Catheter ablation for atrial fibrillation
– effects on rhythm, symptoms and health-related quality of life

To my family

Örebro Studies in Medicine 175

ANNA BJÖRKENHEIM

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Abstract

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Background: AF ablation is an increasingly used treatment in patients with AF to improve patient-reported outcomes (PROs). Atrioventricular junction ablation (AVJA) is a palliative treatment option in therapy refractory AF that improves PROs but renders the patient pacemaker dependent.

Aims: To evaluate rhythm control and PROs before and up to two years after AF ablation. To analyze the long-term incidence of and predictors of hospitalization for HF and all-cause mortality in patients who underwent AVJA and right ventricular pacing.

Methods and Results: Fifty-four patients underwent AF ablation and both continuous rhythm monitoring via an implantable loop recorder (ILR) and intermittent rhythm monitoring three, six, 12 and 24 months after ablation. 76 % of patients had at least one AF recurrence, of whom 24 % were only detected by ILR. One third of symptom recordings did not show AF. The AF-specific AF6 scores, physician-assessed EHRA symptom class and both SF-36 summary scores all improved significantly from before to two years after ablation. There was a weak correlation between the change in AF6 scores and EHRA class from before to six and 12 months but not to 24 months after ablation. Responders to ablation (AF burden < 0.5 %), reached age- and sex-matched norms in all SF-36 domains, but non-responders only in social functioning and MCS. All AF6 scores showed at least moderate improvement in both responders and non-responders. Higher AF burden was independently associated with poorer PCS and AF6 scores. In 162 patients who underwent AVJA, hospitalization for HF occurred in 20 % of patients (two-year cumulative incidence 9.1 %) and 22 % died (two-year cumulative incidence 5.2 %) during a median follow-up of five years. QRS ≥ 120 ms and left atrial diameter were independent predictors of hospitalization for HF, and hypertension and previous HF of death.

Conclusions: Continuous rhythm monitoring was superior to intermittent monitoring. The AF-specific AF6 was more sensitive to changes related to AF burden after AF ablation than both EHRA class and the SF-36. The long-term hospitalization rate for HF and all-cause mortality was low after AVJA.

Keywords: Atrial fibrillation, catheter ablation, symptoms, quality of life.

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LIST OF PAPERS

This thesis is based on the following original papers, henceforth referred to by their Roman numerals:

I. Björkenheim A, Brandes A, Andersson T, Magnuson A, Edvardsson N, Wandt B, Sloth Pedersen H, Poçi D. Predictors of hospitalization for heart failure and of all-cause mortality after atrioventricular nodal ablation and right ventricular pacing for atrial fibrillation. Europace. 2014 Dec;16(12):1772-8.

II. Björkenheim A, Brandes A, Chemnitz A, Magnuson A, Edvardsson N, Poçi D. Rhythm Control and Its Relation to Symptoms during the First Two Years after Radiofrequency Ablation for Atrial Fibrillation. Pacing Clin Electrophysiol. 2016 Sep;39(9):914-25.

III. Björkenheim A, Brandes A, Chemnitz A, Magnuson A, Edvardsson N, Poçi D. Assessment of atrial fibrillation-specific symptoms before and two years after atrial fibrillation ablation - do patients' and physicians differ in their perception of symptom relief? JACC Clin Electrophysiol. 2017 Oct;3(10):1168-1176.

IV. Björkenheim A, Brandes A, Chemnitz A, Magnuson A, Edvardsson N, Poçi D. Patient-reported outcomes in relation to continuously monitored rhythm before and during two years after atrial fibrillation ablation using a disease-specific and a generic instrument. J Am Heart Assoc. 2018 Feb 24;7(5). pii:e008362. doi:10.1161/JAHA.117.008362.

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LIST OF ABBREVIATIONS

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
AF6	Atrial fibrillation 6 questionnaire
AT	Atrial tachycardia
AV	Atrioventricular
AVJA	Atrioventricular junction ablation
BMI	Body mass index
b.p.m.	Beats per minute
CHA_2DS_2-VASc	Congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex (female)
CI	Confidence interval
CRT	Cardiac resynchronization therapy
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
ES	Effect size
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HF	Heart failure
HR	Hazard ratio
HRS	Heart Rhythm Society
HRQoL	Health-related quality of life
ICD	Implantable cardioverter defibrillator
ILR	Implantable loop recorder
IQR	Interquartile range
LV	Left ventricular
LVEF	Left ventricular ejection fraction
OAC	Oral anticoagulation
OR	Odds ratio
PV	Pulmonary vein
QoL	Quality of life
RV	Right ventricular
RF	Radiofrequency
SD	Standard deviation
SF-36	Short form 36 health survey
TIA	Transient ischaemic attack

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia and the number of patients with AF is expected to increase substantially in the coming decades[1]. The presence of AF is independently associated with an increased risk of all-cause mortality and morbidity, largely due to stroke and heart failure (HF), dementia and impaired health-related quality of life (HRQoL)[2-8]. The management of AF aims to reduce symptoms, improve HRQoL and prevent AF-related complications[9].

Catheter ablation for AF, AF ablation, is an increasingly used treatment for symptomatic AF in patients who have failed antiarrhythmic medication and in selected patients as a first-line treatment. Arrhythmia recurrences are common, however, and repeat ablation is often required to achieve symptom control[9]. Success after AF ablation has primarily been reported as freedom from or reduction of AF recurrences based on intermittent rhythm monitoring. This strategy may overestimate success rates due to an increased proportion of asymptomatic AF after ablation[10, 11]. Implantable loop recorders (ILRs) have proven highly sensitive in detecting AF and an accurate AF burden[12] and may be useful in determining whether patients are truly free of AF recurrences. However, the main purpose of AF intervention is a reduction of symptoms and improvement in HRQoL, i.e. improvement of patient-reported outcomes (PROs)[9]. The effect on PROs has mainly been reported as secondary endpoints, predominantly using generic instruments[13, 14]. The optimal follow-up strategy after AF ablation has yet to be defined.

Atrioventricular junction ablation (AVJA) and pacemaker implantation is a palliative intervention option in therapy refractory AF. AVJA has been shown to reduce symptoms and healthcare utilization and to increase the HRQoL[7, 15]. However, patients become permanently pacemaker dependent after the AVJA and long-term right ventricular (RV) pacing may cause a deterioration of HF and even new HF in some patients[16, 17].

In the papers presented in this thesis, I studied (1) the long-term risk of HF and all-cause mortality in patients who underwent AVJA and RV pacing and (2) the effects of AF ablation on symptoms and HRQoL in relation to the continuously monitored rhythm up to two years after ablation.

BACKGROUND

Epidemiology

AF affects approximately 3 % of adults aged 20 years or older in Western countries[2, 3] with the prevalence increasing further with age[18] and risk factors such as hypertension, structural heart disease, obesity, diabetes mellitus and chronic kidney disease[19-21]. The number of patients with AF is expected to increase substantially in the coming decades due to population ageing and accumulation of cardiovascular diseases and risk factors[1, 22], Figure 1. The prevalence of AF is lower in women but the all-cause mortality is higher in women (twofold increase) than in men (1.5-fold increase)[18, 23, 24]. Even when patients with AF receive adequate oral anticoagulation (OAC) therapy, many still die prematurely, often from HF or sudden death, while stroke can largely be prevented[25-27].

