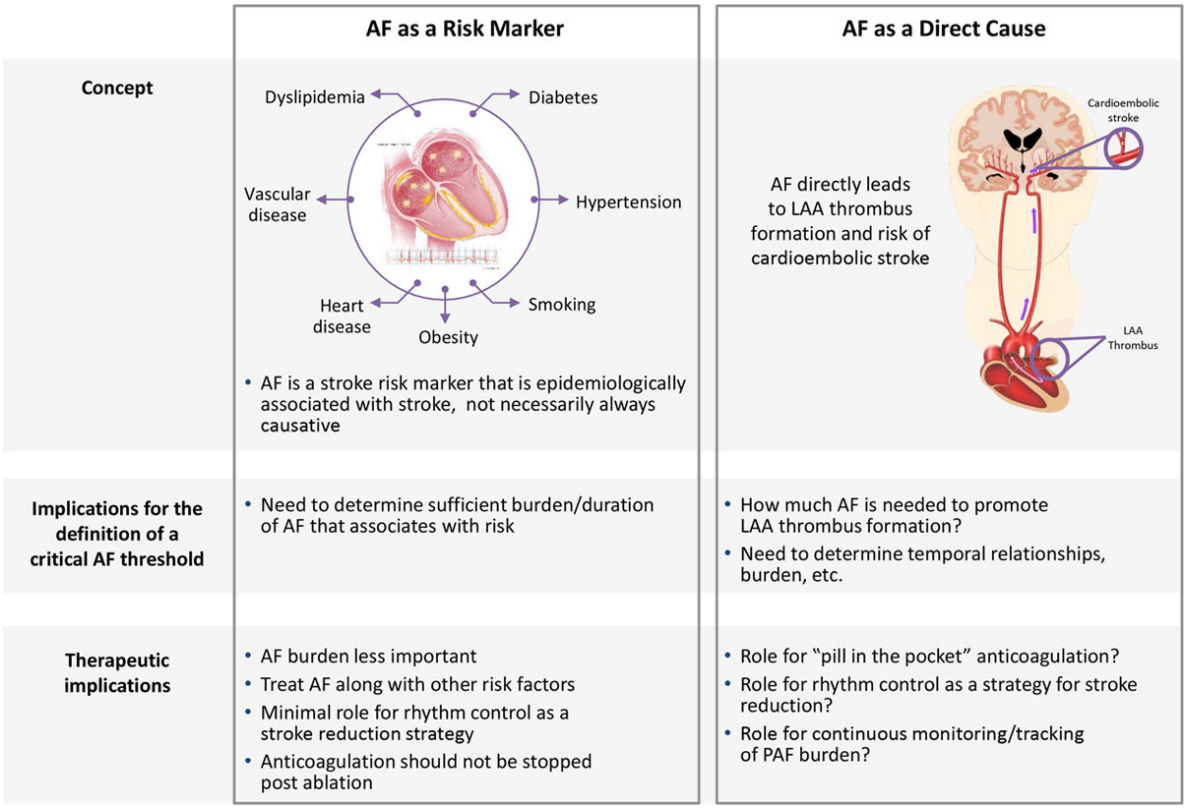

Figure 9. The association between AF and ischaemic stroke conceptualised in two models: AF as a risk marker and AF as the direct cause. AF, atrial fibrillation; LAA, left atrial appendage; PAF, paroxysmal AF. Reprinted with permission from "AHA Scientific Statement: Subclinical and Device-Detected Atrial Fibrillation: Pondering the Knowledge Gap" by Noseworthy PA, Kaufman ES, Chen LY, et al., 2019. Circulation, 140, e944-e963. Copyright © 2019 American Heart Association, Inc.

3.3.5 Device-detected atrial fibrillation and anticoagulation treatment

There is convincing evidence that device-detected AF is associated with increased risk of thromboembolic events, but there is a lack of evidence whether these patients require the same therapeutic action as patients with clinical documented AF (73). As mentioned above, the stroke risk seems to be lower than for clinical AF.

Another knowledge gap involves whether there is a cut-off value for the subclinical AF/AHRE burden (proportion of time spent in subclinical AF/AHREs divided by the total amount of time the patient is monitored (74)) when OAC treatment will give a net benefit, or if there is a continuous increase in thromboembolic risk following increased duration of AF. In a recent analysis from the ASSERT trial, Van Gelder et al. reported that only episodes longer than 24 hours were associated with a threefold increased risk of thromboembolic events (75). On the other hand, there is a growing body of evidence which establishes a link

between short episodes of subclinical AF/AHRE and the risk of ischaemic stroke (43, 76). This could justify OAC for all patients with subclinical AF /AHREs at risk of stroke, with the reservation that no results from randomised clinical trials have yet been published (36).

In the absence of solid evidence from randomised trials, there are rather divergent recommendations from the ESC, the European Heart Rhythm Association (EHRA) and the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) regarding OAC treatment for subclinical AF/AHREs (Figure 10 and Table 1) (20, 41, 77).

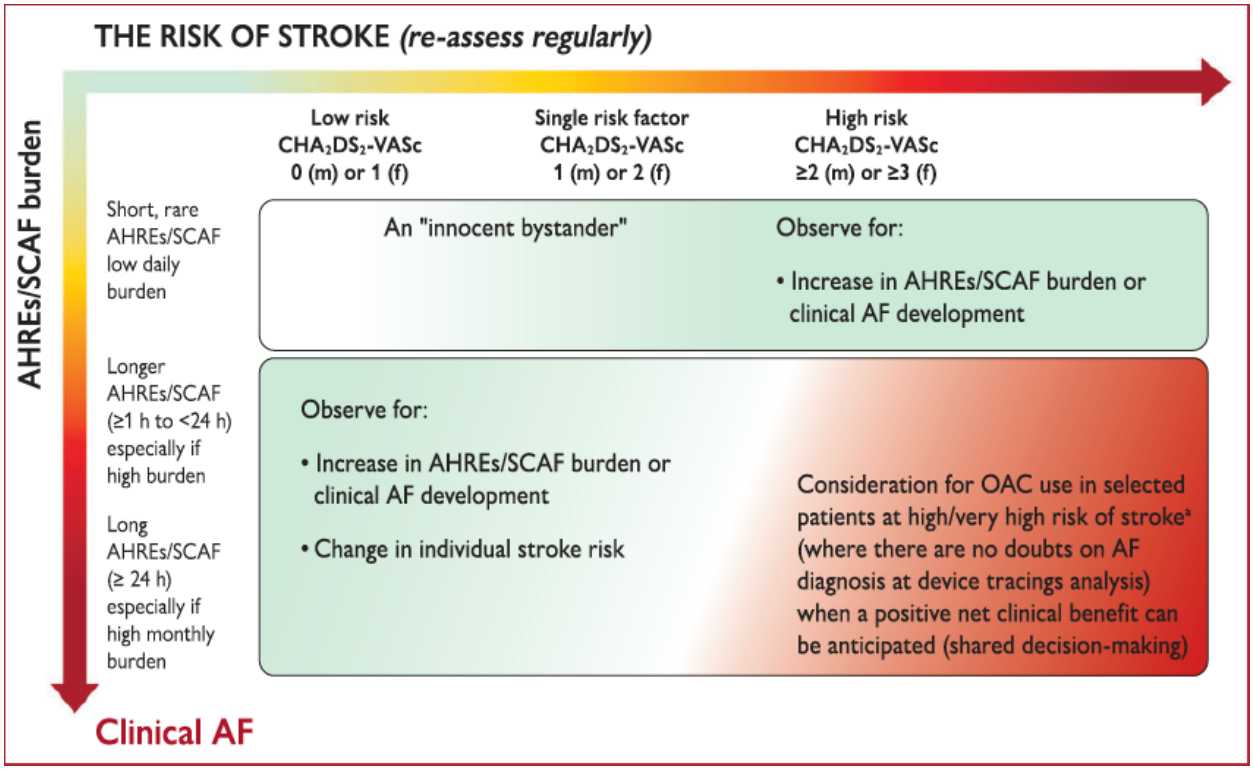

Figure 10. Proposed management of subclinical AF/AHREs. AF, atrial fibrillation; AHRE, atrial high-rate episode; CHA_2DS_2-VASc, (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)); f, female; h, hour; m, male; OAC, oral anticoagulation; SCAF, subclinical AF. Reprinted with permission from "2020 ESC guidelines for the diagnosis and management of atrial fibrillation" developed in collaboration with the European Association of Cardio-Thoracic Surgery" by Hindricks G, Potpara T, Dagres N, et al., 2020. European Heart Journal, 00, 1-125. Copyright © 2020 Oxford University Press.

Table 1. Recommendations regarding OAC treatment in patients with subclinical AF/AHREs.

ESC (20)	Implantable devices should be interrogated on a regular basis for AHREs (class I). Patients with subclinical AF/AHREs should undergo: • Complete cardiovascular evaluation with ECG recording, and thromboembolic risk assessment using the CHA_2DS_2-VASc score (class I). • Intense follow-up to detect clinical AF and to reassess subclinical AF/AHRE burden (class I). Considered OAC treatment in patients with long episodes of subclinical AF/AHRE (i.e. ≥24 hours) at high risk of stroke (CHA_2DS_2-VASc ≥2 in men and ≥3 in women), provided that AF is verified by a simultaneous EGM recording.
EHRA (41)	EGMs should be reviewed when available. Subclinical AF/AHRE duration over 5.5 hours can justify OAC treatment when CHA_2DS_2-VASc criteria are fulfilled. A shorter subclinical AF/AHRE duration can merit OAC when multiple risk factors are present. In patients with only a five-minute episode of subclinical AF/AHRE, observation of the subclinical AF/AHRE burden is recommended before OAC is started.
AHA/ACC/HRS (77)	The presence of subclinical AF/AHREs prompts further evaluation for clinically relevant AF (class I).

ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AHRE, atrial high-rate episode; CHA_2DS_2-VASc, (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)); ECG, electrocardiogram; EGM, electrogram; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; OAC, oral anticoagulation.

Three ongoing randomised trials ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation, NCT01938248), NOAH-AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes, NCT02618577) and SILENT (Subclinical Atrial Fibrillation and Stroke Prevention Trial, NCT02004509) will improve knowledge on how to manage OAC in patients with device-detected AF (Table 2) (78-80).

Table 2. Ongoing trials evaluating OAC treatment in patients with subclinical AF/AHREs.

	Inclusion criteria	Treatment arms	Primary outcome	Compl.
ARTESiA (78)	Patients ≥55 years with AHREs (>6 minutes, but <24 hours duration) and additional stroke-risk factors.	Apixaban, 5 mg twice daily (2.5 mg twice daily when appropriate) or aspirin, 81 mg daily.	Composite, consisting of ischaemic stroke and systemic embolism.	April 2021.
NOAH-AFNET 6 (79)	Patients ≥65 years with AHREs (>6 minutes duration) detected at least two months after implantation.	Endoxaban 60 mg once a day (30 mg once a day when appropriate), or 100 mg acetylsalicylic acid plus placebo matching endoxaban or placebo matching acetylsalicylic acid plus placebo matching endoxaban.	Time to first occurrence of stroke, systemic embolism or cardiovascular death with a time frame of 28 months.	March 2022.
SILENT (80)	Patients aged ≥18 years with $CHADS_2$ score ≥2 and sinus rhythm.	Experimental arm: collection of device data every two months and OAC if AHREs >5.5 hours per day. Active comparator arm: no device data are analysed. Clinical AF are treated at the physician's discretion.	Occurrence of stroke or systemic embolism.	October 2020.

AF, atrial fibrillation; AHRE, atrial high-rate episode; $CHADS_2$, Congestive heart failure, Hypertension, Age >75 years, Diabetes, Stroke (2 points); compl., completion; OAC, oral anticoagulation.

3.3.6 Remote monitoring

Remote monitoring of implantable devices is safe and effective for early detection of atrial arrhythmias, particularly AF (81-83), but it is not clear whether it improves clinical outcome. The IMPACT (Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk) study, designed to investigate initiation and termination of OAC treatment through remote monitoring of AF, failed to show a reduction in the primary outcomes: stroke and bleeding incidence (64). The neutral outcome may have been affected by the low number of newly diagnosed AF cases, which in turn may be due to the low mean age of the study population. Furthermore, OAC treatment was underused, and most importantly there were low number of endpoints due to study design. Therefore, even if the usefulness of remote monitoring for early detection of AF is documented, it remains to be demonstrated whether initiating of OAC treatment for subclinical AF/AHREs guided by remote monitoring improves clinical outcomes and reduces the risk of stroke and systemic embolism. In this context, it should also be mentioned that remote monitoring is associated with costs for device and sometimes with increased workload.

3.4 THE IMPLANTABLE LOOP RECORDER

3.4.1 History and basic concepts of the implantable loop recorder

The ILR was developed in the early 1990s (84, 85), and is a small device, capable of detecting and storing episodes of arrhythmia. It is usually implanted subcutaneously in the left parasternal region under local anaesthetic. Initially, cutaneous mapping techniques were used to help position the device (86), but fairly soon anatomical approaches were developed, and superseded the time-consuming mapping methods (87, 88). This was followed by the launch of injectable devices in 2014, which further simplified the implantation procedure (88).

The ILR has a pair of built-in sensing leads located on the shell of the device, to allow a single-lead bipolar ECG to be recorded. The device operates in “loops”, which means that it continuously monitors ECG signals in time windows. In older devices, the patient or someone else had to activate the memory or “freeze the loop”, but this shortcoming was resolved with automatic detection in newer models. The device stores ECG data automatically if predefined criteria for brady- or tachyarrhythmia are met, or in response to patient activation. Newer devices also include specific algorithms for atrial tachycardia and AF detection. Stored episodes can be downloaded via radio frequency with a special programmer. Battery longevity is 36-48 months, depending on the device model and the manufacturer (89, 90).

3.4.2 Limitations of implantable loop recorder diagnostics

One of the drawbacks of single-lead ECG is its inability to obtain a clean and stable signal, due to a susceptibility to interference. Oversensing episodes due to artefacts are common, as well as undersensing episodes due to decreased signal amplitude or baseline drift. In turn, this leads to non-diagnostic interrogations, which limit the clinical value (91, 92). To minimise the influence of myopotentials, the electrodes should be introduced facing the skin (86). The signal quality can also be hampered by the subcutaneous position, risking migration of the device, which can cause reduced signal amplitudes over time (85). To avoid this problem, it is important to choose an appropriate implantation site and create a tight subcutaneous pocket. This is facilitated by the new injectable devices (93).

Another possible drawback of ILR monitoring is its limited memory capacity, leading to a risk of memory saturation as a result of frequent arrhythmia episodes and/or episodes with inappropriate under- or oversensing, meaning that data are lost. This limitation can be resolved with regular in-office visits, or by offering the patient remote monitoring. Remote monitoring of ILRs has the potential to avoid loss of data, which could be overwritten, and to facilitate earlier diagnosis of asymptomatic events (94). It also saves time and effort for the patient, who does not need to visit the hospital so often. Although remote monitoring has the above-mentioned advantages, it risks introducing a need for data to be reviewed more often.

3.5 SYNCOPE

3.5.1 Definition and prevalence of syncope

Syncope is a clinical syndrome characterised by transient and self-limited loss of consciousness (95) and postural tone due to cerebral hypoperfusion, with complete recovery.

Syncope is a common reason for visits to emergency departments, and its incidence and prevalence are age-dependent. Current estimates show that syncope accounts for 3% of all visits to emergency departments, and 6% of all hospitalisations (96-98). The prevalence is high, with a lifetime experience of 42% in a general population. It increases with age, showing an annual incidence approaching 2% in those over 80 years of age (99).

3.5.2 Pathophysiology and classification of syncope

The pathophysiological basis for classifying syncope centres on a fall in systemic blood pressure with a decrease in global cerebral blood flow, and 6-8 seconds of cessation of cerebral blood flow are sufficient to cause syncope. Systemic blood flow is the product of total peripheral resistance and cardiac output, and a fall in either can cause syncope. Usually both mechanisms act together to a varying degree to cause syncope.

Syncope can be classified into three main groups (Figure 11) (100):

- *Reflex (neurally mediated) syncope* – including vasovagal-, situational-, carotid sinus syndrome and non-classic forms of syncope. The common denominator in this group is the fact that the autonomic reflexes controlling circulation are intact but hyperreactive, and respond inappropriately to a stimulus, involving sympathetic withdrawal or unopposed vagal tone. This causes an inadequate decrease in peripheral resistance or heart rate.
- *Orthostatic syncope* – syncope due to orthostatic hypotension is defined as an abnormal decrease in systolic blood pressure upon standing, as opposed to reflex syncope, which is caused by impaired autonomic function, i.e. insufficient response from the autonomic reflexes. This group includes volume depletion, drug-induced orthostatic hypotension and primary or secondary autonomic failure.
- *Cardiac (cardiovascular) syncope* – syncope due to arrhythmias or structural diseases. Structural diseases can be cardiac, such as acute myocardial ischaemia, valve diseases, hypertrophic cardiomyopathy and pericardial diseases. Alternatively, they can be extracardiac diseases such as pulmonary embolism and acute aortic dissection. Arrhythmias include brady- and tachyarrhythmias, as well as drug-induced brady- and tachyarrhythmias.

3.5.3 Prevalence and prognosis for different types of syncope

Reflex syncope accounts for almost two-thirds of all syncope episodes, whereas arrhythmic and structural cardiovascular aetiologies account for the minority (101). Orthostatic syncope is rare before the age of 40 years (100), and the prevalence of bradyarrhythmia and tachyarrhythmia increases with age (102).

The prognosis is related both to underlying comorbidities and to aetiology. Patients with cardiac syncope or unknown aetiology have the highest incidence of recurrence, and patients with recurrence in turn, are at increased risk of subsequent death and major adverse cardiovascular events (103). Reflex syncope has a benign course, while cardiac syncope has a

significantly higher mortality than syncope with non-cardiac causes, and annual mortality is reported to reach between 18% and 33% (104).

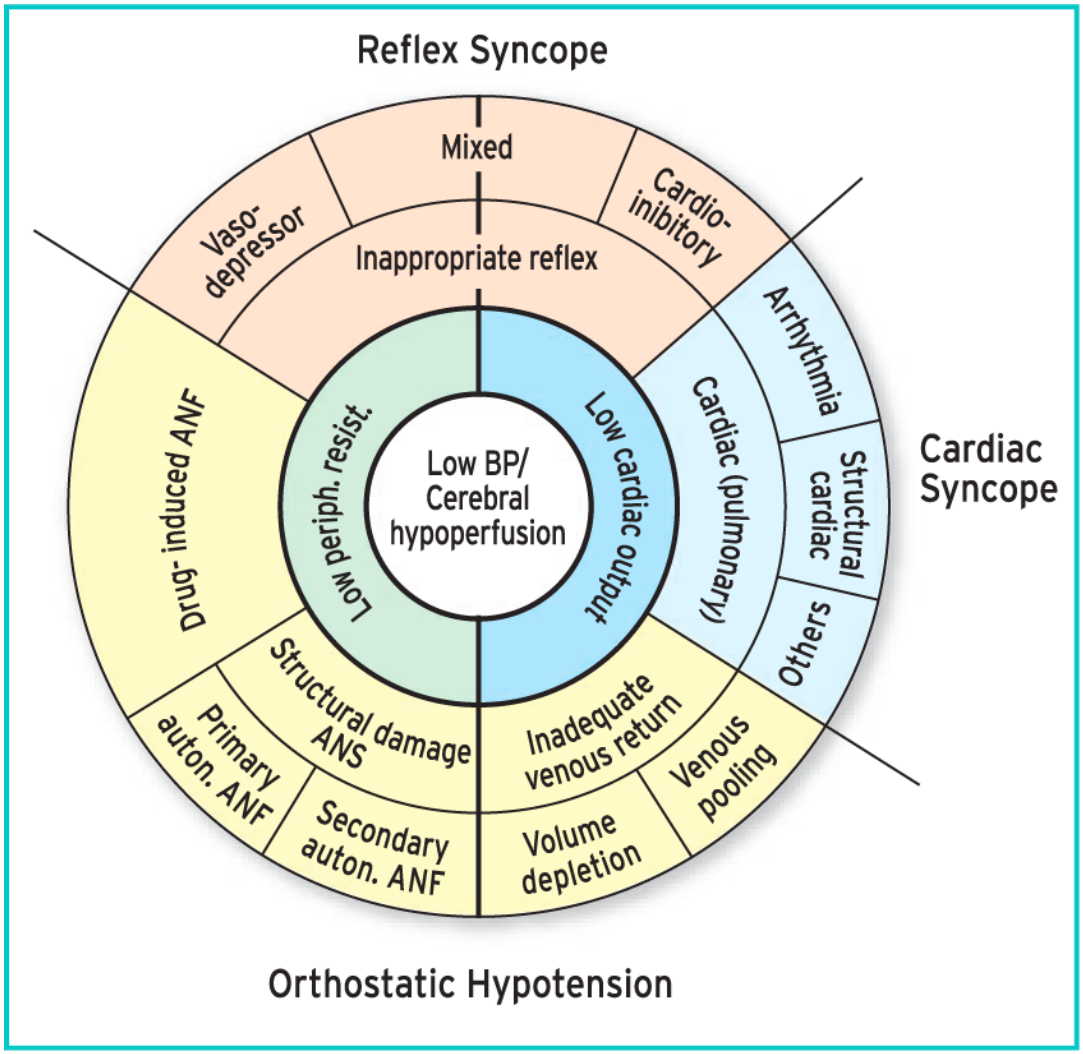

Figure 11. The classification of syncope based on underlying pathophysiology. ANF, autonomic failure; ANS, autonomic nervous system; BP, blood pressure. Reprinted with permission from "2018 ESC guidelines for the diagnosis and management of syncope" by Brignole M, Moya A, de Lange F, et al., 2018. European Heart Journal, 39, 1883-1948. Copyright © 2018, Oxford University Press.

3.6 THE IMPLANTABLE LOOP RECORDER IN EVALUATING SYNCOPE

3.6.1 Initial evaluation and risk stratification of syncope patients

Syncope is often a diagnostic challenge, due to its infrequent and unpredictable nature. An initial diagnostic workup is imperative, consisting of medical history, ECG, and physical examination including orthostatic blood pressure measurements. This is able to explain the cause of syncope in 23-50% of patients (105, 106).

If the cause of syncope remains uncertain after the initial evaluation, the next step involves risk stratification to identify patients with high-risk features which indicate increased risk of major cardiovascular events or sudden cardiac death. Examples of high-risk features include a syncope event associated with chest discomfort or palpitations, syncope during exertion or supine, and abnormal physical examination or ECG. Additional high-risk features include known structural heart diseases and a family history of sudden cardiac death (100). The presence of high-risk features informs decisions about whether the patient can be discharged and seen in an out-patient clinic, or whether admission for monitoring and diagnosis is warranted.

3.6.2 The role of non-invasive electrocardiogram monitoring in syncope

The gold standard involves recording cardiovascular parameters during a spontaneous event, e.g. symptom versus ECG correlation (107), and the likelihood of establishing a symptom-ECG correlation increases with longer monitoring times. There are several different ambulatory modalities to enable long-term ECG monitoring. The most common initial evaluation is short-term telemetry or Holter monitoring for 24-48 hours, but the overall diagnostic yield of Holter monitoring is low. In patients with syncope or presyncope, Linzer et al. reported a 4% correlation between ECG and symptoms with Holter monitoring for more than 12 hours (108). Another option for non-invasive long-term ECG monitoring is an external loop recorder which continuously monitors and stores ECG data with a 4 to18-minute memory buffer. When symptoms appear, the patient activates the device, which stores the previous 3-14 minutes and the following 1-4 minutes of recorded information (109). The device can also store recordings automatically according to specific predefined criteria for brady- or tachyarrhythmia. The ECG recordings can subsequently be uploaded and analysed. This system allows monitoring time to extend to months, but long-term compliance is challenging because of skin-related problems. The diagnostic yield for external loop recorders in syncope patients ranged from 24-36% in two studies with a monitoring time of one month (110, 111).

3.6.3 Efficacy and diagnostic yield of the implantable loop recorder in syncope patients

The ILR permits prolonged ECG monitoring without external electrodes, and is an appealing alternative for long-term ECG monitoring in patients with infrequent recurrent syncope. A considerable number of studies have investigated and documented the clinical use of an ILR in syncope patients (Table 3) (112-118).

The driving factor in terms of the clinical utility and high diagnostic yield reported for the ILR in patients with unexplained syncope involves a combination of the elusive nature of syncope with infrequent and unpredictable recurrences, and the opportunity for prolonged monitoring with an ILR. Furukawa et al. have reported the importance of the duration of monitoring, and the fact that the diagnostic yield increases with increased monitoring time. They estimated cumulative diagnostic rates of 30% ,43% ,52% and 80% after one, two, three and four years of monitoring time respectively (119).

The ILR has also been shown to be more cost-effective than conventional testing in evaluating patients with unexplained syncope (120, 121).

Table 3. Studies on the clinical use of an ILR in patients with syncope.

	Krahn et al. (112)	Krahn et al. (113)	ISSUE (114)	ISSUE (114)	ISSUE (115)	ISSUE (116)	PICTURE (117)	PICTURE (118)
n	16	60	82	29	52	35	570	514
Men	12	33	45	11	43	31	264	241
Mean age	57±19	66±14	63±17	64±15	71±8	66±13	61±17	61±18
Study design	PC.	Randomised 1:1.	PC.	PC.	PC.	PC.	PC.	“initial” vs “full” eval.
Study population	Concomitant HD in 8.	SHD in 23. Excl. if LVEF <35%.	No SHD, TTT-neg.	No SHD, TTT-pos.	BBB and neg. EPS.	SHD and neg. EPS.	Unexplained syncope.	Unexplained syncope.
Evaluation/ Intervention	48h AECG, TTE, TTT and EPS.	Before randomisation:24h AECG, TTE and PBPT. Conventional:2-4 weeks ELR, TTT and EPS. Intervention: ILR.	History, 12-lead ECG, CSM, TTE, 24h AECG.	History, 12-lead ECG, CSM, TTE, 24h AECG.	History, 12-lead ECG, CSM, TTE, 24h AECG, EPS.	History, 12-lead ECG, CSM, TTE, 24h AECG, EPS.	Pre-implant tests med. 13 (IQR 9-20). Most frequent 12-lead ECG, AECG, TTE, exercise test and PBPT.	No definition of "initial" or "full eval". Pre-implant tests med. 8 (IQR 6-14) vs 14 (IQR 10-21), p< .0001.

Follow-up	Mean 4.4±4.2 months.	12 months.	Mean 9±5 months.	Mean 10±5 months.	Minimum 3 months.	Mean 16±11 months.	At least 12 months.	12 months.
Outcome syncope	Syncope in 94% (15/16).	Diagnosis in 52% (14/27) in ILR group vs 20% (6/30) in conventional group, p= .012.	Syncope 29% (24/82).	Syncope 28% (8/29).	Syncope 37% (19/52).	Syncope 17% (6/35). Presyncope 37% (13/35).	Syncope 38% (218/570), diagnosis in 78% (170/218).	Syncope 32% (41/128) vs 36% (139/386). ILR-guided diagnosis 52% vs 75%.
Outcome (number with arrhythmic syncope)	9 patients.	11 patients in ILR group. 4 patients in conventional group.	15 patients.	6 patients.	17 patients.	5 patients with syncope. 4 patients with presyncope.	128 patients.	90% vs 79%.

AECG, ambulatory ECG; BBB, bundle branch block; CSM, carotid sinus massage; ECG, electrocardiogram; ELR, external loop recorder; EPS, electrophysiology study; eval., evaluation; excl., exclusion; h, hour; HD, heart disease; ILR, implantable loop recorder; IQ, interquartile range; ISSUE-1, The International Study on Syncope of Uncertain Etiology; LVEF, left ventricular ejection fraction; med., median; neg., negative; PC, prospective cohort study; PBPT, postural blood pressure test; PICTURE, Place of Reveal In the Care pathway and Treatment of patients with Unexplained Recurrent Syncope; pos., positive; SHD, structural heart disease; TTE, transthoracic echocardiography; TTT, tilt-table test; vs, versus.

3.6.4 Current recommendations for the use of an implantable loop recorder in syncope

With the publication of the 2009 ESC Syncope guidelines (122), the ILR gained a more prominent position in terms of evaluating syncope, and in the 2018 edition of the ESC Syncope guidelines, an ILR is recommended for evaluating syncope in the early phase in patients who are not high risk (class I), or after comprehensive workup in high-risk patients (class I). Furthermore, an ILR should be considered in patients with suspected or confirmed reflex syncope, who are presenting with frequent or severe syncopal episodes (class IIa). It can also be considered in patients where epilepsy is suspected but treatment has proved ineffective (class IIb), as well as in patients with unexplained falls (class IIb) (100). In the ACC/AHA/HRS 2017 Syncope guidelines, an ILR is recommended (class IIa) in patients with recurrent, unexplained syncope with a suspected arrhythmic cause, after a non-diagnostic initial workup, regardless of the presence of structural heart disease (123).

3.6.5 Baseline 12-lead electrocardiogram

Few studies have investigated the relationship between baseline 12-lead ECG and the syncope mechanism. The above-mentioned ISSUE-1 (International Study on Syncope of Uncertain Etiology) study reported an incidence of 32% (22/52 had syncope recurrence, 17 due to complete heart block) of syncope due to complete heart block in patients with bundle branch block (113). A study conducted by Kadmon et al. found a positive predictive value (PPV) of 56.3% (9/16) for conduction abnormalities (including long PR interval and bundle branch block) in predicting a diagnosis of bradyarrhythmia (124).

Two studies have examined the use of empiric permanent pacing in patients with bifascicular block and syncope. In the SPRITELY trial (Syncope: Pacing or Recording In ThE Later Years, NCT01423994), a strategy with empiric permanent pacing was compared to implanting an ILR in older patients. The study design was published in 2012 (125) and the study completion date was 1st November 2017, but the results have not yet been published. However, preliminary results have been presented, and with a strategy involving direct permeant pacing they reveal a reduced rate of major adverse events, but the same rate of recurrence of syncope (126). The second study was a prospective cohort study, and compared empiric permanent pacing to a treatment strategy based on the results of an electrophysiology study. The researchers found a high incidence of advanced atrioventricular (AV) block during follow-up. They also found no additional benefit for treatment based on an electrophysiology study compared with a strategy involving direct permeant pacing (127).

Both European and American Pacing guidelines stress the importance of using available diagnostic tests, e.g. external and internal loop recorders, to reach a diagnosis before implanting a pacemaker (128, 129). One reason for this recommendation is that a significant proportion (38%) of patients with bundle branch block and unexplained syncope have syncope spells for reasons other than complete heart block (130), e.g. ventricular arrythmias or non-arrhythmic causes. Another reason is that, compared to inactive cardiac pacing, active pacing mainly improves symptoms. Only a very small proportion (14%) of patients benefit from pacing because of actual bradyarrhythmia (131). If positive electrophysiology study permanent pacing is indicated, but if the electrophysiology study is inconclusive, an ILR is preferred, and permanent pacing has a class II indication (128, 129). However, the ESC 2013 Cardiac pacing guidelines leave an opening for the physician to carry out an individual cost-benefit evaluation for selected patients, especially for older patients with recurrent unpredictable syncope episodes without prodromes (128).

3.7 POSTOPERATIVE ATRIAL FIBRILLATION

3.7.1 Incidence and pathophysiology of postoperative atrial fibrillation

New-onset postoperative AF is common, and develops in about 3% of unselected patients undergoing non-cardiac surgery (132). It affects approximately one-third after cardiac surgery (133-137). Typically, it occurs on the second or third postoperative day, and converts spontaneously to sinus rhythm within 24-48 hours (133).

The pathophysiology of postoperative AF is probably multifactorial, with contributing factors such as activation of the sympathetic system, hypovolemia, anaemia, trauma and interoperative hypotension. Additional factors are metabolic imbalance (e.g. electrolyte disturbances or hypoglycaemia), hypoxia and hypervolemia (138). Furthermore, systemic inflammation can play a role (139), and for cardiac surgery significant lesions in the coronary arteries supplying right and left atria are an independent predictor (i.e. atrial ischaemia), as well as direct injury to the atrial myocardium (133).