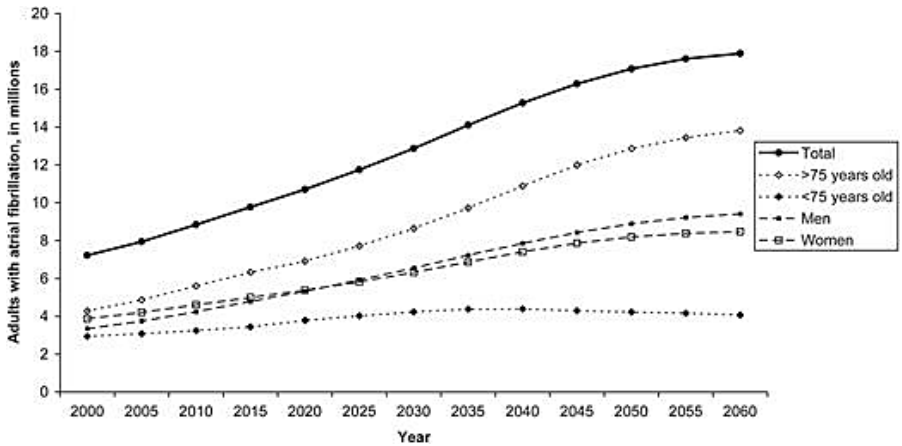

Figure 1. Projected number of adults with atrial fibrillation in the European Union between 2000 and 2060. Reprinted with permission from Oxford University Press[22].

Definitions and Classification

Definition of AF

The diagnosis of AF is based on an electrocardiogram (ECG) characterized by an absolutely irregular RR interval, no distinct P waves and an atrial cycle length, when visible, of less than 200 ms. By accepted convention, an episode with these ECG characteristics lasting for at least 30 seconds is diagnostic of AF[9, 28].

Classification of AF

AF is a progressive disease that typically progresses from short, infrequent self-terminating episodes to longer and more frequent episodes and, after variable time, sustained episodes[9]. AF is classified into five types[9]:

1. First diagnosed AF: AF that has not been diagnosed before
2. Paroxysmal AF: AF that terminates spontaneously or with intervention within seven days of onset
3. Persistent AF: AF that last longer than seven days. Episodes often require pharmacologic or electrical cardioversion to restore sinus rhythm
4. Long-standing persistent AF: AF that has lasted for more than 12 months
5. Permanent AF: AF that is accepted by both the patient and the physician and for which no further attempts to restore or maintain sinus rhythm will be undertaken

It is recommended that patients be categorized by the predominant pattern if both persistent and paroxysmal episodes are present[9].

Patient-Reported Outcomes (PROs)

PROs, such as symptoms, functioning, quality of life, HRQoL and utility, are reported directly by the patient, without interpretation by physicians or others, and inform about disease burden and overall well-being[29], Figure 2.

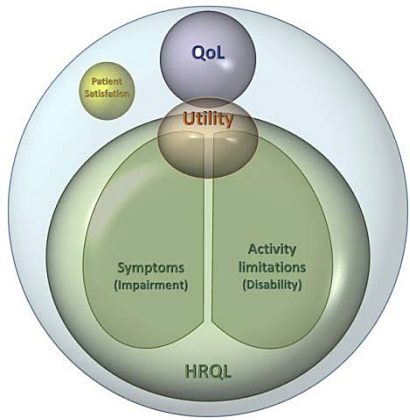

Figure 2. Different types of patient-reported outcomes. HRQL = health-related quality of life; QoL = quality of life. Reprinted with permission under the terms of the Creative Commons Attribution License http://creativecommons.org/licences/by/3.0/[30].

Symptoms

About one third of AF patients do not have any perceived AF-associated symptoms, silent AF[31], but up to one fourth of patients report severe symptoms[32]. Patients with silent AF are still at risk for complications[33] and not uncommonly first present with stroke[34]. Furthermore, asymptomatic AF episodes are common even in patients who are highly symptomatic[10]. AF is usually associated with a variety of symptoms such as palpitations, dyspnoea, chest discomfort, dizziness and syncope[35, 36]. In addition, one third of patients with symptomatic AF suffer from psychological distress (anxiety and/or depression)[37, 38]. Several symptom scales to assess the severity of various tachyarrhythmias exist, including the Symptom Checklist, Frequency and Severity scale[39], the Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia[40] and the Umea 22 Arrhythmia Questions protocol[41]. In the last decades, purely AF-specific instruments have been validated but have different measurement properties, Table 1.

Quality of Life

Quality of life is defined by the Food and Drug Administration (FDA) as a general concept that implies an evaluation of the effect of all aspects of life on general well-being[29]. The term HRQoL is frequently used in order to focus on aspects of quality of life that are related to health and is a complex concept composed of multiple domains that comprehensively measure symptoms and functional limitations[30]. HRQoL is measured by patient-reported questionnaires. Generic instruments, for example the Short form 36 health survey (SF-36), allow comparisons across different patient populations and with the general population and are extensively validated. However, generic instruments measure general health rather than symptoms specific to a single disease and are therefore influenced by patient demographics and comorbidities and may lack responsiveness to changes in patients' health status. Disease-specific instruments are developed to address those aspects of outcome that are important for a particular patient population, i.e. have a high specificity. Both the FDA and the European Heart Rhythm Association (EHRA) recommend the use of a comprehensive, validated AF-specific questionnaire to measure HRQoL in patients with AF[29, 42]. However, published validation data for AF-specific instruments are very limited, Table 1.

HRQoL is impaired in the majority of patients with AF compared to both the general population, healthy controls and patients with coronary artery disease[35, 43, 44]. In addition to symptoms caused by AF, comorbidities and treatment for AF including side effects of drugs and interventions, and anxiety associated with AF, may have a negative impact on HRQoL[38]. Female sex and younger age are also known to adversely affect the HRQoL in patients with AF[45]. Interestingly, even patients who report no symptoms of AF have an impaired HRQoL compared to the general population[7, 31].

Table 1. Existing AF-specific PRO instruments

Instrument	Number of items	Domains	Response options	Advantages	Disadvantages
AF symptom scales					
AF6[46, 47]	6	Breathlessness at rest and on exertion, limitations in daily life, discomfort, fatigue, anxiety due to AF	10 point Likert scale	Simple and short. Fair internal consistency and structural validity.	Evaluated in 2 studies utilizing the same cohort. Unknown cross-cultural validity. Uncertain generalizability.
AFSymp[48]	11	Heart symptoms, tiredness, chest discomfort, dizziness and shortness of breath	7 point Likert scale	Simple. Strong internal consistency. Fair content validity and cross-cultural validity.	Responsiveness not evaluated.
MAFSI[49]	12	Symptoms, frequency of symptoms	5 point and 3 point Likert scale	Responsive to ablation outcome.	Not validated. Unknown measurement properties.
SCL[39]	16	Symptoms frequency scale and symptom severity scale	3 point Likert scale for severity and 5 point for frequency	Widely used. Fair responsiveness.	No development or validation information in AF patients. Exists in different versions. Unknown measurement properties. Relatively time-consuming.
University of Toronto AFSS[35, 50]	14	Frequency, duration and severity of episodes, and healthcare use	11 point Likert scale	Fair internal consistency, test-retest reliability, construct validity and responsiveness.	Relatively time-consuming. Uncertain generalizability.