Risk factors for postoperative AF include advanced age, male gender, history of congestive heart failure, increased extent of operation and elevated B-type natriuretic peptide (BNP), obesity, metabolic syndrome, chronic obstructive pulmonary disease, history of AF, valvular surgery and the withdrawal of beta blockers or angiotensin-converting enzyme inhibitors postoperatively (135, 140-142).

3.7.2 Short and long-term risks of postoperative atrial fibrillation

In both a short and long-term perspective, postoperative AF is associated with increased risk of complications. Short-term complications include higher risk of ischaemic stroke and myocardial infarction, longer length of hospital stay and increased in-hospital mortality (134, 143). In the long term, postoperative AF is associated with increased risk of future AF, ischaemic stroke and cardiovascular mortality (144-150). According to a meta-analysis including six studies, the incidence rate of AF recurrence after discharge with non-invasive monitoring in the first month was 28.3% (95%CI 23.0-33.6%). In addition, two studies with implantable devices report an AF recurrence rate of 60.9% and 100% respectively (151-153). A study by Ahlsson et al. showed an eightfold increased risk of developing AF (25.4% versus 3.6%) and a doubled risk of long-term cardiovascular mortality in patients with postoperative AF compared to those who remained in sinus rhythm after aortocoronary bypass surgery (146). In terms of postoperative AF after non-cardiac surgery, a recent meta-analysis including 28 studies showed a threefold increased risk of stroke and all-cause mortality, and a fourfold increased risk of myocardial infarction (154).

3.7.3 Prevention of postoperative atrial fibrillation

Beta blockers have been shown to reduce the incidence of postoperative AF (155, 156), as well as amiodarone (155, 157). In the AHA/ACC/HRS 2014 AF guidelines, peroperative administration of amiodarone to reduce the risk of postoperative AF in high-risk patients has a class IIa recommendation (26). The American Association for Thoracic Surgery (AATS) published specific guidelines for the prevention and management for postoperative AF in 2014, and their recommendations involve continuing (i.e. not withdrawing) beta blockers in all patients (class I), as well as considering amiodarone administration in intermediate to high-risk patients (class IIa) (158). The ESC 2020 AF guidelines give perioperative administration of beta blockers or amiodarone a class I indication (20). No other drugs have been shown to reduce the incidence of postoperative AF.

3.7.4 Anticoagulation treatment for postoperative atrial fibrillation

It is essential to weigh the benefits of OAC treatment for stroke prevention against the risks of postoperative bleeding. Current recommendations, from European and American societies, regarding OAC treatment in patients with postoperative AF are delineated in Table 4 (20, 26, 158).

Table 4. Recommendations regarding OAC treatment in patients with postoperative AF.

AHA/ACC/HRS (26)	Reasonable to start OAC treatment in accordance with the recommendations for non-surgical patients (class IIa).
AATS (158)	AF ≥48 hours: reasonable to start OAC treatment in accordance with the recommendations for non-surgical patients, weighing the prevention of stroke against the risk of bleeding (class I). AF <48 hours: OAC treatment should be considered based on the CHA_2DS_2-VASc score, but also taking into consideration that the presence of impaired renal function weighs in favour of OAC treatment (class I). Minimum duration of OAC treatment is four weeks after restoration of sinus rhythm (class I). More prolonged OAC treatment can be beneficial in the presence of stroke-risk factors according to the CHA_2DS_2-VASc score, or if the patient has had a previous stroke (class IIa).
ESC (20)	Long-term OAC treatment should be considered in the presence of stroke-risk factors, taking individual stroke and bleeding risk into consideration (class IIb).

AATS, American Association for Thoracic Surgery; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; CHA_2DS_2-VASc, (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)); ESC, European Society of Cardiology; HRS, Heart Rhythm Society; OAC, oral anticoagulation.

3.8 THE IMPLANTABLE LOOP RECORDER FOR DETECTING ATRIAL FIBRILLATION

3.8.1 Performance of the implantable loop recorder in detecting atrial fibrillation

Modern ILRs are equipped with an automatic algorithm for AF detection, and all manufacturers base the algorithm on the identification of QRS signals and analyses of the RR interval stability. If a predefined pattern of variability is identified, the heart rate is classified as AF (91). These algorithms have been validated using continuous Holter monitoring as the gold standard. The sensitivity for detecting AF ranged from 96-100%, while the specificity ranged from 67-86%. When all AF episodes were considered, the sensitivity was somewhat lower, at 88-95% (42, 159, 160). In terms of AF detection rate, an ILR is superior to all other modalities (161, 162), and in the LOOP (Atrial Fibrillation Detected by Continuous ECG Monitoring, NCT02036450) study the detection rate was highest in the elderly, males and those who had high N-terminal-prohormone BNP levels (162).

Manufacturers are constantly trying to improve the performance of their AF-detection algorithms. One vendor has further developed its AF-detection algorithm by checking the presence of P-waves once the RR variability exceeds the threshold for AF detection (163, 164). Recently, this manufacturer further refined the P-sense algorithm, reaching a sensitivity of 100% for AF episodes ≥2 minutes in duration with a PPV of 97% (165). Another vendor has enhanced its detection by redesigning its device to enable a very long sensing vector, resulting in a sensitivity of 97% for AF episodes ≥6 minutes' duration and a PPV of 72.5% (166).

One major advantage of an ILR, worth noting, is its ability to quantify the AF burden.

4 AIMS

4.1 OVERALL AIM

Cardiac implantable electronic devices (CIEDs) enable continuous monitoring of the heart rhythm, and as the duration of cardiac monitoring is of the utmost importance for the detection rate of arrhythmias, CIEDs constitute a unique opportunity for arrhythmia detection. Nevertheless, it is often difficult to know how to manage all the information from device diagnostics, and how it should influence clinical decisions.

This thesis aims to highlight different aspects of arrhythmias diagnosed with CIEDs from both a diagnostic and therapeutic point of view, with an emphasis on diagnosis of syncope and detection of subclinical AF/AHREs, aimed at preventing strokes.

4.2 STUDY I

To describe the incidence of subclinical AF/AHREs in a population of patients implanted with a dual-chamber pacemaker, as well as to describe their OAC treatment and incidence of ischaemic stroke and vascular dementia.

4.3 STUDY II

To evaluate the role of baseline 12-lead ECG in predicting the syncope mechanism during continuous ECG monitoring with an ILR in a consecutive group of patients with unexplained syncope, selected to receive an ILR after the initial syncope investigation was non-diagnostic.

4.4 STUDY III

To study the role of age and gender in the evaluation before implanting an ILR, and in the subsequent diagnostic yield of the ILR, in a population of patients selected to receive an ILR after the initial investigation had failed to disclose the syncope mechanism.

4.5 STUDY IV

The primary aim was to test the hypothesis that patients with incident AF during inpatient care after coronary artery bypass graft (CABG) surgery often relapse into AF within a year, with little chance of clinical detection. The secondary aim was to calculate the AF burden.

5 PATIENTS AND METHODS

5.1 STUDY I

This was an observational cohort study including consecutive patients implanted with a dual-chamber pacemaker or cardiac resynchronisation therapy pacemaker, during the period 2010-2014 in Halland County in Sweden. The device indications were sinus node disease or AV block/bundle branch block. For the study flowchart, see Figure 12.

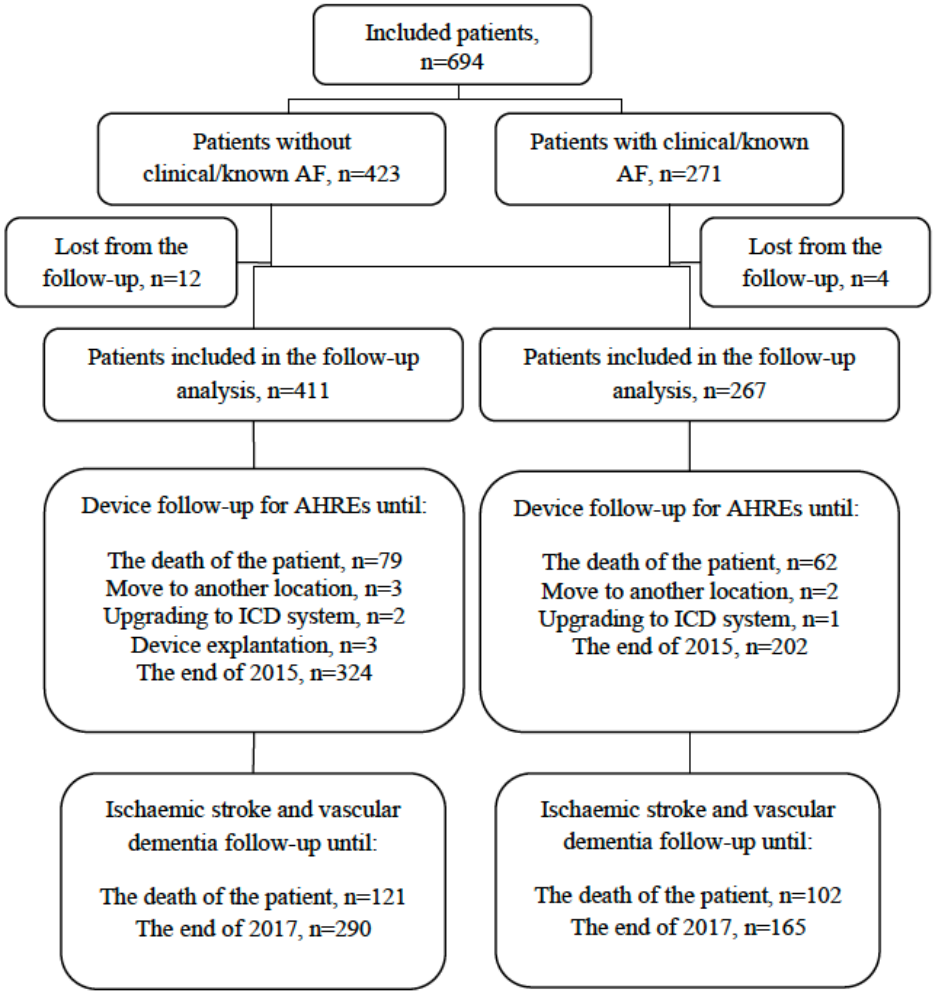

Figure 12. Flowchart of the study design for study I. AF, atrial fibrillation; AHRE, atrial high-rate episode; ICD, implantable cardioverter defibrillator. Reprinted with permission from "Stroke incidence and anticoagulation treatment in patients with pacemaker-detected silent atrial fibrillation" by Sandgren E, Rorsman C, Edvardsson N, et al., 2018. PLoS One, 13, e020366 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6136732). Copyright © 2018, The Authors. Licensed under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Medical records were used to retrieve clinical data, and protocols from the pacemaker interrogations were used to retrieve information about the occurrence of subclinical AF/AHREs. AF was confirmed when an episode of at least five minutes was captured by an AF-detection algorithm, or captured as an AHRE supported by a stored rhythm strip available for adjudication. AHREs which were not supported by a rhythm strip were simply called AHREs. For patients with no clinical/known AF, subsequent initiation of OAC treatment was noted, and for patients with clinical/known AF, ongoing OAC treatment and any changes in this treatment were noted. Follow-up lasted until the end of 2015 for the detection of subclinical AF/AHREs and until the end of 2017 for the incidence of ischaemic stroke and vascular dementia. Information about the incidence of ischaemic stroke and vascular dementia was obtained from the Regional Patient Register.

5.2 STUDIES II AND III

These two observational studies are based on the same patient cohort, including consecutive patients with unexplained syncope during the period 2007-2016, who were selected to receive an ILR after an initial non-diagnostic evaluation at one of two hospitals in Halland County in Sweden. Patients did not proceed to ILR implantation if there was a positive diagnostic evaluation, and therefore our patient population comprised a selected portion of the syncope population. Flowcharts for studies II and III are shown in Figures 13 and 14 respectively.

Clinical data and baseline 12-lead ECG were retrieved through medical records. Baseline 12-lead ECG was adjudicated (ES, NE, JE) and classified according to recommendations for ECG findings suggestive of arrhythmic syncope in the ESC 2018 Syncope guidelines (100). If disagreement, a second assessment was performed to reach consensus (was required for five ECGs). Bifascicular block included findings of left bundle branch block (LBBB) or right bundle branch block (RBBB) plus left anterior hemiblock (LAH) or left posterior hemiblock (LPH). AV block I was defined as PR interval ≥200 milliseconds.

The ILRs automatically stored the following events: pauses >3 seconds, bradycardia <30 bpm during at least four beats, and tachycardia >176 bpm during at least 16 beats. An AF-detection algorithm was activated if available.

To confirm the underlying syncope mechanism, an ECG recording during recurrent syncope was required. If the ECG recording captured an arrhythmia, diagnosis was arrhythmic syncope, and if the ECG recording was normal it was non-arrhythmic syncope. Presyncope was considered non-diagnostic, and asymptomatic ECG findings highly suggestive of arrhythmic syncope (AV block II:II or III, persistent bradycardia or ventricular pauses >3 seconds, or sustained episodes with paroxysmal supraventricular or ventricular tachycardia)

(100) were considered to be potentially diagnostic of the syncope mechanism. All ECG recordings were reviewed by at least one cardiologist.

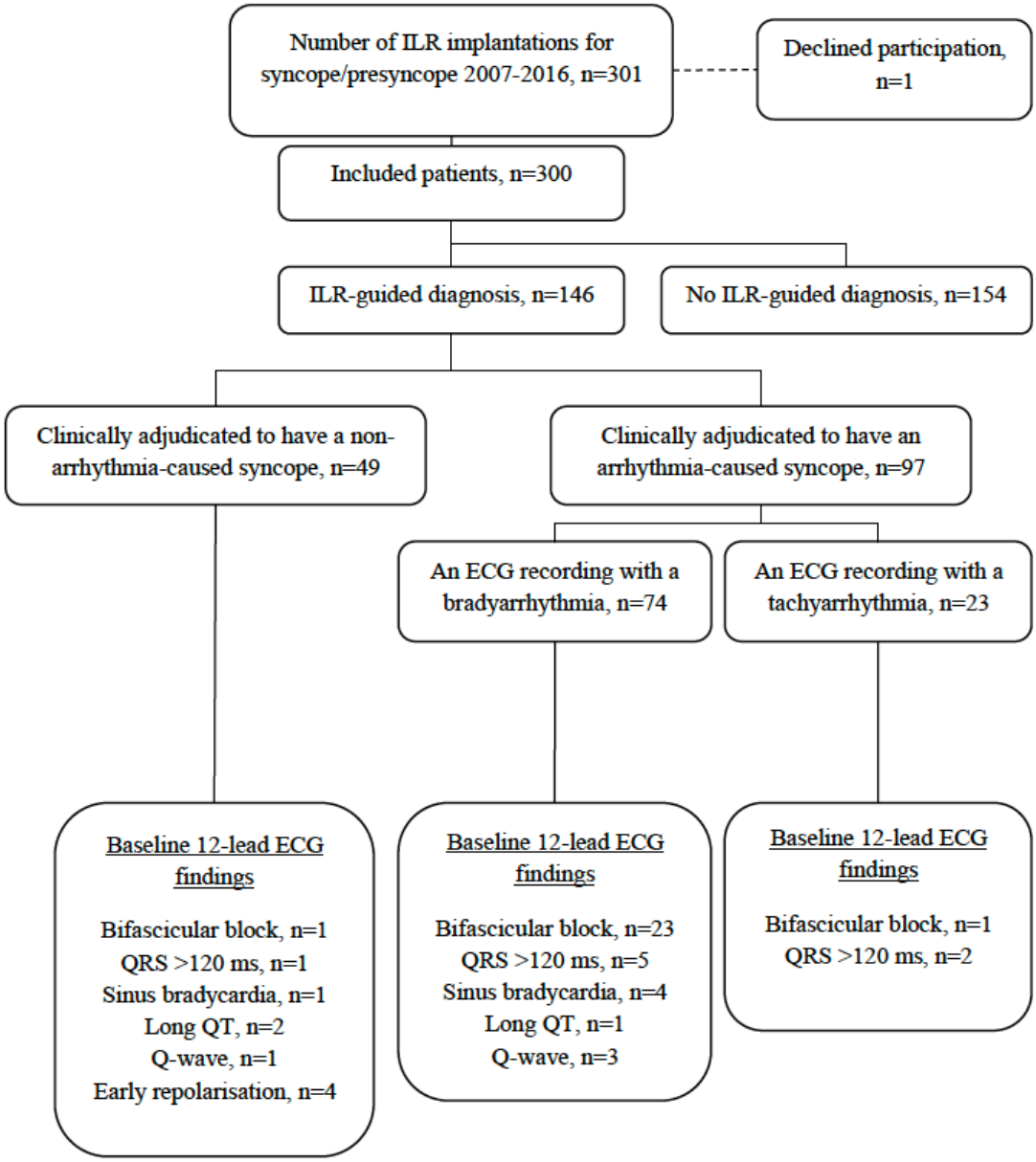

Figure 13. Flowchart of the study design for study II. ECG, electrocardiogram; ILR, implantable loop recorder; ms, millisecond. Reprinted with permission from "Role of baseline 12-lead ECG in predicting syncope caused by arrhythmia in patients investigated using an implantable loop recorder" by Sandgren E, Rorsman C, Edvardsson N, et al., 2019. International Journal of Cardiology Heart & Vasculature, 24, 100386 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6603332/). Copyright © 2019, The Authors. Licensed under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

It is worth noting the difference between the two terms ILR-guided diagnosis and ECG-based diagnosis, used in the results section for studies II and III respectively. ILR-guided diagnosis (study II) includes all patients where the ILR has informed the clinical diagnosis, i.e. where captured ECG recordings both during syncope recurrence or other times have enabled a clinical diagnosis to be made. ECG-based diagnosis (study III) only includes those with recurrence of syncope.