AF-specific quality of life instruments					
AFEQT[51]	20	Symptoms, daily activities, treatment concerns, treatment satisfaction	7 point Likert scale	Simple. Well validated and consistently strong measurement properties.	Unknown measurement error and cross-cultural validity.
AFImpact[52]	18	Vitality, emotional distress, sleep	7 point Likert scale	Well validated. Strong internal consistency and fair content validity.	Uncertain generalizability.
AFQLQ[53, 54]	26	Variety and frequency of symptoms, severity of symptoms, limitation in daily and special activities and mental anxiety	4-6 options of ranging severity dependent on domain	Fair internal consistency, test-retest reliability and structural validity.	Time-consuming. Several measurement properties unknown. Uncertain generalizability.
AFQoL[55, 56]	18	Psychological, physical, sexual activity	5 point Likert scale	Strong content validity, fair internal consistency and structural validity.	Unknown cross-cultural validity. Uncertain generalizability.
QLAF[57]	22	Palpitations, chest pain, breathlessness, dizziness, drugs, electrical cardioversion, ablation	Letters assigned to text options and yes/no tick boxes	Fair test-retest reliability.	Relatively time-consuming. Mostly unknown measurement properties. Uncertain generalizability.

AF = atrial fibrillation; AF6 = atrial fibrillation 6; AFEQT = atrial fibrillation effect on quality of life questionnaire; AFImpact = atrial fibrillation-specific impact questionnaire; AFSS = atrial fibrillation severity scale; AFSymp = atrial fibrillation-specific symptom questionnaire; AFQLQ = Japanese Society of Electrocardiology's atrial fibrillation quality of life questionnaire; AFQoL = atrial fibrillation quality of life; MAFSI = Mayo atrial fibrillation-specific symptom inventory; SCL = symptom checklist, frequency and severity scale; SF-36 = short form 36 health survey; QLAF = quality of life in atrial fibrillation.

Physician-Assessed Outcomes

The physician-assessed EHRA classification is used for symptom severity assessment in patients with AF, relating specifically to the time when patients feel symptoms of AF[42]. A modification subdividing EHRA class II into mild (IIa) or moderate (IIb) symptoms was proposed in 2014 to identify patients with a health utility benefit of rhythm control (EHRA class IIb)[58], Table 2. Limitations of the EHRA classification include that it only takes symptoms and no other HRQoL dimension into account and that it is the physician who assesses the patients' symptoms.

Table 2. The modified European Heart Rhythm Association symptoms scale[58]

	Symptoms	Description
I	None	AF does not cause any symptoms
IIa	Mild	Normal daily activity not affected by symptoms associated with AF
IIb	Moderate	Normal daily activity not affected, but patient troubled by symptoms associated with AF
III	Severe	Normal daily activity affected by AF
IV	Disabling	Normal daily activity disrupted because of AF

The Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale (CCS-SAF) is a similar score validated against SF-36 and University of Toronto atrial fibrillation severity scale[59, 60]. Patients in class 0 are considered to have no symptoms, in class I minimal, class II minor, class III moderate, and in class IV symptoms of AF that have a severe effect on patients' quality of life.

AF Management

AF management includes acute stabilization of the patient, detection and management of underlying cardiovascular conditions, OAC therapy for stroke prevention and a rate or rhythm control strategy[9]. OAC therapy has prognostic benefits[27, 61] while rate and rhythm control strategies are mainly used to improve symptoms[62] but may also preserve left ventricular (LV) function. The decision to use a rate or rhythm control strategy requires an integrated consideration of several factors, including severity of symptoms, type of AF, likelihood of successful cardioversion, patient age and comorbidities, and patients' preference.

Anticoagulation

Systemic embolization, particularly stroke, is the most frequent major complication of AF. AF, untreated, confers to a four- to fivefold increased risk of stroke compared to the general population[63]. OAC therapy can prevent the majority of ischaemic strokes in AF patients[61]. The stroke risk in AF patients is commonly estimated using the CHA_2DS_2-VASc score[9, 64] (Table 3 and Table 4) and OAC therapy is recommended for men with a score of 2 or more, and for women with a score of 3 or more, and should be considered for men with a score of 1 and women with a score of 2[9]. Interventional left atrial appendage occlusion may be considered in patients with contraindications for long-term OAC therapy[65-67].

Table 3. The CHA_2DS_2-VASc risk score[64]

Risk factor	Score
C - Congestive heart failure	1
H – Hypertension	1
A_2 - Age ≥75 years	2
D – Diabetes	1
S_2 - Prior stroke / TIA /thromboembolism	2
V - Vascular disease	1
A - Age 65-74 years	1
Sc – Sex category (female)	1

Maximum score 9. TIA = Transient ischaemic attack.

Table 4. Stroke risk stratification with the CHA_2DS_2-VASc score[64]

CHA_2DS_2-VASc score	Annual risk (%)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Rate Control

Many patients who present with AF require a slowing of the ventricular rate, i.e. rate control, to relieve AF-related symptoms and prevent a tachycardia-related impairment of LV function. A lenient rate control approach (resting heart rate <110 beats per minute (b.p.m.)) seems as effective as strict rate control (resting heart rate <80 b.p.m. and <110 b.p.m. during moderate exercise) in many patients based on one randomized study with composite outcomes[68] and a pooled analysis of the rate control arms of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control Efficacy in permanent atrial fibrillation) trials[69]. A stricter rate control is indicated for patients with persistent symptoms or tachycardia-related HF[9]. Rate control is generally achieved with drugs that slow conduction across the atrioventricular (AV) node, such as β blockers or non-dihydropyridine calcium channel blockers, in selected patients added by digoxin.

Atrioventricular junction ablation (AVJA)

AVJA and implantation of a pacemaker is a palliative treatment option in patients in whom pharmacological rate control or rhythm control is either unsuccessful or not tolerated[9, 70]. AVJA is effective in controlling the ventricular rate and regularising the rhythm and has been shown to improve both symptoms and HRQoL, based mostly on observational studies[70]. The procedure has a high success rate and a low complication rate[71, 72], in particular when the pacemaker is implanted several weeks before the AVJA and the initial pacing rate is set to 70 to 90 b.p.m. to decrease sympathetic activity and thus reducing the risk of ventricular arrhythmias and sudden death[73, 74]. However, the procedure is irreversible and renders the patient pacemaker dependent and long-term RV pacing can cause interventricular dyssynchrony which may impair LV systolic function[17]. In patients with impaired left ventricular ejection fraction (LVEF) prior to AVJA, cardiac resynchronization therapy (CRT) might be preferable to RV pacing to prevent worsening of HF[75-77].

Rhythm Control

Restoration and maintenance of sinus rhythm, i.e. a rhythm control strategy, is indicated to improve symptoms in patients with AF who remain symptomatic on rate control therapy, using cardioversion, antiarrhythmic drug (AAD) therapy, AF ablation, and/or a surgical procedure. After restoration of sinus rhythm, spontaneously or after pharmacological or elec-

trical cardioversion, AAD therapy is generally recommended as a first-line therapy. Some AADs are, however, associated with a potential for serious cardiac and/or extracardiac adverse side effects, particularly the induction of proarrhythmia[78]. Drug selection is based on the presence or absence of structural heart disease or HF, ECG variables and other comorbidities to ensure safety[9].

Importantly, a rhythm control strategy does not ensure the attainment of sinus rhythm or the outcomes that might accrue from it[62, 79] and is not proven more effective in improving HRQoL than rate control[44, 80]. In the ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400mg twice a day for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter) trial, however, dronedarone decreased the incidence of the combined endpoint cardiovascular hospitalization and death in patients with non-permanent AF[81]. AF ablation is proven to be more effective in maintaining sinus rhythm than therapy with AADs[82, 83]. A preliminary single-center study indicated improved morbidity and mortality with AF ablation compared to AADs[84] and a post-hoc on-treatment analysis of the AFFIRM study revealed that the presence of sinus rhythm was associated with a significant reduction in mortality, whereas the use of AADs increased mortality by 49 %[85]. This suggests that sinus rhythm may be preferred over rate control if not achieved by AADs. The ongoing, large, randomized CABANA (Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) and EAST (Early treatment of Atrial fibrillation for Stroke prevention Trial) trials will shed new light on whether AF ablation, combination therapy and early therapy lower the incidence of major cardiovascular events compared with drug therapy for rate or rhythm control. The recently published CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial showed that AF ablation in patients with HF was associated with a significantly lower rate of a composite endpoint of death or hospitalization for HF than medical therapy[86].

AF Ablation

Catheter ablation of AF is an increasingly used treatment for paroxysmal and persistent AF, and the main indication is symptomatic AF. AF ablation is indicated in selected patients with paroxysmal AF as first-line therapy, but more commonly in patients in whom AADs are not effective. AF ablation for persistent AF is less effective than for paroxysmal AF but can be considered in symptomatic patients who have failed AAD therapy[9].

Development of AF requires both a trigger that initiates AF and a susceptible substrate that generates and/or perpetuates AF. The primary trigger for most AF episodes involves electrical discharges within one or more pulmonary veins (PVs)[87]. The autonomic nervous system likely influences the initiation and perpetuation of AF[88]. The precise mechanisms for the development of AF are not fully understood, but the main goal in most AF ablation procedures is achievement of complete isolation of all PVs using a circumferential approach[89]. This approach mainly eliminates the trigger but may also alter the arrhythmogenic substrate[90] and interrupt innervation from cardiac autonomic ganglia[91]. The most common energy sources for ablation are radiofrequency (RF) energy applied in a point-by-point mode and cryogenic energy applied with a balloon in a single-step mode. Outcomes seem to be similar with both energy sources[92, 93]. AF ablation is performed either with conscious sedation or with anaesthesia. Patients are typically hospitalized for one night after the procedure.

AF ablation is an effective but complex procedure and 4 to 5 % of patients experience major complications such as stroke or transient ischaemic attack (TIA), tamponade, PV stenosis and atrio-oesophageal fistula[94]. Available data suggest that experienced centers are associated with lower rates of adverse events[95].

Arrhythmia Recurrences after AF Ablation

AF recurrences are common after AF ablation and most patients require more than one ablation procedure. Early AF recurrences during the first three months following the AF ablation procedure may occur, probably due to short-term inflammation, maturation of lesions and transient autonomic imbalance[96-98]. Early recurrences may resolve spontaneously and AADs are recommended rather than immediate reablation[28, 99]. Early AF recurrences, however, strongly predict later recurrences[100]. AF recurrences after the first three months are considered late recurrences and are mostly

due to PV reconnection[101]. Although the highest risk of recurrence is during the first six to 12 months following ablation, patients will be at risk of very late AF recurrence no matter how long the follow-up. The most consistent predictor of late recurrence is persistent AF[101]. Patient age, comorbidities, obesity, sleep apnoea and left atrial size may also have an effect on the outcome of ablation[101, 102]. Macroreentrant atrial tachycardia (AT) is common after AF ablation, mostly originating from the left atrium[103, 104]. In symptomatic patients, recurrences of AF or AT can warrant repeat ablation or continued or reinitiated AAD therapy[28, 82].

Follow-up after AF Ablation

Success rates for AF ablation depend on several variables. First, a follow-up strategy based solely on symptoms is unreliable mainly due to the high incidence of asymptomatic AF[5, 76], overestimating the success rate. There is also a poor symptom-arrhythmia correlation[105]. Furthermore, there is a close relationship between the intensity of rhythm monitoring and the detection of AF recurrence[106, 107] and therefore the methods used in detecting AF recurrence after ablation have a significant impact on success rates. The duration of follow-up and the type of AF are also of utmost importance and lastly the definition of success.

According to the 2012 and 2017 Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, patients should be followed up three months after the ablation procedure and every six months for at least two years[28, 82]. Furthermore, a blanking period of three months is recommended after AF ablation, during which arrhythmia recurrences are not included in the primary efficacy endpoint. In clinical practice, intermittent rhythm monitoring is usually employed. Procedural success is defined as freedom from symptomatic or asymptomatic AF, AT or atrial flutter, lasting ≥ 30 seconds from the end of the blanking period to 12 months for one-year success, or 36 months for long-term success. More commonly in clinical practice, success is defined as a pronounced reduction of AF recurrences and a reduction of symptoms. The conventional use of time to first AF recurrence as an end-point of efficacy also appears inadequate, as AF has a temporal pattern. Even reduction of the AF burden depends on temporal fluctuations in AF burden. There are indications that current recommendations for intermittent monitoring underestimate AF recurrences[108]. A recent prospective multinational registry study of over 3500 patients undergoing AF ablation had a success rate of 74 % at one year after abla-

tion, but only 60 % of patients had appropriate rhythm monitoring after the procedure[109].

Rhythm Monitoring

A variety of ECG monitoring techniques is available for assessment of rhythm, and they differ mainly in the duration of monitoring and the involvement of the patient, Table 5.

Table 5. ECG monitoring techniques

Type of recorder	Duration of monitoring	Continuous monitoring	Event recording	Auto trigger	Limits/advantages
Intermittent (external, noninvasive) monitoring					
Holter monitor	24-48 hours, 7-30 days	Yes	Yes	N/A	Dependent on compliance. Ability to record 3- to 12-lead ECG.
External loop recorder	7-28 days	Yes	Yes	Variable	Dependent on compliance.
External non-loop recorder	Months	No	Yes	No	Dependent on compliance. Symptomatic events or repeated planned recordings.
Mobile cardiac telemetry	30 days	Yes	Yes	Yes	Dependent on compliance. Real-time monitoring.
Patch monitor	1-3 weeks	Yes	Yes	N/A	No lead wires, water resistant. Excellent patient acceptance.
Smartphone monitor	Indefinite	No	Yes	No	Dependent on compliance.
Wearable multisensor ECG monitors	Indefinite	Yes	Yes	Yes	Dependent on compliance.
Continuous monitoring (implanted devices)					
ILR	Up to 3 years	Yes	Yes	Yes	Not able to detect <2min AF episodes. Limited memory. Not dependent on compliance.
Pacemakers or ICDs with atrial leads	Indefinite	Yes	Yes	Yes	Only PM/ICD patients. Not dependent on compliance.

AF = atrial fibrillation; ICD = implantable cardioverter defibrillator; ILR = Implantable loop recorder; N/A = not applicable; PM = pacemaker.

Intermittent Monitoring

Intermittent rhythm monitoring after AF ablation mainly includes 12-lead ECGs, Holter-ECGs of various duration (usually 24 hours to seven days), patient-activated external loop recorders and non-loop recorders. Devices used for longer periods of time have a higher sensitivity for detecting AF, especially paroxysmal AF, but patient compliance decreases with increased monitoring time[106, 110], Figure 3. The high incidence of asymptomatic AF also limits the yield of external monitoring. Depending on the monitoring method, the sensitivity ranges between 31.3 % and 71.0 %, whereas the negative predictive value ranges between 21.5 % and 64.6 %[110, 111].