Follow-up lasted until a mechanism of syncope was revealed or the battery expired.

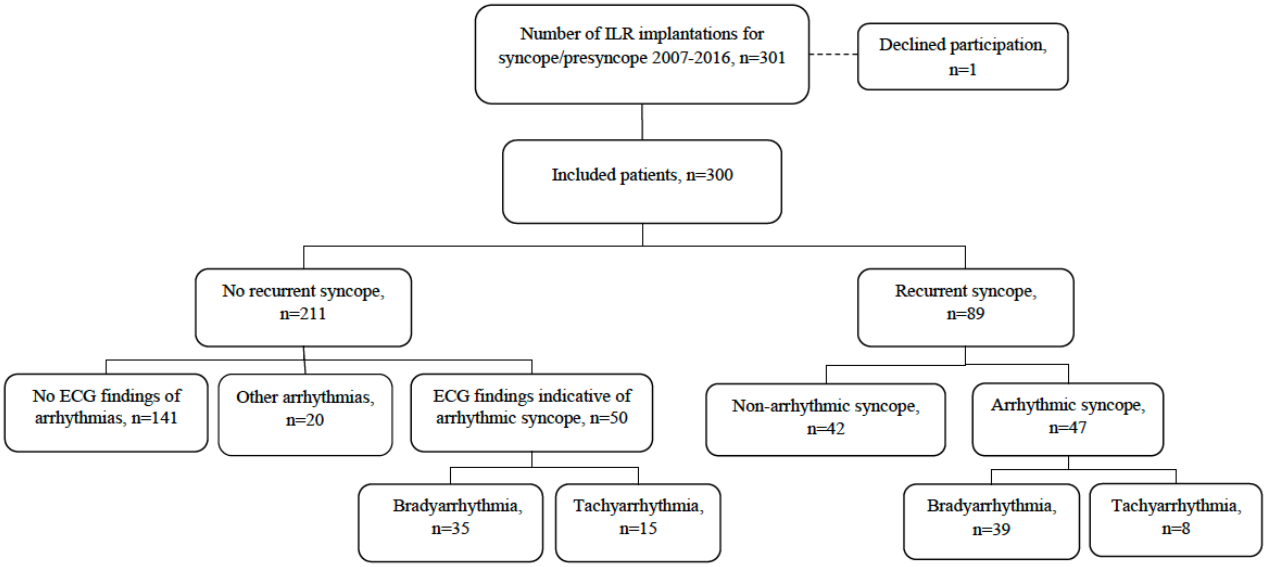

Figure 14. Flowchart of the study design for study III. ECG, electrocardiogram; ILR, implantable loop recorder.

5.3 STUDY IV

This was a sub-study of the prospective AFAF study (Atrial Fibrillation AFter CABG and percutaneous coronary intervention). The AFAF study investigates the incidence of AF after percutaneous coronary intervention or CABG surgery. Non-invasive handheld ECG recordings are conducted three times daily during the first postoperative month, and for two weeks at three, 12 and 24 months in addition to routine care. The patients were instructed to perform ECG recordings at the same times every day, and in case of symptoms. Each ECG recording was 30 seconds.

In addition to the handheld ECG, this sub-study included continuous ECG monitoring with an ILR. The ILR was implanted during the CABG surgery, and data collection and remote monitoring were activated at discharge. The ILRs were programmed to detect brady- and

tachyarrhythmias according to predefined criteria (bradyarrhythmia <30 bpm for at least four beats and pause >3 seconds; tachyarrhythmia >176 bpm for at least 16 beats), and an investigator checked the ILR data weekly via the remote monitoring system. False positive strips were excluded by manual adjudication.

Clinical data, echocardiographic measurements and information about medications were retrieved from medical records, as well as from digital report forms completed by phone at baseline and after one, three, and 12-months of follow-up within the AFAF study. To diagnose AF during the in-hospital stay at least a 30-seconds telemetry recording or a 12-lead ECG was required.

Exclusion criteria involved a history of AF, pacemaker treatment or other non-sinus rhythm, bleeding disorder where OAC treatment was contraindicated, cognitive impairment or communication problems leading to difficulties in taking instructions and completing the written informed consent form, malignancy or other diseases with life expectancy less than one year and ongoing anticoagulation treatment.

5.3.1 Outcome measures

The primary endpoint of the study was the proportion of patients diagnosed with incident or recurrent AF during the 12-month follow-up. The secondary endpoint was the AF burden, i.e. the total time in AF calculated from all AF recordings with at least two minutes duration.

Any other significant arrhythmias were recorded as exploratory variables, e.g. atrial flutter or atrial tachycardia, according to their algorithms.

5.4 STATISTICS

5.4.1 General

Descriptive statistical analysis was used in studies I-IV. Continuous variables were reported as mean and standard deviation (SD), median and range, median and interquartile range (IQR), median with 25^{th} and 75^{th} percentiles and minimum and maximum value or 95% confidence interval (CI). Categorial variables were reported as frequencies and percentages. Univariate analysis of the continuous variables was performed using the independent samples T-test, or if assumptions were not met, the non-parametric Mann-Whitney U test. A one-way analysis of variance (ANOVA) was used to compare means of more than two groups. For categorical variables, Fisher's exact test or chi-squared test were used. All tests were two-sided with a significance threshold of $p < .05$.

Kaplan-Meier curves were used in studies I-II. In study I, these were used to illustrate time from pacemaker implantation to first episode with subclinical AF/AHRE, and time from pacemaker implantation to subclinical AF/AHRE diagnosis. In study II, they were used to describe time to clinical diagnosis separately for those with bifascicular block, AV block I or normal baseline 12-lead ECG. The non-parametric log rank (Mantel Cox) test was used for statistical comparison.

Positive and negative predictive values were calculated in study II to describe the performance of bifascicular block in predicting a clinically adjudicated arrhythmia-caused syncope.

Multivariate logistic regression was used in studies II-IV. In study II, it was applied twice, to calculate the adjusted odds ratios for risk factors for a clinically adjudicated arrhythmia-caused syncope, and in the entire population to calculate the adjusted odds ratios for baseline 12-lead ECG findings predictive of a clinically adjudicated arrhythmia-caused syncope due to bradyarrhythmia. In study III it was used to evaluate the impact of age, gender and the number of pre-implant diagnostic tests on the outcome of an ECG-based diagnosis and a diagnosis of arrhythmic syncope. Finally, in study IV multivariate analysis was used to calculate the adjusted odds ratios for variables predicting the occurrence of AF during the 12-month follow-up after CABG surgery. In study IV, the Cox and Snell R^2 and the Nagelkerke R^2 values provided an indication of the amount of variation in the dependent variable explained by the model. The Enter method was used for all analyses, and variables with a probability value of less than 0.1 were included in the final model. Collinearity diagnostics were performed with a variance inflation factor.

Data processing and analyses were carried out using Microsoft Excel and IBM SPSS version 24-27.

5.4.2 Power calculations

Studies I-III were cohort studies, and the sample size was limited to the available cohorts. CI were calculated for primary outcomes. Study IV was a pilot study intended to investigate the feasibility of ILR diagnostics after CABG surgery. Data from this study will form the basis for power calculations for future studies.

5.5 ETHICAL CONSIDERATIONS

All four studies conform to the ethical principles of the 1975 Declaration of Helsinki, and have been approved by the Regional Ethical Review Board in Lund (study I: Dnr 2015/648, studies II and III: Dnr 2014/653) and Uppsala (study IV: Dnr 2015/413).

Studies I-III were observational cohort studies, and patient consent for these studies was obtained through an opt-out procedure. Due to their retrospective design, they did not involve any physical risks and did not affect the participants' treatment. However, the studies could have caused anxiety and injury due to violation of integrity as a result of collecting patient data outside the scope of ordinary medical care. To prevent harm to the patients' integrity, all personal data were processed in accordance with applicable privacy laws and were stored in the principal's network, so that they were only available to the investigator.

Study IV was prospective, and patient consent was obtained in written form before enrolment. The privacy violation was considered exiguous, as sensitive personal data were collected only after informed consent was given. All patients had an ILR inserted, and this could potentially have caused discomfort and infection at the site of surgery. The patients were informed that the ILR could be removed at any time. Patients who have undergone CABG surgery are at increased risk of developing AF and the potential benefits of finding a treatable AF were considered greater than the risks associated with minor surgery. Accordingly, the study meant that patients diagnosed with AF were assessed and offered OAC treatment according to the guidelines. The potential benefit for the participant, i.e. being offered OAC treatment, was considered greater than the potential inconvenience of participating, or the risk of bleeding if they received OAC treatment.

6 RESULTS

6.1 STUDY I

Mean follow-up time was 38±17 months for the detection of subclinical AF/AHREs, and 65±17 months for the ischaemic stroke and vascular dementia diagnosis. In total, 694 patients were enrolled (395 men). At the time of pacemaker implantation 271 patients had clinical/known AF and their median CHA_2DS_2-VASc score was 4 (IQR 2), while the 423 patients with no AF diagnosis had a score of 3 (IQR 2), p= .003. (Baseline data Table 5 and 6). Of patients with clinical/known AF, 38% (102/267) had died at the end of follow-up compared to 29% (121/411) of patients with no clinical/known AF at implantation, p= .02.

Table 5. Patient demographics at implantation for those with and without subclinical AF/AHREs during follow-up.

	AHREs, n=125	No AHREs, n=286	*p-value*
Age	79.0±8	73.3±11	***<0.001***
<50 years	0(0%)	14(5%)	***.001***
50-65 years	7(6%)	45(16%)	
>65 years	118(94%)	227(79%)	
CHA_2DS_2-VASc	3(2.5-4, 0-7)	3(2-4, 0-7)	***.01***
Congestive heart failure	12(10%)	11(4%)	***.04***
Hypertension	80(64%)	157(55%)	*.10*
Diabetes	19(15%)	55(19%)	*.40.*
History of ischaemic stroke	15(12%)	34(12%)	*.76.*
Vascular disease	38(30%)	63(22%)	*.08*
Sinus node disease*	29(23%)	76(27%)	*.54*
AV block I-III/ bundle branch block**	95(76%)	199(70%)	*.19*
Sinus node disease + AV block I-III	1(0.8%)	6(2.1%)	*.68*
Vagal reaction	0(0%)	1(0.4%)	*1.0*
Tachy-brady syndrome	0(0%)	4(1.4%)	*.32*

**Exclusive tachy-brady syndrome. **Including bifascicular block + syncope (n=2) and trifascicular block (n=6). Reported values are mean±SD, median (25^{th}-75^{th} percentiles and minimum-maximum value) or n (%). AF, atrial fibrillation; AHRE, atrial high-rate episode; AV, atrioventricular; CHA_2DS_2-VASc, (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)); IQR, interquartile range; SD, standard deviation. Statistical tests used: independent samples T-test, ANOVA (analysis of variance), non-parametric Mann-Whitney U test, chi-squared test and Fisher's exact test.*

Table 6. Distribution of the components of the CHA_2DS_2-VASc score at implantation.

	C n (%)	**H** n (%)	**A** n (%)	**D** n (%)	**S** n (%)	**V** n (%)	**A** n (%)	**Sc** n (%)
All patients, n=694	37(5.3)	430(62)	433(62)	119(17)	92(13)	197(28)	188(27)	297(43)
Known AF at implantation, n=271	13(4.8)	186(69)	189(70)	43(16)	40(15)	93(34)	69(25)	136(50)
AF not known at implantation, n=423	24(5.7)	244(58)	244(58)	76(18)	52(12)	104(25)	119(28)	161(38)
p-value	*.73*	***.004***	***.002***	*.54*	*.36*	***.006***	*.48*	***.002***
AHREs during FU, n=125	12(9.6)	80(64)	89(71)	19(15)	15(12)	38(30)	31(25)	40(32)
Free of AHREs during FU, n=286	11(3.8)	157(55)	147(51)	55(19)	34(12)	63(22)	86(30)	115(40)
p-value	***.03***	*.10*	***.0002***	.40	*1.00*	*.08*	*.29*	*.12*

AF, atrial fibrillation; AHRE, atrial high-rate episode; CHA_2DS_2-VASc, (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)); FU, follow-up. Statistical test used: chi-squared test.

Of 411 patients with no clinical/known AF at implantation, 125 were diagnosed with subclinical AF/AHREs during follow-up. AF diagnosis was verified in 61 patients (stored EGM: 59; 12-lead ECG: 2), and the diagnosis was based solely on AHREs in 64 patients (only one patient had AHREs which lasted less than one hour). Seven patients reported symptoms. The median time from implantation to the first episode of subclinical AF/AHRE and from the first episode to confirmation was seven (range 0.1-62) months and five (range 0-28) months respectively. Two-thirds (79/125) of the patients had their first episode during the first year of monitoring, and one-third (44/125) within the first three months. Patients with incident subclinical AF/AHREs during follow-up were older (AHRE: 79±8 years; no AHRE: 73.3±11 years; p< .001) and more often had congestive heart failure (AHRE: 12/125, 10%; no AHRE: 11/286, 4%; p= .04).

At implantation, 80% (216/271) of patients with clinical/known AF were on OAC treatment. Of the 125 patients diagnosed with subclinical AF/AHREs during follow-up, almost two-thirds received OAC treatment (six patients had OAC treatment for reasons other than AF; 72 were prescribed OAC treatment).

The annual stroke incidence was as follows: 2.1% in patients with clinical/known AF at implantation, 1.9% in patients with incident subclinical AF/AHREs and 1.4% in patients with no subclinical AF/AHREs. Divided by duration of the episode with subclinical AF/AHRE, patients with episodes shorter than 5.5 hours (72/125, 58%) had a total ischaemic stroke incidence of 9.7% and an annual incidence of 1.5%, and the corresponding numbers for patients with episodes longer than 5.5 hours (53/125, 53%) were 11.3% and 1.0% respectively.

The incidence of vascular dementia during follow-up was 11.2% (30/267) for patients with clinical/known AF at implantation, 5.6% (7/125) in patients with incident subclinical AF/AHREs, p= .09, and 6.2% (18/286) in patients without subclinical AF/AHREs, p= .048. Further data on the ischaemic stroke and vascular dementia incidence are shown in Table 7.

Table 7. Ischaemic stroke and vascular dementia incidence during follow-up, indicated separately for patients with clinical/known AF, subclinical AF/AHREs and no subclinical AF/AHREs.

	Clinical/known AF, n=267	AHREs, n=125	No AHREs, n=286
Number of ischaemic strokes	31	13	20
Total incidence	11.0%	10.0%	7.0%
Annual incidence	2.1%	1.9%	1.4%
OAC treatment (total/ with stroke)	216/23	78/5	-/3
Vascular dementia	30	7	18
Total incidence	11.2%	5.6%	6.2%
Annual incidence	2.1%	1.0%	1.2%

AF, atrial fibrillation; AHRE, atrial high-rate episode; OAC, oral anticoagulation.

6.2 STUDY II

The study population consisted of 300 patients, as one patient declined to participate. Half of the study population consisted of women (n=147, 49%) and the mean age was 66±16.5 years. Two hundred eighty-eight received the ILR due to syncope, and 12 due to presyncope. Mean follow-up time was 21±15.4 (median 19, range 0.25-60) months, and mean time to receiving an ILR-guided diagnosis 11±10.8 (median 7, range 0.25-42) months.

At baseline, the most common pathological 12-lead ECG findings were bifascicular block (n=33) and AV block I (n=48). Patients with bifascicular block were distributed as follows: 24 LBBB, eight RBBB + LAH and one RBBB + LPH. Baseline 12-lead ECG findings are reported in Table 8, and results are indicated separately for patients clinically adjudicated to have an arrhythmia-caused syncope, non-arrhythmia-caused syncope and no ILR-guided diagnosis during follow-up.

Table 8. Baseline 12-lead ECG findings, indicated separately for patients clinically adjudicated to have an arrhythmia-caused syncope, non-arrhythmia-caused syncope and no ILR-guided diagnosis during follow-up.

	Arrhythmia-caused syncope, n=97	Non-arrhythmia-caused syncope, n=49	No ILR-guided diagnosis, n=154
Bifascicular block	24	1	8
QRS >120 ms	7	1	5
Sinus bradycardia <50 bpm	4	1	3
Sinus tachycardia	0	0	0
Ventricular tachycardia	0	0	1
Preexcitation	0	0	0
Long QT	0	2	1
Q-waves	3	1	6
Early repolarisation	0	4	1
AV block I	21	5	22
None of above ECG findings	54	36	115

26 patients had more than one ECG abnormality. AV, atrioventricular; bpm, beats per minute; ECG, electrocardiogram; ILR, implantable loop recorder; ms, millisecond.

One hundred forty-six patients (49%) received an ILR-guided diagnosis. Ninety-seven (66%) were clinically adjudicated to have an arrhythmia-caused syncope and 49 (33%) to have a non-arrhythmia-caused syncope. Of patients clinically adjudicated to have an arrhythmia-caused syncope, 76% (74/97) of cases had an ECG recording of a bradyarrhythmia and 24% (23/97) an ECG recording of a tachyarrhythmia.

Patients with pathological findings at baseline 12-lead ECG more often received an ILR-guided diagnosis and were more often clinically adjudicated to have an underlying arrhythmia as the cause of syncope compared to those with a normal baseline 12-lead ECG: 59% (56/95) vs 44% (90/205), p= .018, and 45% (43/95) vs 26% (54/205), p= .001 respectively. The highest incidence of ILR-guided diagnosis at 76% (25/33) and clinically adjudicated arrhythmia-caused syncope at 96% (24/25) was in patients with bifascicular block at baseline 12-lead ECG. Of these patients, 23 had an ECG recording of a bradyarrhythmia (intermittent complete heart block:19, sinus pauses: three, and sinus bradycardia: one) and one had an ECG recording of a tachyarrhythmia (atrioventricular nodal re-entrant tachycardia). One patient with bifascicular block was clinically adjudicated to have a non-arrhythmia-caused syncope, as no arrhythmia was recorded at the time of syncope recurrence.

In particular, bifascicular block was common in patients over 60 years of age (94%, 31 out of 33 patients). Bifascicular block was a strong predictor of a clinically adjudicated arrhythmia-caused syncope, with an adjusted odds ratio of 5.5 (95%CI 2.3-13.2), p< .001, and a PPV of 73%. In the total population, bifascicular block predicted a clinically adjudicated arrhythmia-caused syncope due to bradyarrhythmia, with an adjusted odds ratio of 11.4 (95%CI 5.0-26.2), p< .001.

Patients with bifascicular block had significantly shorter time to ILR-guided diagnosis than those with AV block I and normal baseline 12-lead ECG (Figure 15).

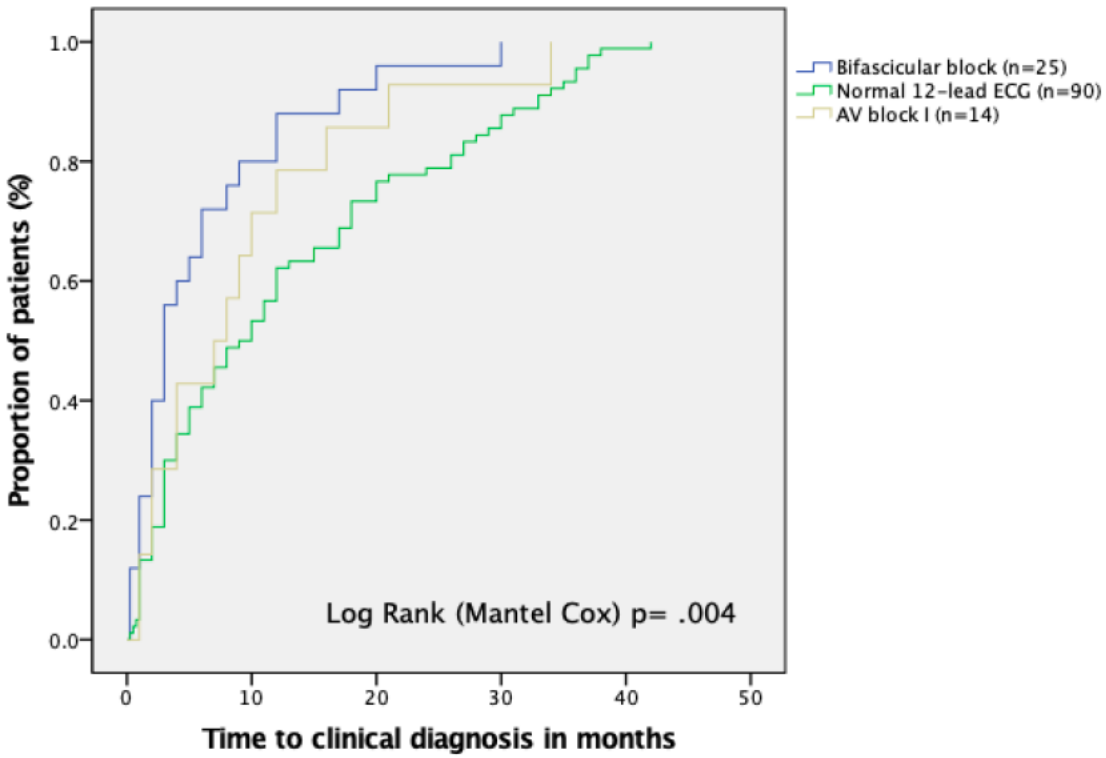

Figure 15. Kaplan-Meier curve illustrating time to clinical diagnosis, separated according to those with bifascicular block (median three months, range 0.25-30), AV block I (median seven months, range 1-34) or normal baseline 12-lead ECG (median nine months, range 0.25-42), p= .004. AV, atrioventricular; ECG, electrocardiogram. Statistical test used: Log rank (Mantel Cox). Reprinted with permission from "Role of baseline 12-lead ECG in predicting syncope caused by arrhythmia in patients investigated using an implantable loop recorder" by Sandgren E, Rorsman C, Edvardsson N, et al., 2019. International Journal of Cardiology Heart & Vasculature, 24, 100386 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6603332/). Copyright © 2019, The Authors. Licensed under CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

6.3 STUDY III

Three hundred patients were included, and their age and gender distribution are visualised in Figure 16. At baseline, men more often had AV block I (men: 35/153, 23%; women: 13/147, 9%; p< .001), and women more often had a normal 12-lead ECG (men: 90/153, 59%; women: 115/147, 78%; p< .001).

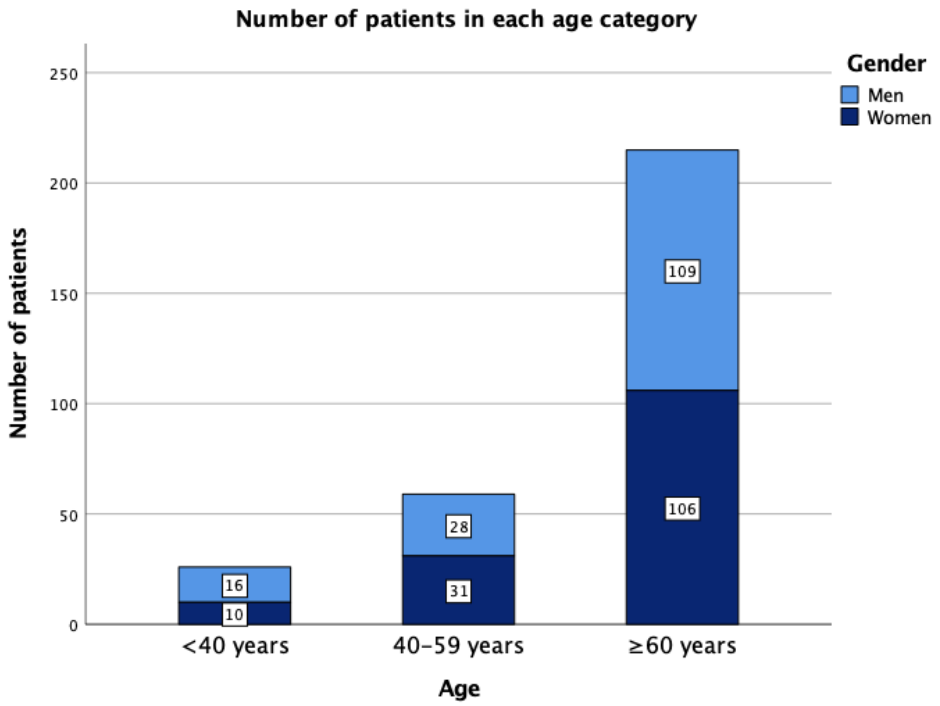

Figure 16. Of 300 patients, 9% of patients were younger than 40 years of age, 20% were between 40 and 59 years of age, and 71% of patients were ≥60 years of age.

Eighty-nine patients had syncope recurrence during follow-up and accordingly received an ECG-based diagnosis, which was more common in women than in men (women: 56/147, 38%; men: 33/153, 22%; p= .001). In 47 patients the underlying cause was an arrhythmia, while 42 suffered recurrent syncope with a normal ECG recording, i.e. non-arrhythmic syncope; this was most common in women (women: 27/147, 18%; men 15/153, 10%; p= .045).

Syncope recurrence due to arrhythmia was more common in patients ≥60 years of age (<40 years: 3/11, 27%; 41-59 years: 7/18, 39%; and ≥60 years: 37/60, 62%; p= .045), and especially syncope recurrence due to a bradyarrhythmia (<40 years: 1/11, 9%; 40-59 years: 5/18, 28%; ≥60 years: 33/60, 55%; p= .006) (Figure 17).

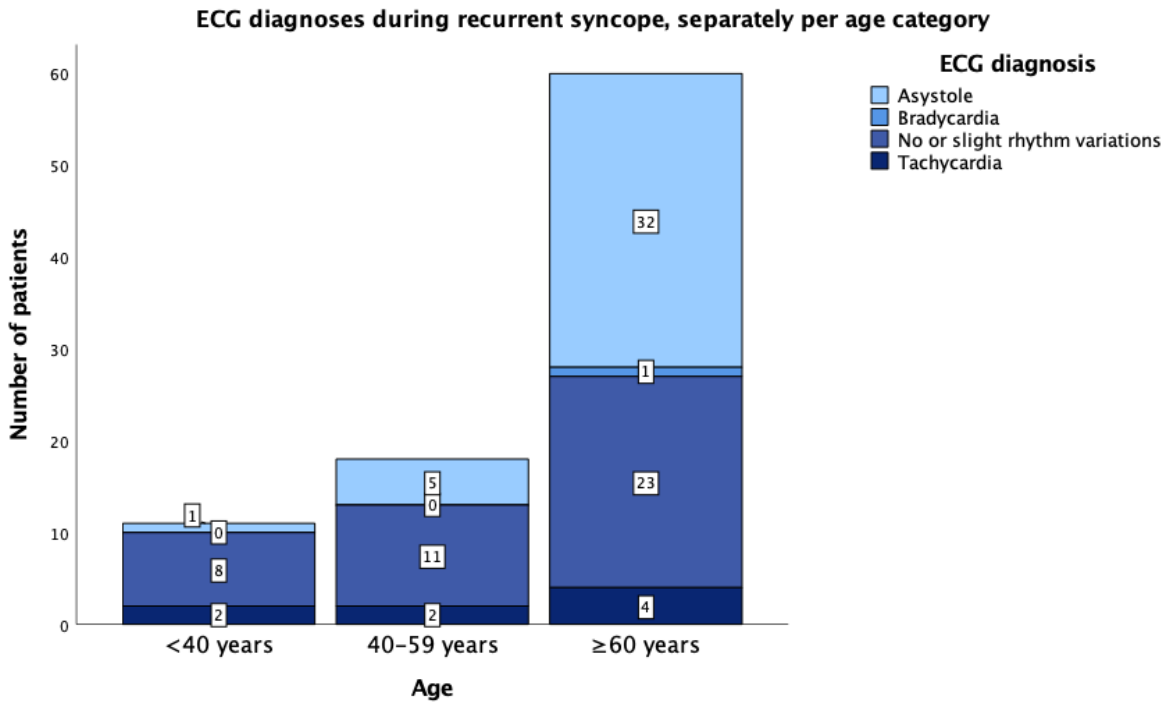

Figure 17. ECG, electrocardiogram.

In another three patients, the recurrent event turned out to be a seizure, which was suggested according to tonic-clonic activity in ECG recordings.

Fifty patients with no recurrent syncope (42 with presyncope and eight with no symptoms) had ECG recordings which may be indicative of arrhythmic syncope according to the ESC 2018 Syncope guidelines (100), with no gender or age difference (Figure 18). Another 20 asymptomatic patients, three-quarters of whom were men (women: 5; men: 15; p= .04), had an ECG recording involving other arrhythmias.

For the total number of diagnostic tests upfront ILR implantation, there were no gender differences, but there was an age difference, as patients ≥60 years of age underwent fewer diagnostic tests upfront ILR implantation (<40 years: 6.5±1.2; 40-59 years: 5.75±1.0; and ≥60 years: 5.1±1.9; p= .002). However, broken down into the different tests, women more often underwent ambulatory ECG monitoring (women: 79/147, 54%; men: 60/152, 39%; p= .015) and myocardial scintigraphy (women: 7/147, 5%; men: 0/152, 0%; p= .0006), while men were more often hospitalised for ECG monitoring (women: 89/147, 61%; men: 111/152, 73%; p= .037) and referred for cardiac magnetic resonance imaging (women: 16/147, 11%; men: 26/152, 17%; p= .027). The total number of pre-implant tests did not impact the diagnostic yield of the ILR.