Continuous Monitoring

Continuous monitoring includes both ILRs and pacemakers or defibrillators with atrial leads. Continuous monitoring is superior to intermittent monitoring for the detection of AF recurrence, especially in patients with high AF density[112].

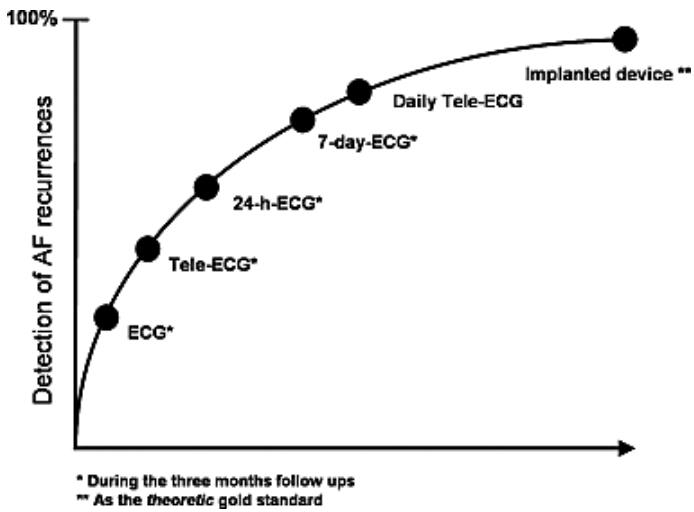

Figure 3. Estimated correlation between the intensity of the follow-up strategy and atrial fibrillation detection rate. Reprinted with permission from John Wiley and Sons[106].

Implantable Loop Recorder

ILRs are used in clinical practice for diagnosing patients with unexplained syncope, Figure 4. Recent models have been equipped with AF detection algorithms. The subcutaneous leadless device has a battery longevity of up to three years, a high sensitivity and specificity for detecting arrhythmias, and overcomes the limitation with patient non-compliance. In the XPECT trial, Hindricks et al. demonstrated that ILRs had a sensitivity, specificity, positive predicted value and negative predicted value of 96.1 %, 85.4 %, 79.3 % and 97.4 %, respectively, for detecting patients with AF, and an accurately measured AF burden[12]. AF episodes shorter than two minutes are not detected due to the device algorithm. False positive episodes are mostly due to frequent premature atrial or ventricular complexes. The limited memory can result in ECGs not being retrievable to verify the correct rhythm diagnosis due to overflow.

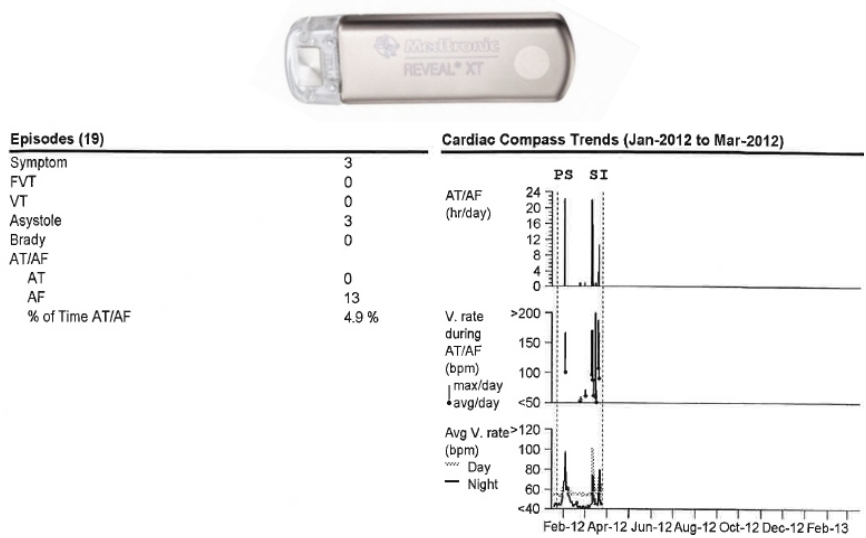

Figure 4. Implantable loop recorder (ILR), Reveal® XT, and an example of a report from a patient with paroxysmal AF. The arrhythmia episode information shows the number of automatically detected and patient-activated (symptom) episodes and the percentage of time that the device detected AT/AF since the last session. Graphs show trends in total time in AT/AF per day, heart rate during AT/AF and average heart rate during day and night. AF = atrial fibrillation; AT = atrial tachycardia; FVT = fast ventricular tachycardia; VT = ventricular tachycardia. Reprinted with permission from Medtronic, Inc.

Pacemaker or Defibrillator

Implanted permanent pacemakers and cardioverter defibrillators (ICDs) with an atrial lead allow continuous monitoring of AF episodes[113, 114]. They have the advantage of larger memory capabilities and improved discrimination of AF from other atrial arrhythmias compared to ILRs. However, these devices are limited to a small group of patients with a standard indication for pacing or ICD.

Patient-Reported Outcomes

Symptoms

The main indication for AF ablation is to improve PROs. However, there is a poor correlation between symptoms and AF burden even before ablation and the perception of AF may change after ablation, increasing the proportion of asymptomatic AF episodes. In the large prospective multicenter Discerning Symptomatic and Asymptomatic Episodes Pre and Post Radiofrequency Ablation of Atrial Fibrillation (DISCERN AF) study, Verma et al. evaluated the incidence of asymptomatic AF episodes before and after AF ablation using ILRs[11]. The ratio of asymptomatic to symptomatic AF episodes increased from 1.1 before to 3.7 after AF ablation, and 12 % of patients had only asymptomatic AF recurrences after ablation. The postablation state was the strongest independent predictor of asymptomatic AF recurrences, and patients also suffered significantly shorter AF episodes after ablation. Furthermore, symptoms may not relate to AF episodes as shown in a study of pacemaker patients where 40 % of patients reported symptoms suggestive of AF but device interrogation proved the absence of AF[105]. Symptoms like palpitations often result from atrial or ventricular premature beats in AF ablation patients[115] and are therefore not reliable indicators of AF recurrence.

Quality of Life

Studies of AF ablation outcomes have, in addition to fewer AF recurrences, demonstrated significant and sustained improvement in generic HRQoL compared to AADs[116-118]. This implies that patients with a lower AF burden have a greater improvement in HRQoL, but a significant improvement in HRQoL was observed even in patients with AF recurrence. AF-specific instruments are more responsive to HRQoL change and correlate better with ablation outcome than generic instruments[119, 120]. As blinding of patients to ablation is not possible, the assessment of HRQoL after

AF ablation is also complicated by patient expectations that may influence HRQoL scores. Furthermore, it is possible that the closer follow-up within a clinical study per se could reduce anxiety and increase psychological well-being.