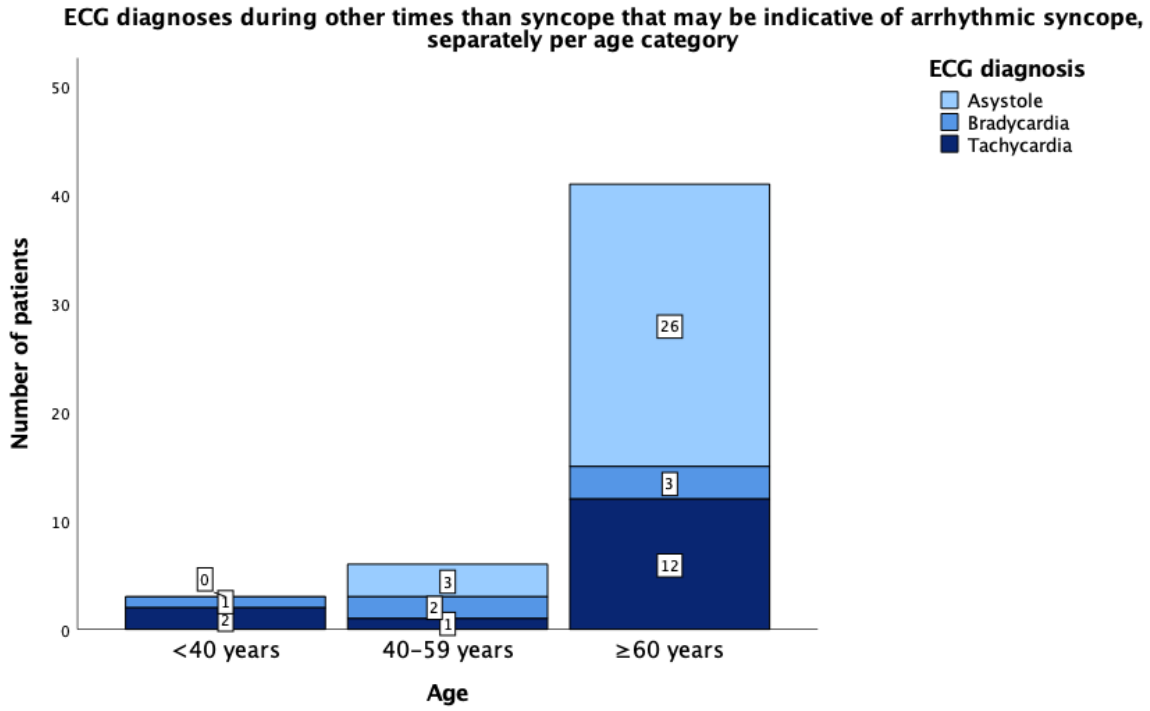

Figure 18. ECG, electrocardiogram.

In a subgroup analysis where patients with presyncope (women: 7; men: 5) as the indication were included, no difference was found to the total population regarding mean age and number of diagnostic tests upfront ILR implantation. Of these 12 patients, one suffered syncope and three presyncope during follow-up. The three patients with presyncope and one patient without symptoms had ECG findings which may be indicative of arrhythmic syncope according to the ESC 2018 Syncope guidelines (100). Another two patients had asymptomatic arrhythmias.

6.4 STUDY IV

Thirty-nine men and one woman with a mean age of 68±8 years were included, and all of them except two were alive (death occurred three and four months after surgery respectively) and followed until the end of the 12-month follow-up. Table 9 shows their baseline characteristics, indicated separately for patients with and without AF during follow-up. The CHA_2DS_2-VASc score was higher for patients with AF than for patients who remained in sinus rhythm, with median 4 (IQR 1) and median 3 (IQR 2) respectively, p= .006. Mean time spent in hospital was 6.7±3 days, range 4-21 days. Two patients suffered peroperative complications (pericardial effusion and cardiac ischaemia).

Table 9. Baseline characteristics in patients with and without AF during 12-month monitoring after CABG surgery.

	No AF	AF	*p-value*
Total number	13	27	
Age	63.6(95%CI 58.2-69.1)	70.4(95%CI 67.7-73.2)	***.012***
Women	0(0%)	1(3.7%)	*1.0*
Body mass index	29.3(95%CI 26.4-32.2)	30.1(95%CI 28.0-32.2)	*.650*
CHA_2DS_2-VASc score	3(IQR 2)	4(IQR 1)	***.006***
Smoking status			*.200*
Non-smoker	8(62%)	11(40.7%)	
Former (>1 month)	5(38%)	11(40.7%)	
Smoker	0(0%)	5(18.5%)	
Alcohol consumption*			*.320*
None	1(8%)	3(11.5%)	
<8 units/week	10(84%)	23(88.5%)	
>8 units/week	1(8%)	0(0%)	
Congestive heart failure	1(7.7%)	6(22.2%)	*.390*
Previous myocardial infarction	3(23%)	16(59.3%)	***.046***
COPD	0(0%)	0(0%)	-
Obstructive sleep apnoea	1(7.7%)	1(3.7%)	*1.0*
Hypertension	7(54%)	22(81.5%)	*.130*
Diabetes	5(38%)	10(37%)	*1.0*
Previous stroke**	0(0%)	4(16%)	*.240*
Peripheral vascular disease	0(0%)	3(11.1%)	*.540*
Disease definition			*.690*
Unstable angina	4(31%)	5(18.5%)	

Stable angina	7(54%)	17(63%)	
Non-STEMI	2(15%)	5(18.5%)	
Extent of disease (No of vessels)			*.540*
1	0(0%)	0(0%)	
2	0(0%)	3(11.1%)	
3	13(100%)	24(88.9%)	
Echocardiography			
Left ventricular ejection fraction	53.1(95%CI 47.9-58.2)	50.9(95%CI 45.7-56.1)	*.600*
Left atrium area***	18.3(95%CI 15.9-20.7)	20.9(95%CI 18.0-23.7)	*.063*

Data is missing for one patient with no AF and one patient with AF. ** Data is missing for two patients with AF. * Data is missing for one patient with no AF and two patients with AF. Reported values are n (%). AF, atrial fibrillation; CHA_2DS_2-VASc, (Congestive heart failure, Hypertension, Age >75 years (2 points), Diabetes, Stroke (2 points), Vascular disease, Age 65-74 and Sex (female)); CI, confidence interval; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; no, number; STEMI, ST-elevation myocardial infarction. Statistical tests used: independent samples T-test, non-parametric Mann-Whitney U test, chi-squared test and Fisher's exact test.*

Twenty-seven of 40 patients (68%) had incident AF during follow-up. Twenty-one were diagnosed during hospitalisation, three during the first month after discharge and a further three during months 2-12 of post-discharge monitoring. Three patients developed persistent AF: one patient already at discharge as first episode, one patient after nine days as first episode, and one patient after seven months after experiencing paroxysmal AF episodes. In total, 18/27 patients with incident AF had a recurrence of AF (including the one patient who progressed to persistent AF), and 15 of these were within the first 30 postoperative days. The incidence and recurrence of AF over time is shown in Figure 19.

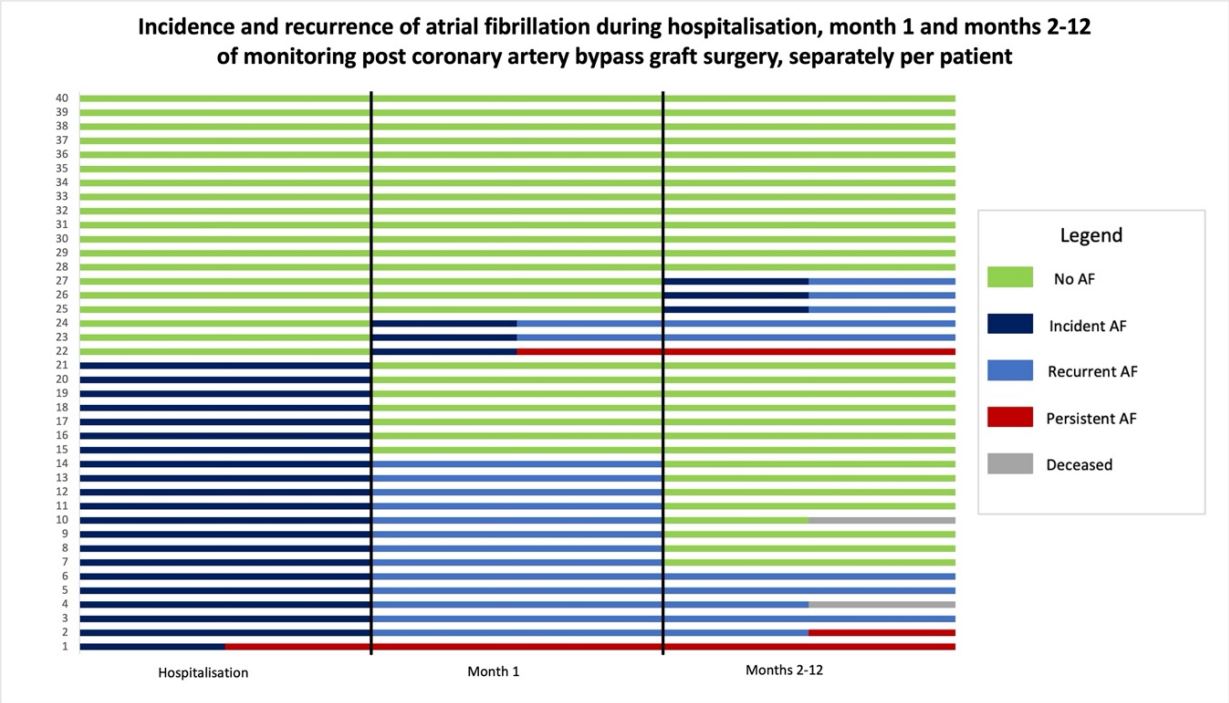

Figure 19. In total 27 out of 40 patients had incident AF, and 18 of these also suffered one or more recurrences during follow-up. AF, atrial fibrillation.

Prior to CABG surgery, 33/40 were on beta blocker therapy, 18/21 of them with incident AF during postoperative hospitalisation. Seventeen of 21 with incident AF during hospitalisation received intravenous amiodarone and all except one were in sinus rhythm at discharge. All patients with AF received OAC treatment. Antiarrhythmic treatment was prescribed for three patients during the first month (one amiodarone, one amiodarone plus direct current cardioversion and one dronedarone). During months 2-12, no new patients were prescribed antiarrhythmic drugs.

Multivariate analyses were used to identify baseline predictors of any AF during the 12-month follow-up. The four variables age, hypertension, previous myocardial infarction and left atrium area were included in the final model, which was statistically significant x^2 (4, N=37) =16.8, p= .002. It explained 37-51% of the variance and correctly classified 78.4% of cases. After adjustment, only age was significant (Table 10).

Table 10. Logistic regression identifying predictors for the likelihood of any AF during the 12-month monitoring period after CABG surgery.

	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)	*p-value*
Age	1.1(95%CI 1.02-1.24)	1.2(95%CI 1.01-1.36)	***.043***
Hypertension	3.8 95%CI 0.88-16.24)	8.4(95%CI 0.95-74.09)	*.055*
Previous MI	4.8(95%CI 1.08-21.76)	4.4(95%CI 0.57-33.68)	*.155*
Left atrium area	1.2(95%CI 0.98-1.46)	1.2(95%CI 0.91-1.47)	*.243*

AF, atrial fibrillation; CABG, coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction. Statistical test used: binary logistic regression.

The ILR identified that 20 patients had episodes of AF during the 12-month post-discharge monitoring time, while handheld ECG identified nine of them, p= .001. The ILR was more effective at detecting AF in month 1, as well as in months 2-12 (Figure 20). However, one patient had two episodes of AF in the first week after discharge, and this was only captured by a handheld ECG as the ILR had not been activated. Accordingly, the ILR detected 98% (102/104) of all individual AF episodes, while handheld ECG detected 29% (30/104), p< .0001.

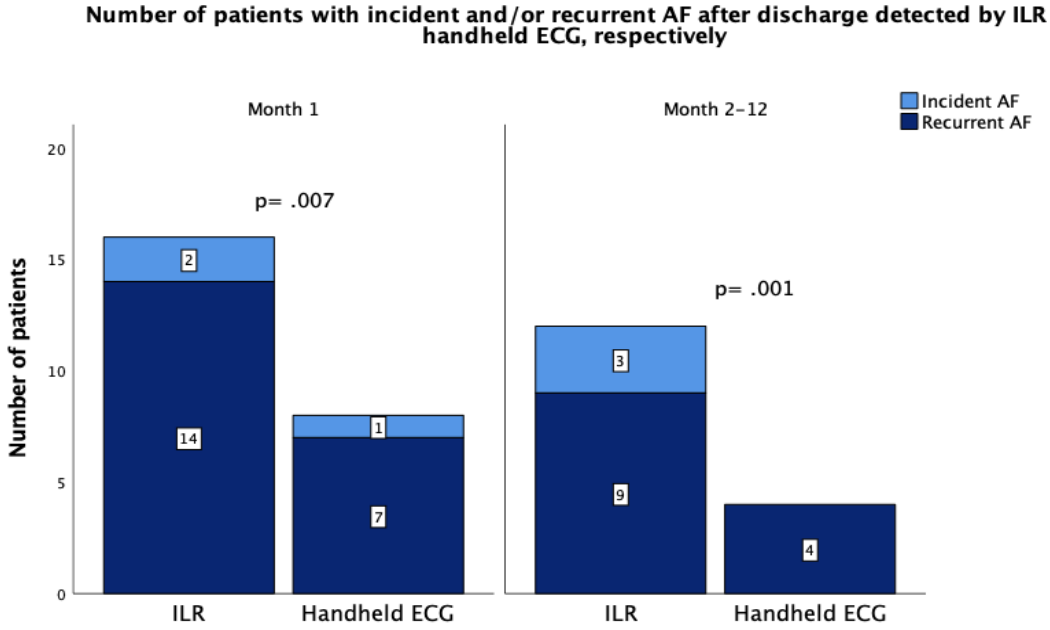

Figure 20. The detection rate was higher for the ILR than the handheld ECG for month 1 and months 2-12: 94% (16/17) versus 47% (8/17), p= .007, and 100% (12/12) versus 33% (4/12), p= .001 respectively. AF, atrial fibrillation; ECG, electrocardiogram; ILR, implantable loop recorder. Statistical test used: Fisher's exact test.

The ILR, but not handheld ECG, captured asymptomatic arrhythmias in eight patients: one patient had non-sustained monomorphic ventricular tachycardia, one had intermittent AV block III and six patients had sinus arrest and/or sinus bradycardia.

The median AF burden was 0.1% (IQR 0.28) or 718 (IQR 1296) minutes (Figure 21). Fourteen out of 17 patients with paroxysmal AF had AF episodes with a duration of ≥6 minutes, and in total AF episodes ≥6 minutes constituted 57% (58/101) of all paroxysmal AF episodes.

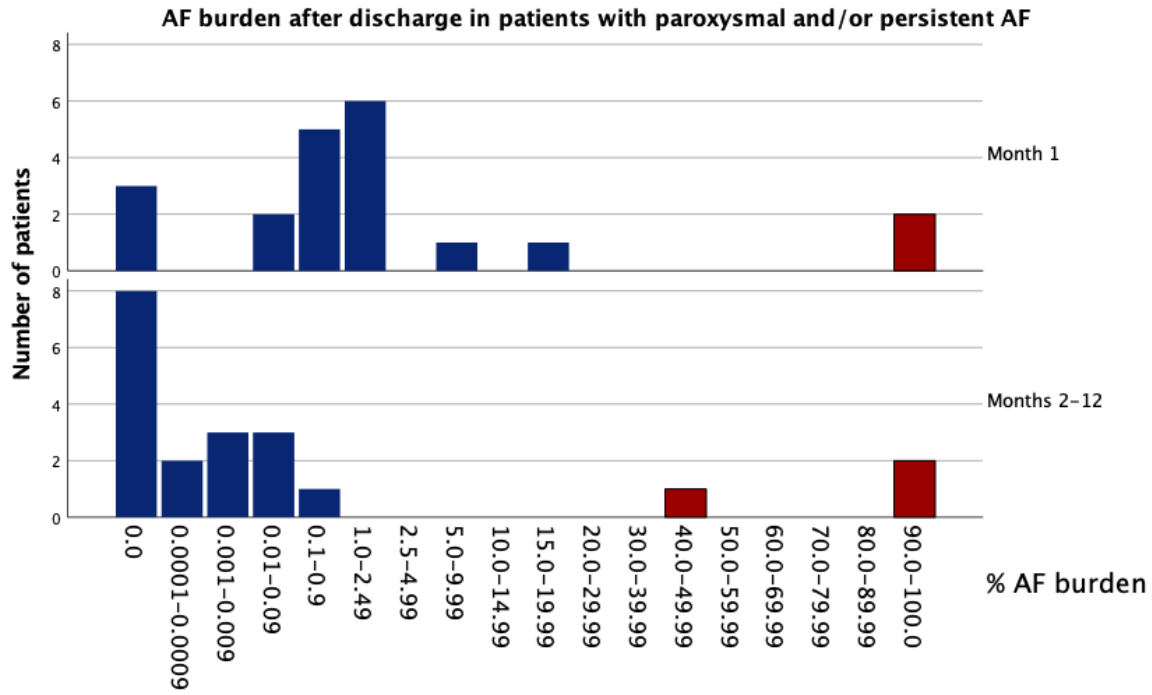

Figure 21. The AF burden was low in all patients except the three patients in red who developed persistent AF, and it gradually decreased during the 12-month follow-up. AF, atrial fibrillation.

7 GENERAL DISCUSSION

7.1 MAJOR FINDINGS

This Ph.D. project aimed to highlight different aspects of device-based arrhythmia diagnoses, and the findings can be summarised briefly in three paragraphs.

First, study I showed that episodes of subclinical AF/AHREs were common in the pacemaker population, and were associated with older age and congestive heart failure. The stroke incidence was low, but clinical/known AF was associated with an increased risk of vascular dementia.

Second, studies II and III, on ILR monitoring in syncope patients, observed that women experienced a recurrence of syncope more often than men, a difference mainly driven by higher incidence of syncope with non-arrhythmic cause. Age ≥60 years was associated with fewer pre-implant tests, but higher recurrence rate of syncope with an arrhythmic cause. In addition, conduction disturbance in terms of bifascicular block was a strong predictor of an underlying bradyarrhythmia (i.e. intermittent complete heart block) as the cause of a clinically adjudicated arrhythmia-caused syncope.

Finally, in study IV patients with incident AF during postoperative inpatient care after CABG surgery often suffered recurrent AF during the first 30 postoperative days. Patients with AF had higher CHA_2DS_2-VASc scores than patients who remained in sinus rhythm, and the ILR was more effective than the handheld ECG in identifying patients with AF. Furthermore, the AF burden was low.

7.2 THE MYSTERY OF DEVICE-DETECTED AF REMAINS UNRESOLVED

Previous studies (52-56) have shown that device-detected AF is common in the pacemaker population, and the total incidence of 30% in our study is in line with results from these aforementioned studies. It ranged from 30-55%, depending on whether patients with a history of clinical AF were included (53, 54) or not (55, 56). The high incidence of device-detected AF in our study and other studies can be explained by the fact that it reflects the pacemaker population in general. Conduction disturbances requiring the implantation of a pacemaker are usually associated with older populations, and age is acknowledged to be one of the strongest risk factors for incident AF (167, 168). Belonging to an older age group also means that the person has had more time to accumulate other comorbidities, some of which may be true risk factors for AF. Given this reasoning, as expected, we found an association between a high CHA_2DS_2-VASc score and clinical/known AF, as several components of the CHA_2DS_2-VASc score are listed as risk factors for AF in the ESC 2020 AF guidelines (20). An

overwhelming majority of the episodes with device-detected AF were asymptomatic, at least not so symptomatic that the patients visited the emergency department. Of course, we cannot rule out that symptoms were under-reported, as our study was observational, though similar numbers have been demonstrated in earlier studies (51, 169). Again, comorbidity may be a contributing factor to these findings, as competing symptoms can conceal or resemble symptoms which are actually due to episodes of AF.

In contrast to previous studies (53, 56, 59, 63), we could not establish an association between device-detected AF and increased risk of ischaemic stroke. Furthermore, the annual ischaemic stroke incidence was low in our study population compared to earlier reports from device patients (170), and even compared to the general population (171). Several factors may have contributed to these findings. These include, first, the sample size. Second, the high proportion of patients with device-detected AF who received OAC treatment in our study. Of note, it may be worth pointing out here that most of the patients in our study began OAC treatment before 2016, and first in the ESC 2016 AF guidelines were clinical AF and device-detected AF distinguished as two different entities (172). Third, these patients had regular healthcare appointments associated with pacemaker treatment, which may favour assessment and treatment for stroke-risk factors. Finally, their heart rhythm was continuously monitored through the pacemaker, and there was a particular awareness of observed arrhythmias in our study.

There remains a knowledge gap whether device-detected AF should be treated with OAC treatment, and if so, whether there is a specific cut-off value for the AF burden when benefit exceeds risk. Even though guidelines generally agree that a high AF burden motivates assessment for OAC treatment (20, 41), there are no randomised trials on the topic, though there are several observational studies and some systematic reviews. A report from the ASSERT trial demonstrated increased risk of stroke and systemic embolism only for patients with device-detected AF lasting over 24 hours (75). However, in the next few years results are expected from three ongoing randomised trials: ARTESiA (NCT01938248), NOAH-AFNET 6 (NCT02618577) and SILENT (NCT02004509), and these should provide some clarity in terms of when to prescribe OAC treatment in these patients (78-80).

7.3 THE EFFECTIVENESS OF AN ILR IN SYNCOPE PATIENTS IS AFFECTED BY GENDER, BUT NOT BY AGE OR PRE-IMPLANT EVALUATION

Syncope is common but remains challenging due to its often infrequent and unpredictable nature. As such, an ILR is an appealing tool for enabling long-term ECG monitoring. Syncope patients often undergo an extensive diagnostic workup which provides no indication of the underlying syncope mechanism (117). This is not particularly unexpected, as monitoring at the precise onset of syncope is the key to finding the syncope mechanism. Our findings with the same diagnostic yield, irrespective of the extent of the workup, are in line with a previous study (118) and are quite encouraging. There may be potential for saving time and healthcare resources by considering an ILR early in the evaluation of patients from older age groups with recurrent unexplained syncope, where a detailed history has not revealed the syncope mechanism. Earlier studies have indicated that an ILR can be more cost-effective than conventional testing in syncope patients (120, 121). This reasoning is also in accordance with current guidelines, which advocate an ILR early in the evaluation of individuals with unexplained syncope who are not high-risk (100).

Interestingly, we found no differences in the diagnostic yield in terms of age, due to the fact that non-arrhythmic syncope was common in younger patients. It may be at least as important to be able to exclude an arrhythmic cause and explain the syncope mechanism as it is to diagnose an arrhythmia.

Somewhat more expected were our finding that older patients had a higher incidence of arrhythmic syncope than the younger age-groups, most often due to bradyarrhythmia. A theoretically appealing explanation for this finding is that fibrosis and sclerosis of the atrial myocardium and conduction system is the most common reason for acquired conduction disorders (173, 174), and these changes increase with age. It is well-known that the prevalence of arrhythmias increases with age (102), and this awareness is probably, in turn, the reason why patients over 60 years of age in our study underwent significantly fewer diagnostic tests upfront ILR implantation. It may reflect a higher clinical suspicion of underlying arrhythmic mechanism in this age category.

Last, women in our study suffered a recurrence of syncope and received an ECG-based diagnosis more often than men. We can find no obvious explanation for this finding, but it may involve the evaluation of risk in individual patients and possible gender differences in the presentation of syncope (175, 176). Earlier studies have also observed gender differences in the incidence, characteristics and treatment of cardiac arrhythmias (177, 178).

7.4 BASELINE 12-LEAD ECG HELPS IN FINDING PATIENTS AT HIGH RISK OF CLINICALLY ADJUDICATED ARRHYTHMIA-CAUSED SYNCOPE

Twelve-lead ECG is a simple and easily accessible investigation that can give clues to underlying structural or electrical heart disease. However, few studies have investigated the relationship between baseline 12-lead ECG and syncope mechanisms. We found that bifascicular block was strongly associated with a clinically adjudicated arrhythmia-caused syncope, most often due to bradyarrhythmia in terms of intermittent complete heart block. Bifascicular block occurred almost exclusively in patients over 60 years of age. This is a reasonable finding if bifascicular block is seen as an expression of delayed conduction of electrical signals in the heart as an underlying conduction disorder.

Two previous observational cohort studies, have pointed in the same direction (115, 124), and a prospective cohort study did not find any additional value in treatment guided by an electrophysiology study compared to a strategy of direct permanent pacing (127). Furthermore, primary results from the randomised SPRITELY trial (NCT01423994) showed that a strategy of empiric permanent pacing in patients with syncope and bifascicular block resulted in a reduction in major adverse events, but not the proportion of patients with recurrence of syncope (126). Their conclusion was that permanent pacing is a preferred strategy in elderly patients with bifascicular block and few, but recent, syncope spells (126). Our findings agree with their conclusion, and we find it reasonable, in consultation with the patient, to consider permanent pacing instead of an implantable loop recorder in older patients with bifascicular block and unexplained syncope.

7.5 AF AS A MARKER OF HIGH CARDIOVASCULAR RISK

Previous reports have demonstrated that AF is common in the early postoperative period after CABG surgery (179, 180), and this is in line with our findings. However, we also observed that continued episodes of AF were especially common during the first month after surgery. This finding could possibly be explained by the fact that it takes some time for the inflammatory response associated with surgery (181, 182) to subside. Furthermore, some patients were diagnosed with AF several months after surgery. Most probably our study population represents a group of patients with relatively high cardiovascular comorbidity explains this finding, and many of the risk factors for cardiovascular disease are also risk factors for AF (20, 26). So far, few data have come to light on the course of postoperative AF. Our study had a small sample size, but our findings indicate that this is a high-risk group for developing AF, and that it may be cost-effective to invest screening resources for this group, improving detection of AF aiming at stroke reduction. The AF burden was low, but patients with AF diagnosed with implantable devices commonly progress to a higher AF

burden (183), and risk of ischaemic stroke increases with increased AF burden (184). However, it is not clear whether prolonged ECG monitoring with subsequent OAC initiation for AF has an effect on stroke recurrence. More will be known about this when results from the LOOP study (NCT02036450), which aims to evaluate whether screening for AF with an ILR, and initiating OAC if AF is detected, will reduce the risk of ischaemic stroke or systemic embolism in patients with stroke risk factors, will be published (185).

The question whether the very existence of AF is the root of the problem, or whether it involves the presence of multiple cardiovascular risk factors, so that AF rather is a risk-marker remains to be answered. This argument has also been raised in the debate about device-detected AF, i.e. that subclinical AF/AHREs are a marker for patients at high risk of ischaemic stroke rather than the actual cause. Intracardiac thrombus formation and cardioembolic stroke need not to be caused by AF itself, but instead a consequence of atrial cardiomyopathy. To develop this idea further, the association between clinical AF and vascular dementia observed in study I, and demonstrated in earlier studies (186), is probably not only due to the presence of AF, i.e. on the casual pathway. Instead, it is the result of a number of factors, including high cardiovascular risk-factor load and underlying atrial cardiomyopathy.

AF and subclinical AF/AHREs should be treated with OAC according to the guidelines (20), but OAC treatment neither reduces AF episodes nor relieves AF symptoms. Instead, it reduces possible future negative effects like ischaemic stroke and dementia (24, 35).

7.6 LIMITATIONS

Study I is an observational study, and accordingly poses a risk of bias due to unmeasured confounders. Nevertheless, observational studies play an important scientific role in generating hypotheses, and data can be adjusted for known confounders. The strength of this study is that all consecutive patients within a county were included, and it can therefore report real-world data about the pacemaker population. As the entire cohort consisted of patients with an indication for pacemaker implantation, we had no control group of patients with device-detected AF but no indication for pacing. Therefore, as patients with sinus node disease and AV block are often of advanced age and have comorbidities, the ischaemic stroke risk associated with device-detected AF may have been overestimated, i.e. not solely dependent on the occurrence of device-detected AF. Instead, it may have represented an overall high ischaemic stroke risk due to advanced age and multiple risk factors. The same reasoning applies to the group with clinical/known AF at implantation, and it can be argued that this cohort constitutes a selected part of the AF population with a higher risk of

ischaemic stroke and dementia in general. There is emerging evidence that AF is often associated with overt or hidden cardiovascular disease (187, 188).

Studies II and III were observational studies, and hence also carry the risk of unmeasured confounding. The cohort was recruited from syncope patients who, after initial investigation, were either referred to a cardiologist or hospitalised due to syncope, which means that there was a selected group of syncope patients, i.e. selection bias. Our cohort is likely to represent patients with a slightly higher risk of underlying arrhythmia, rather than the syncope population as a whole. All patients had a clinical indication for an ILR, and we had no control group of patients with no ILR. As selecting patients is an aspect of internal validity, and internal validity is a pre-requisite for external validity, the results from these studies should be interpreted in their proper context and not generalised to the syncope population as a whole. On the other hand, the strength of the studies is that they represent real experience of the use and diagnostic yield of an ILR in syncope patients.

Study IV was a prospective cohort study and should theoretically be less exposed to biases and confounding. The cohort constituted a subgroup of patients in the AFAF study, and as the patients were not recruited by randomisation but through questioning, there is a risk of selection bias. The gender distribution was somewhat skewed, with only one of 40 patients being a woman. Furthermore, the small sample size brings a degree of uncertainty to the results and its generalisability to the general population. Moreover, we cannot exclude the possibility that some patients had asymptomatic AF before inclusion, as they were not monitored prior to surgery. The interpretation of the ECG recordings was not blinded, and accordingly there is a risk of information bias in terms of differential misclassification, i.e. we may have been more prone to classify a recording as AF if it was in line with our hypothesis. To address this risk, recordings interpreted as AF by primary investigator always underwent a second interpretation by a second investigator. Additional strength of the study is the low number of dropouts. Regarding the nature of confounders, we know that postoperative AF is associated both with CABG surgery and the risk of having a future diagnosis of AF (146, 179), but we do not know about causation.

8 CONCLUSIONS

CIEDs are a valuable resource in arrhythmia diagnostics, and can provide guidance in making clinical decisions.

Asymptomatic episodes of subclinical AF/AHREs were common in the pacemaker population, and were associated with older age and congestive heart failure. The ischaemic stroke incidence was low, most likely due to the high proportion of patients receiving OAC treatment. Nevertheless, clinical/known AF was associated with increased risk of developing vascular dementia.

In syncope patients receiving an ILR bifascicular block at baseline 12-lead ECG was a strong predictor of a clinically adjudicated arrhythmia-caused syncope, with the most common cause being an underlying bradyarrhythmia due to intermittent complete heart block. It would therefore seem reasonable to consider direct permanent pacing without further investigation in older patients with bifascicular block and unexplained syncope.

Recurrence of syncope was more common in women than in men, a difference mainly driven by a higher incidence of syncope with non-arrhythmic cause. Patients ≥60 years of age had the lowest rate of pre-implant tests, probably because of a strong clinical suspicion of an underlying arrhythmia, and they also had the highest rate of arrhythmic syncope.

In patients treated with CABG surgery, those with incident AF during hospitalisation had a high recurrence rate, most often within the first 30 postoperative days. AF recurrence after the first month was less frequent. The CHA_2DS_2-VASc score was higher in patients with AF than patients who remained in sinus rhythm. Handheld ECG identified fewer than half of the patients with AF episodes after discharge, probably because of a low AF burden.

9 CLINICAL IMPLICATIONS

Where AHREs are detected, the diagnosis should be verified by e.g. intracardiac EGMs, and the patient should be assessed in terms of indication for OAC treatment. Moreover, stroke-risk factors should be addressed (20). Therefore, there is potential value in diagnosing subclinical AF/AHREs early, as it enables physicians to assess the patients for OAC treatment according to current guidelines, potentially offer them treatment, and initiate appropriate lifestyle interventions. However, results are awaited from randomised trials on the benefit of OAC treatment in this population.

In evaluating syncope patients, gender has implications for the rate of syncope recurrence while the number of diagnostic tests upfront ILR implantation does not impact the diagnostic yield. In individual patients, given a non-diagnostic workup, in combination with a risk assessment with raised concerns of an underlying arrhythmia, it may be reasonable to bypass aspects of recommended investigations (100) in favour of long-term ECG monitoring. As bifascicular block proved to be a strong predictor of a clinically adjudicated arrhythmia-caused syncope due to bradyarrhythmia with intermittent complete heart block, we propose adopting a more liberal attitude in terms of considering direct permanent pacemaker in these patients.

After CABG surgery, episodes of incident AF are common during the early postoperative period, but a proportion of AF diagnoses were detected later, during the out-of-hospital monitoring period. Detecting these episodes is of clinical interest, due to the fact that AF in this setting is associated with increased mortality and morbidity (137, 145, 146, 149, 189, 190), and that both European (20) and American (26, 77) AF guidelines recommend considering long-term OAC treatment in patients with postoperative AF with stroke-risk factors. In brief, our study indicated that long-term ECG monitoring, especially during the first 30 postoperative days, had a high yield of incident and recurrent AF episodes. Thus, after the first month, the AF incidence and recurrence rate was low. Our study is small and should be seen as hypothesis-generating, but long-term ECG monitoring seems most important during the first postoperative month.