AIMS

The overall aim of this thesis was to study different outcome measures of catheter ablation for AF. The specific aims were to investigate:

I. The long-term risk of HF and all-cause mortality in patients who underwent AVJA and RV pacing for therapy refractory AF and to identify predictors of these events

II. The rhythm control during the first two years after AF ablation, assessed by continuous monitoring and intermittent monitoring, and its relationship with reported symptoms

III. Patient-reported and physician-assessed AF-related symptoms up to two years after AF ablation, in relation to the AF burden

IV. Effects of AF ablation on AF-specific and generic PROs, their association to the AF burden, and to compare generic PRO to a Swedish age- and sex-matched population before and up to two years after ablation

MATERIALS AND METHODS

Ethical Considerations

All studies comply with the Declaration of Helsinki. The Central Ethical Review Board in Stockholm, Sweden, (reference number Ö1/2011/2011-02-04) and the Regional Scientific Ethical Committees for Southern Denmark, Denmark, considered the study protocol for paper I to be part of the on-going quality assurance programs of the clinics and did not require signed informed consent from participants. The study included no intervention, and thus the participants were not subjected to harm. All data collected were coded in order to protect the privacy of research participants.

The protocols of papers II-IV were approved by the Ethical Review Board in Uppsala, Sweden, (reference number 2010/127/2010-04-21 and the Regional Scientific Ethical Committees for Southern Denmark, Denmark (S-20080066/2008-05-22). Signed informed consent was obtained from all participants in papers II-IV. Patients were already scheduled for AF ablation before inclusion in the study, which means that the study itself conveyed no extra risk of complications of AF ablation. All patients were, however, implanted with a subcutaneous ILR which could potentially cause infection as well as discomfort. All patients were informed that the ILR could be removed at any time as well as of the opportunity to withdraw from the study. All patients were also followed with intermittent rhythm monitoring, which is known to have poor patient compliance because of discomfort. The careful follow-up may have caused an extra awareness of the patients' symptoms and increase anxiety but the patients were probably, conversely, assured by the extra monitoring.

Study Designs

Paper I was based on a retrospective cohort study and papers II-IV on a prospective cohort study. An overview of the study designs, number of subjects, objectives, outcomes, data sources, and primary statistical methods is presented in Table 6.

Table 6. Overview of the study designs

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Study design	Retrospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
Subjects	162	57	57	57
Objectives	To estimate the incidence of and predictors for HF hospitalization and all-cause mortality after AVJA	To evaluate rhythm control after AF ablation and its relation to symptoms	To evaluate patient- and physician-assessed AF-related symptoms after AF ablation in relation to the AF burden	To evaluate effects of AF ablation on AF-specific and generic PROs, assess the association between the PROs and the AF burden and to compare the generic PROs to an age- and sex-matched population
Outcomes	First hospitalization for HF or all-cause mortality	Time to first AF recurrence, AF burden, symptoms	Change in AF6, EHRA class and AF burden from before to after ablation	Change in AF6 and SF-36 after ablation in relation to AF burden, SF-36 compared to norms
Data sources	Review of hospital records	Intermittent monitoring, ILR	Self-reported questionnaire, physician-assessed symptoms, ILR	Self-reported questionnaires, ILR
Primary statistical method	Kaplan-Meier method, Cox regression	Kaplan-Meier method, Cox regression for clustered observations, Wilcoxon paired rank sum test	Spearman rank correlation	Unpaired t-test, linear mixed model for repeated measurement

AVJA = atrioventricular junction ablation; EHRA = European Heart Rhythm Association; HF= heart failure; ILR = implantable loop recorder; PRO = patient-reported outcome.

Paper I

Consecutive patients with AF who underwent AVJA between January 2001 and December 2011 at Örebro University Hospital, Sweden, and Odense University Hospital, Denmark, were included in this retrospective cohort study. Indications for AVJA were (1) inadequate symptom control by pharmacological treatment as part of a rate control strategy or (2) unsuccessful AF ablation in a rhythm control strategy. Patients with CRT before the AVJA were excluded from further analysis. Outcomes were the time to the first hospitalization for HF during follow-up censored for all-cause mortality or end of follow-up on 31 December 2012, whichever came first, and time to all-cause mortality.

Data were collected retrospectively from hospital medical records and hospitalizations for HF, deaths and time and causes of deaths were recorded at the end of the study period. Transthoracic echocardiography was assessed before the AVJA and at least one year after the AVJA. Medication was assessed at the time of the procedure and one year after the AVJA. AF was classified as either paroxysmal or non-paroxysmal, the latter including both persistent and permanent AF. Normal QRS duration was defined as < 120 ms.

Statistical Analyses

The time to the first hospitalization for HF and all-cause mortality, respectively, were estimated using the Kaplan–Meier method and presented as cumulative incidence. Univariate associations for potential prognostic factors for HF hospitalization and all-cause mortality were assessed by Cox regression. The proportional hazard assumption was evaluated and tested with Schoenfeld residuals but no deviation from proportional assumption was found. Multiple Cox regression models were used to identify independent prognostic factors for hospitalization for HF and all-cause mortality. Measures of association were hazard ratios (HRs) with 95 % confidence intervals (CIs). A p value < 0.05 was considered statistically significant.

Papers II-IV

Papers II-IV are based on a prospective two-center cohort study that is registered at ClinicalTrials.gov (NCT00697359). Patients who were scheduled for AF ablation between April 2009 and January 2013 at Örebro University Hospital, Sweden, and Odense University Hospital, Den-

mark, were eligible for inclusion. In Örebro, the inclusion in the study started in October 2010. Inclusion criteria were (1) documented symptomatic paroxysmal or persistent AF (< 3 months); and (2) an age of 30 to 70 years. Exclusion criteria were (1) left atrial diameter > 60 mm; (2) LVEF < 40 %; (3) significant structural heart disease; and (4) contraindication to OAC therapy with warfarin. Patients were followed for a minimum of two years after ablation.

Patients underwent AF ablation at least two weeks following ILR implantation and were followed at clinical visits three, six, 12, 18 and 24 months after ablation with device interrogation (continuous monitoring) and an 48-96 hour external ECG (intermittent monitoring). An AF-specific (AF6) and a generic (SF-36) questionnaire were administered to patients before and six, 12 and 24 months after AF ablation and physicians were asked to rate the patients' symptoms using the EHRA classification at the same time intervals. Transthoracic echocardiography was performed before ablation and six, 12 and 24 months after ablation.

A general population sample was randomly selected from the Swedish SF-36 normative database (n = 8930; response rate 68 %; validated in Sweden 1991-92)[121], matched for age and sex, and comprised 742 persons (453 males) with a mean age of 56.9 years (9.3 SD).

Paper II

Outcomes

The main outcomes were time to first AF recurrence using both continuous and intermittent rhythm monitoring, and AF burden at all times after ablation. Symptoms and their relationship with rhythm were secondary outcomes. The rhythm analysis was performed with and without a three-month blanking period after ablation.

Statistical Analyses

The time to the first AF recurrence was estimated using the Kaplan–Meier method, and continuous and intermittent monitoring was compared with Cox regression for clustered observations, due to the paired design with every patient using both monitoring methods. The Mann-Whitney U-test and the Wilcoxon paired rank sum test were used to evaluate the AF burden between and within subgroups. Logistic regression was used to evaluate predictors of AF recurrence detected with intermittent and continuous monitoring, respectively. Both univariable and multivariable logistic re-

gression analyses were performed. The point estimates of the odds ratio (OR) were shown with a 95 % CI. A p value < 0.05 was considered statistically significant.

Paper III

Outcomes

The main outcomes were change in AF6 scores and EHRA class from before and six, 12 and 24 months after ablation, and the correlation between AF6 scores and EHRA class at the same times in relation to the continuously measured AF burden.

Statistical Analyses

The Pearson correlation coefficient was used to measure the linear association for AF6 scores before and after ablation. The Spearman rank correlation coefficient was used in cases of ordinal or continuous but not normally distributed variables (EHRA class before and after ablation and AF6 scores versus EHRA class, and all analyses involving the AF burden). The correlation was considered strong ($r \geq 0.70$), moderate to substantial ($0.30 < r > 0.70$) or weak ($r \leq 0.30$)[122]. The predictive ability was estimated by calculating the correlation coefficient squared (r^2) as a measure of the proportion of variance accounted for by the correlation. A p value < 0.05 was considered statistically significant.

Paper IV

Outcomes

Outcomes were SF-36 scores in patients before and 24 months after AF ablation compared to a Swedish age- and sex-matched population and change in generic and AF-specific PROs six, 12 and 24 months after ablation in relation to the continuously measured AF burden.

Statistical Analyses

Unpaired t-tests were used for comparison of SF-36 domains between patients and norms. The linear mixed model for repeated measurement with unstructured covariance was used to compare mean PRO scores before and six, 12 and 24 months after ablation, in all patients and in responders (AF burden < 0.5 % at each scheduled visit) and non-responders (AF burden > 0.5 %). The magnitude of differences between patients and

norms and patients before and after ablation was determined by calculation of effect sizes (ESs). ES was estimated by calculating the mean difference, divided by the pooled standard deviation (Cohen's *d*). ES was interpreted according to standard criteria: trivial (< 0.20), small (0.20-0.49), moderate (0.50-0.79) and large (≥ 0.80)[123].

Linear regression was used to evaluate potential prognostic variables for PRO scores at 24 months after ablation and the change in PRO scores from baseline to 24 months adjusted for the baseline score of the outcome. All potential prognostic variables were further included in a multiple linear regression to identify independent prognostic variables for the PROs. The potential prognostic variables were sex, age, body mass index, persistent AF, hypertension, previous stroke/TIA, LVEF, left atrial diameter and AAD therapy before ablation and AF burden three to 24 months after ablation. A p value < 0.05 was considered statistically significant. To account for multiple testing, Bonferroni correction was performed for the number of tests applied in each analysis.

Statistical Soft Wares

The analyses were conducted using SPSS versions 21 and 22 (IBM Corp, Armonk, NY, USA) and STATA release 11 (StataCorp, College Station, TX, USA).

Methods

Pacemaker Implantation and AVJA – Paper I

Pacemakers were implanted in most patients at least one month before the AVJA, but, in the beginning of the study period, pacemaker implantation was performed on the same day as the AVJA. The AVJA was accomplished with RF ablation under conscious sedation with the endpoint of complete AV block persisting for at least 30 minutes. After the ablation procedure, the pacemaker was programmed to a basic rate of 75 or 80 b.p.m. for at least two weeks.

AF Ablation Procedure – Papers II-IV

The catheter ablation procedure was performed on uninterrupted OAC therapy with warfarin within the therapeutic international normalized ratio interval at least four weeks before ablation. Real-time 3D electroanatomic mapping was performed (CARTO Merge, Biosense Webster, Diamond Bar, CA, USA). Circumferential lines were produced around each

pair of PV ostia. The endpoint was the absence of PV signals for at least 15 minutes during sinus rhythm. Electrical cardioversion was performed as needed. After ablation, all patients were observed on telemetry monitoring for 24-48 hours. Reablation was permitted at the investigator's discretion.

Rhythm Monitoring – Papers II-IV

All patients were implanted with an ILR (Reveal ® XT, Medtronic Inc., Minneapolis, MN, USA) and were equipped with the Patient Assistant activator that enables the patient to save and store ECG in the ILR when experiencing symptoms of AF. The AF detection algorithm uses irregularity and incoherence in RR intervals to identify and classify patterns in the ventricular conduction. The RR intervals are analysed within two-minute periods, and the difference in duration between consecutive RR intervals (ΔRR) is calculated. The variability of these ΔRR intervals is subsequently calculated in a way similar to constructing a Lorenz plot[124]. When RR intervals within the two-minute interval show a certain pattern of uncorrelated irregularity, the rhythm in this interval is classified as AF, Figure 5. Patients are also able to save and store ECG when experiencing symptoms of arrhythmia. The episode log shows up to 30 automatically detected AF episodes and up to ten patient-activated episodes. In total, 49.5 minutes of ECG can be stored, which allows manual analysis and confirmation of episodes by the physician. When the memory is full, the first stored episode is overwritten by the latest episode. The AF burden was calculated as the percentage of time in AF between visits and reported based on all manually adjudicated AF episodes. An AF burden cut-off limit of < 0.5 % was used to classify patients as responders and non-responders at each visit, as previously suggested[125].

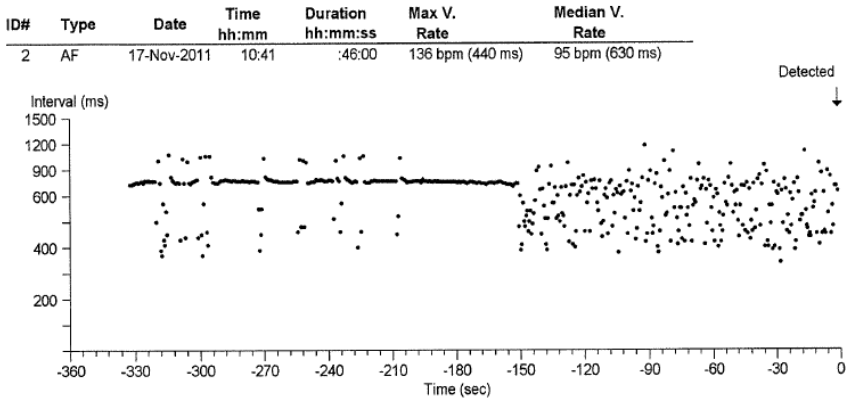

Figure 5. Detailed information about the selected episode in the episode log including date and time of start of AF detection, duration of AF episode and maximum and median heart rate during AF. The episode interval plot displays a graph that plots the RR intervals versus time. AF = atrial fibrillation; V = ventricular.

A 48-96 hour Holter (SpaceLabs Healthcare, Snoqualmie, WA, USA) or external loop monitoring (R.TEST Evolution 3, NOVACOR, Rueil-Malmaison, France) was performed at each visit. A 12-lead ECG was recorded at each visit. AF recurrence was defined as a 30-second episode of AF when detected by intermittent monitoring and an adjudicated two-minute episode when detected by ILR.

Physician-Assessed Outcomes – Paper III

The EHRA classification[42] was used to categorize the patients' symptoms of AF into class I (no symptoms), II (mild symptoms: normal daily activity not affected), III (severe symptoms: normal daily activity affected), or IV (disabling symptoms: normal daily activity discontinued) before and after AF ablation.

Patient-Reported Outcomes – Papers III-IV

After initial instruction, the AF6 and the SF-36 questionnaires were completed by the patient without interaction from physicians or nurses and before the ECG was recorded in order to document the actual cardiac rhythm. **AF6** has undergone validation[46] and test of clinical responsiveness[47] and includes a recall period of the most recent seven days, Table 7. A score of 0 (no symptoms) to 10 (severe symptoms) is self-reported for each item,

and all scores are added into a single sum score. Sum scores range from 0 to 60, with higher values reflecting more severe AF-related symptoms. The internal consistency reliability estimated (Cronbach's α) for the six items was 0.82, 0.88, 0.19, 0.04, 0.39 and 0.93, respectively.