10 FUTURE PERSPECTIVES

It is well-established that clinical AF increases the risk of ischaemic stroke, and that these patients benefit from OAC treatment in the presence of stroke-risk factors. However, the knowledge is more limited when it comes to device-detected AF, i.e. subclinical AF and AHREs. If the three ongoing randomised trials (ARTESiA (NCT01938248), NOAH-AFNET 6 (NCT02618577) and SILENT (NCT02004509)) evaluating the benefit of OAC treatment for ischaemic stroke incidence in patients with subclinical AF/AHREs (78-80) are positive we can expect that device monitoring will become more important. On the contrary, if they are negative observational studies will become more important for studying the effect of AF burden.

A closely related matter involves whether there is a cut-off value for subclinical AF/AHRE burden when OAC treatment results in a positive net benefit, or whether there is a continuing increased risk following increased subclinical AF/AHRE burden? The obvious reason why this is difficult to clarify is that it is not possible to study it within the framework of randomised trials, though it would be possible through observational studies. A large observational study conducted in a country with high-quality registers (e.g. Sweden) could be a complement to aforementioned large randomised trials. Furthermore, a number of factors need to be taken into consideration, such as whether the total subclinical AF/AHRE burden is the important issue, or whether the number of episodes or the longest duration of a single episode of subclinical AF/AHRE are of importance?

Despite the fact that subclinical AF/AHREs are associated with increased risk of ischaemic stroke, no temporal relationship has been shown between the occurrence of subclinical AF/AHREs and ischaemic stroke. This raises a question about the true mechanism involved in ischaemic stroke in patients with subclinical AF/AHREs. More recently, the state of atrial cardiomyopathy has attracted more attention. Atrial cardiomyopathy contributes to a prothrombotic milieu, and perhaps the occurrence of subclinical AF/AHREs is an expression of a diseased atria, and an indication of patients at high risk for ischaemic stroke rather than the actual cause. Moreover, patients with AF often have associated cardiovascular diseases. It would therefore be interesting to investigate the most important action in AF clinics for reducing the symptom burden in AF patients. In future, treatment may be more focused, and there may be specialist clinics for risk-factor prevention.

Does postoperative AF pose the same risk of ischaemic stroke as other types of AF? In study IV, we found that episodes of AF were common in patients both with and without incident AF during inpatient care. Is the presence of AF the key factor, or does it simply indicate a population with high cardiovascular risk, i.e. presence of coronary artery disease with

inflammatory activation, who might benefit from OAC treatment independent of AF? It would have been interesting to see the outcome of a clinical trial randomising patients with postoperative AF after CABG surgery to either OAC or antiplatelet drugs, or to see the results of a clinical trial randomising to extended diagnostics and treatment.

What is the way forward in terms of improving estimates of risk of ischaemic stroke in patients with clinical AF or device-detected AF? Do their different characteristics matter, and what is the significance of frequent or short runs of supraventricular extrasystoles not fulfilling the criteria for AF diagnosis? Or should biomarkers, which can reveal myocardial stretch, disturbed hemostasis and general inflammatory activation in the cardiovascular system, be considered sufficient for estimating the risk of ischaemic stroke?

Another interesting topic making considerable progress is artificial intelligence (AI). AI has shown promising results in diagnosing AF from ECGs in sinus rhythm (191). The AI network can identify subtle ECG patterns not visible to the human eye, and has great potential for improving the effectiveness of ECG screening. Perhaps AI in future can help analysing the atrial signal in patients with CIEDs to identify those at high risk of ischaemic stroke? Our results from studies II and III showed that it is difficult to predict syncope mechanism from pre-implant characteristics other than bifascicular block. In the light of this, it would be interesting to see if AI can also help to discern which syncope patients are at high risk of arrhythmic syncope in future. Because AI analyses require a large amount of data, it may be more difficult to succeed in syncope patients compared to device patients.

11 SVENSK SAMMANFATTNING

11.1 BAKGRUND

Gemensamt för samtliga kardiovaskulära implanterbara device som pacemakers och diagnostiska hjärtmonitorer är att de möjliggör kontinuerlig registrering av hjärtats rytm. Eftersom tiden som hjärtat övervakas har stor betydelse för hur mycket rytmrubbningar man hittar utgör implanterbara device en stor diagnostisk möjlighet.

Patienter som är i behov av implanterbara device är vanligtvis äldre, vilket innebär att de ofta har riskfaktorer för den vanligaste hjärtrytmrubbningen med klinisk relevans nämligen förmaksflimmer. Förutom ålder är hypertoni, diabetes, övervikt, alkohol och underliggande hjärtsjukdom exempel på riskfaktorer för förmaksflimmer, men förmaksflimmer kan också debutera efter en större operation sannolikt pga. en kombination av vätskebrist, stresspåslag och inflammation i operationsområdet. Förmaksflimmer innebär att hjärtat slår oregelbundet, men inte alla patienter har symptom. Det är dock viktigt att upptäcka förmaksflimmer eftersom det obehandlat innebär en kraftigt ökad risk för stroke hos de flesta individer. Behandling med blodförtunnande läkemedel som är indicerat hos de flesta med förmaksflimmer minskar risken för stroke med nästan 70%.

En pacemaker består vanligtvis, förutom av själva dosan där batteriet finns, av två elektroder, en som är placerad i hjärtats högra kammare och en som är placerad i hjärtats högra förmak. Via dessa elektroder övervakas hjärtats rytm kontinuerligt och episoder med snabb frekvens i förmaket kan detekteras och sparas. Dessa episoder kallas device-detekterat förmaksflimmer och innebär ökad risk för stroke även om riskökningen inte tycks vara lika stor som vid förmaksflimmer dokumenterat med 12-avlednings elektrokardiogram (EKG) och nyttan av blodförtunnande behandling hos dessa patienter är ännu inte bevisad.

Svimning innebär en kort medvetandeförlust. Det finns många möjliga orsaker till svimning, varav en kan vara en rubbning i hjärtrytmen. Det är ofta svårt att fånga själva rytmrubbningen på akutmottagningen eftersom EKG registreringen måste göras just vid tillfället för svimningen. Med hjälp av en implanterbar hjärtmonitor som opereras in precis under huden på vänstra sidan av bröstkorgen kan hjärtats rytm övervakas under en längre tid med möjlighet till EKG registrering vid förnyad svimning, vilket kan avslöja om den underliggande mekanismen till svimningen är en hjärtrytmrubbning.

Syftet med denna avhandling är att belysa olika aspekter av hjärtrytmrubbningar diagnostiserade med implanterbara device. I studie I beskrivs förekomsten av device-detekterat förmaksflimmer i en pacemakerpopulation samt patienternas blodförtunnande

behandling och förekomst av ischemisk stroke och vaskulär demens. Studie II och III berör patienter som erhållit en implanterbar hjärtmonitor pga. svimning. I studie II tittade vi på om fynd på 12-avlednings EKG kunde prediktera mekanismen till svimningen och i studie III undersökte vi om ålder och kön påverkade dels utredningen innan implantationen av hjärtmonitorn samt det diagnostiska utbytet av hjärtmonitorn. I det fjärde delarbetet undersökte vi med hjälp av en implanterbar hjärtmonitor om patienter som fått förmaksflimmer precis efter att de genomgått en operation av hjärtats kranskärl hade stor risk att återfå förmaksflimret under 12-månaders tid. Därtill ville vi beräkna total tid patienterna i genomsnitt tillbringar i förmaksflimmer s.k. förmaksflimmerbörda.

11.2 METOD OCH RESULTAT

I studie I inkluderades konsekutiva patienter i Region Halland under åren 2010–2014 som erhållit en pacemaker med förmakselektrod. Under uppföljningen noterades förekomst av device-detekterat förmaksflimmer och insättande av blodförtunnande behandling hos patienter utan känt förmaksflimmer. Hos patienter med känt förmaksflimmer vid implantationen noterades förändring av blodförtunnande behandling. Uppföljningstiden för detektion av device-detekterat förmaksflimmer var till slutet av 2015 och vid slutet av 2017 inhämtades data avseende förekomst av ischemisk stroke och vaskulär demens via Regionalt Patientregister. Vid inklusion hade 271 patienter känt förmaksflimmer och av dem hade 80% (216/271) pågående blodförtunnade behandling. Fyrahundra elva patienter hade inte någon känd förmaksflimmerdiagnos och av dem diagnostiserades 30% (125/411) med device-detekterat förmaksflimmer under uppföljningstiden på 38 månader (medel). Av dessa förskrevs 62% behandling med blodförtunnade läkemedel. Hjärtsvikt (p= .03) och ålder >75 år (p= .0002) var riskmarkörer för att utveckla device-detekterat förmaksflimmer. Den årliga stroke risken var 2.1% hos patienter med känt förmaksflimmer jämfört med 1.9% hos patienter med device-detekterat förmaksflimmer och 1.4% hos patienter helt utan någon typ av förmaksflimmer. Vaskulär demens förekom hos 11.2% av patienterna med känt förmaksflimmer jämfört med 6.2% av patienterna utan förmaksflimmer (p= .048) samt 5.6% av patienterna med device-detekterat förmaksflimmer (p= .09).

Studiepopulationen i studie II och III bestod av konsekutiva patienter i Region Halland som under åren 2007–2016 erhållit en implanterbar hjärtmonitor på indikationen svimning. Notera skillnaden mellan de två begreppen diagnos via hjärtmonitorn (studie II) och EKG-baserad diagnos (studie III). Diagnos via hjärtmonitorn innefattar alla patienter där hjärtmonitorn gett vägledning i diagnostiken dvs. där det funnits EKG registreringar både vid förnyad svimning eller andra tillfällen som möjliggjort att man kunnat ställa en klinisk diagnos. EKG-baserad diagnos innefattar endast de som haft förnyad svimning under uppföljningstiden.

Totalt inkluderades 300 patienter, varav 49% (n=147) var kvinnor. Medelålder 66±16 år. I studie II erhöll 49% (146/300) av patienterna en diagnos via hjärtmonitorn. Patienter med bifascikulärt block på 12-avlednings EKG erhöll oftare en diagnos via hjärtmonitorn 76% (25/33) jämfört med de med normalt 12-avlednings EKG 44% (90/205), p< .001. Bland de med bifascikulärt block på 12-avlednings EKG erhöll 96% (24/25) en klinisk diagnos av bakomliggande hjärtrytmrubbning som orsak till sin svimning, av vilka 23 hade en EKG registrering med bradykardi (långsam hjärtrytm). Bifascikulärt block förekom nästan uteslutande hos de ≥60 år (31/33). Justerat odds ratio för att erhålla en klinisk diagnos av svimning pga. hjärtrytmrubbning vid bifascikulärt block var 5.5 (95%CI 2.3–13.2), p< .001. Positivt prediktivt värde för bifascikulärt block att prediktera en klinisk diagnos av svimning pga. hjärtrytmrubbning var 73%, och negativt prediktivt värde var 73%. Inga andra fynd på 12-avlednings EKG påverkade utfallet av långtids-EKG registreringen. I studie III sågs att kvinnor oftare än män hade förnyad svimning och erhöll en EKG-baserad diagnos (kvinnor: 56/147, 38%; män: 33/153, 22%; p= .001), framförallt utgjordes skillnaden mellan kvinnor och män av svimning pga. annan orsak än hjärtrytmrubbning dvs normal EKG registrering vid tillfället för ny svimning (kvinnor: 27/147, 18%; män: 15/153, 10%; p= .045). Patienter ≥60 år genomgick färre diagnostiska test innan implantationen av hjärtmonitorn, men hade högre förekomst av förnyad svimning pga. hjärtrytmrubbning (<40 år: 3/11, 27%; 41–59 år: 7/18, 39%; and ≥60 år: 37/60, 62%; p= .045). Bradykardi var vanligast bland de ≥60 år (<40 år: 1/11, 9%; 41–59 år: 5/18, 28%; and ≥60 år: 33/60, 55%; p= .06). Dessutom hittades hos en fjärdedel av patienterna utan förnyad svimning EKG registreringar som kan indikera svimning pga. hjärtrytmrubbning.

Studie IV var en substudie till den prospektiva studien som på engelska förkortas AFAF study. I korthet utvärderar studien förekomsten av förmaksflimmer hos 250 patienter som genomgått perkutan koronar intervention eller operation av hjärtats kranskärl genom att jämföra icke-invasiv handhållen EKG-registrering tre gånger om dagen under första månaden och därefter två veckor vid tre, 12 och 24 månader efter operation med rutinsjukvård. I substudien genomgår patienterna som tillägg kontinuerlig monitorering med en implanterbar hjärtmonitor. Primärt utfallsmått var andelen av patienter som återföll eller diagnostiserades med nytt förmaksflimmer under 12-månaders uppföljning, medan sekundära utfallsmått var förmaksflimmerbörda och andelen som utvecklade persisterande (ihållande) förmaksflimmer. Tjugosju (68%) av patienterna diagnostiserades med förmaksflimmer, 21 under sjukhusvistelsen och sex patienter under uppföljningstiden. Arton (67%) av dem hade mer än en episod av förmaksflimmer, varav en patient utvecklade persisterande förmaksflimmer. Två patienter utvecklade persisterande förmaksflimmer redan vid deras första förmaksflimmerepisod. Episoder med förmaksflimmer var speciellt vanligt under de första 30

postoperativa dagarna, då 17/40 patienterna hade minst en episod med förmaksflimmer under denna tid. Efter de första 30 dagarna, nydiagnostiserades bara tre patienter med förmaksflimmer och 10 patienter återföll i förmaksflimmer. Hos patienter med paroxysmalt förmaksflimmer var förmaksflimmerbördan låg, 0.1% (interkvartilavstånd 0.28). Patienter med förmaksflimmer hade högre poäng på CHA_2DS_2-VASc skalan (beslutsstöd inkluderandes riskfaktorer för stroke för att värdera indikation av blodförtunnande läkemedel vid förmaksflimmer) jämfört med patienterna som behöll sinusrytm (median 4, interkvartilavstånd 1; median 3, interkvartilavstånd 2; p= .006). Handhållen EKG-registrering tre gånger dagligen identifierade 45% (9/20) av patienterna med förmaksflimmer identifierade via hjärtmonitorn, p= .001.

11.3 SLUTSATSER

Kardiovaskulära implanterbara device utgör genom sin kontinuerliga övervakning en stor möjlighet för diagnostik av hjärtrytmrubbningar samt för vägledning vid kliniska beslut.

Asymptomatiska episoder av device-detekterat förmaksflimmer var vanligt hos pacemakerpatienter och associerat med högre ålder samt hjärtsvikt. Förekomsten av ischemisk stroke var låg troligtvis pga. att en stor andel av patienterna behandlades med blodförtunnande läkemedel. Däremot var känt förmaksflimmer associerat till ökad risk för vaskulär demens.

Hos patienter med synkope som erhöll en implanterbar hjärtmonitor predikterade bifascikulärt block på 12-avlednings EKG en framtida klinisk diagnos av bakomliggande hjärtrytmrubbning som orsak till svimning, oftast pga. bradykardi orsakat av totalblock. Därav är det rimligt att överväga direkt pacemakerimplantation istället för att implantera en hjärtmonitor hos äldre patienter med bifascikulärt block och oförklarad svimning.

Kvinnor svimmade pånytt oftare än män, en skillnad som huvudsakligen drevs av att kvinnor oftare återföll i svimning pga. annan orsak än hjärtrytmrubbning. Patienter ≥60 år genomgick färre diagnostiska test innan implantation av en hjärtmonitor, troligtvis pga. hög misstanke om svimning orsakat av en hjärtrytmrubbning. Patienter ≥60 år hade också den högsta förekomsten av svimning pga. hjärtrytmrubbning.

Patienter med förmaksflimmer under den postoperativa sjukhusvistelsen efter kranskärlsoperation hade hög förekomst av återfall av förmaksflimmer, speciellt under de första 30 postoperativa dagarna. Därefter var återfallsfrekvensen låg. Handhållen EKG-registrering identifierade mindre än hälften av patienterna med förmaksflimmer på hjärtmonitorn, troligtvis pga. att de flesta förmaksflimmerepisoderna hade kort duration.

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