Table 7. AF6

Item	Symptoms
1	Breathing difficulties at rest
2	Breathing difficulties upon exertion
3	Limitations in day-to-day life due to AF
4	Feeling of discomfort due to AF
5	Tiredness due to AF
6	Worry/anxiety due to AF

SF-36 has a recall period of four weeks and consists of 36 items assessing eight domains reflecting physical and mental health aspects: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Domain scores range from 0 to 100, with higher values indicating better HRQoL. The eight domains generate two summary measures: the physical component summary (PCS) and the mental component summary (MCS) scores. PCS and MCS are calculated using norm-based scoring with a mean of 50 and a value above 50 indicating better HRQoL than the general Swedish population. In the Swedish validation of SF-36, Cronbach's α for the eight domains was 0.91 (physical functioning), 0.88 (role-physical), 0.93 (bodily pain), 0.84 (general health), 0.85 (vitality and social functioning), 0.79 (role-emotional) and 0.87 (mental health)[126].

RESULTS

Paper I

In all, 162 patients underwent AVJA between January 2001 and December 2011 because of symptomatic AF refractory to pharmacological treatment (n = 117) or unsuccessful AF ablation (n = 45). Their clinical characteristics are shown in Table 8. At the decision for AVJA, 69 patients already had a pacemaker and two had ICDs. The use of β blockers, calcium-channel blockers, digoxin and AADs decreased significantly one year after AVJA (all $p < 0.001$).

Table 8. Baseline characteristics paper I

	All, n=162 (%)	**Pharmacological failure, n=117 (72%)**	**Previous AF ablation, n=45 (28%)**	**P**
Women/men	77/85	57/60	20/25	0.63
Age, years (mean ± SD)	67 ± 9	68 ± 10	65 ± 7	0.09
Paroxysmal AF	97 (60%)	64 (55%)	33 (73%)	**0.03**
Non-paroxysmal AF	65 (40%)	53 (45%)	12 (27%)	**0.03**
Duration of AF, months (median, IQR)	68 (IQR 25-120)	60 (IQR 25-120)	72 (IQR 36-116)	0.94
Follow-up period, months (median, IQR)	58 (IQR 32-102)	66 (IQR 37-103)	45 (IQR 24-61)	**0.01**
Concomitant cardiovascular disease				
Heart failure	33 (20%)	27 (23%)	6 (13%)	0.17
Hypertension	67 (41%)	48 (41%)	19 (42%)	0.89
Diabetes	26 (16%)	21 (18%)	5 (11%)	0.29
Coronary artery disease	23 (14%)	21 (18%)	2 (4%)	**0.03**
Valvular heart disease	23 (14%)	20 (17%)	3 (7%)	0.09
Stroke/TIA	14 (9%)	10 (9%)	4 (9%)	1.00
$CHADS_2$ scores				
0 – 1	111 (69%)	76 (65%)	35 (78%)	0.12
≥ 2	51 (32%)	41 (35%)	10 (22%)	0.12
CHA_2DS_2-VASc scores				
0 – 1	58 (36%)	40 (34%)	18 (40%)	0.49
≥ 2	104 (64%)	77 (66%)	27 (60%)	0.49

Electrocardiogram				
QRS duration ≥ 120 ms	25 (15%)	21 (18%)	4 (9%)	0.15
Echocardiogram				
LVEF, % (mean ± SD)	56 ±10	55 ± 10	57 ± 10	0.20
LVEDD, mm (mean ± SD)	50 ± 7	50 ± 7	50 ± 6	0.86
Left atrial diameter, mm (mean ± SD)	46 ± 6	46 ± 6	44 ± 7	0.08
NYHA functional class				0.20
I	90 (56%)	63 (54%)	27 (60%)	
II	39 (24%)	26 (22%)	13 (29%)	
III	32 (20%)	27 (23%)	5 (11%)	
IV	1 (1%)	1 (1%)	0 (0%)	
Medications				
β blockers	115 (71%)	80 (68%)	35 (78%)	0.24
ACE inhibitors/ARB	73 (45%)	52 (44%)	21 (47%)	0.80
Aldosterone antagonists	17 (11%)	11 (9%)	6 (13%)	0.57
Digoxin	83 (51%)	64 (55%)	19 (42%)	0.16
Diuretics	78 (48%)	62 (53%)	16 (36%)	**0.047**
Warfarin	124 (77%)	83 (71%)	41 (91%)	**0.01**
ASA	61 (38%)	45 (39%)	16 (36%)	0.73

Baseline characteristics summarized with percentage, mean ± SD or median (min-max), whenever appropriate. Boldface indicates significance ($p < 0.05$). ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; ASA = aspirin; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke/transient ischaemic attack (doubled); CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 65 or 75 years (doubled), diabetes, prior stroke/transient ischaemic attack (doubled), vascular disease, female sex; IQR = interquartile range; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation; TIA = transient ischaemic attack.

Heart Failure

During the follow-up period of 58 (IQR 32 – 102) months, 23 of the 117 (20 %) patients with failed pharmacological treatment and nine of the 45 (20 %) patients in the AF ablation group had at least one adjudicated hospitalization for HF. Sixteen (50 %) of all patients with HF hospitalization had known HF before the AVJA, three (33 %) in the AF ablation group and 13 (57 %) in the group with failed pharmacological treatment. Hospitalization for HF occurred at a median time of 53 (IQR 20 – 102) months after the AVJA. The one-year cumulative incidence for hospitalization for HF was 5.1 % (95 % CI 2.6 – 9.9) and the two-year cumulative incidence was 9.1 % (95 % CI 5.5 – 14.9), Figure 6. LVEF decreased slightly after the AVJA from 56 ± 10 % to 53 ± 11 % ($p < 0.001$), while the LV end-diastolic diameter and the left atrial diameter did not change.

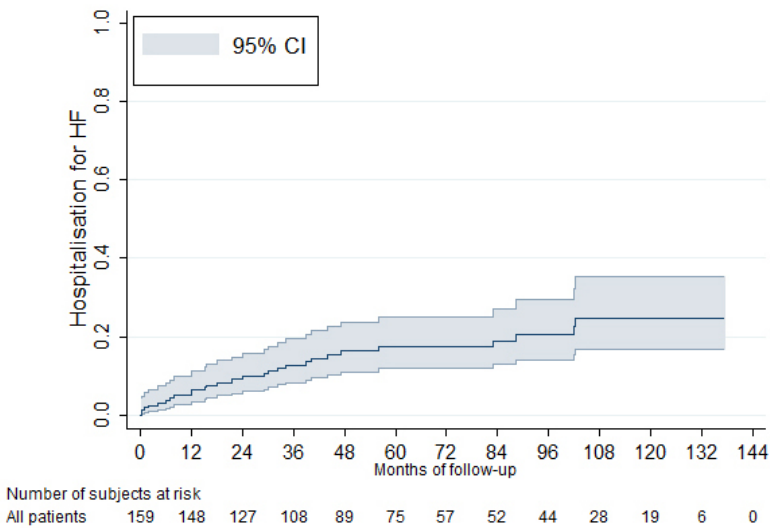

Figure 6. Cumulative incidence of hospitalization for heart failure estimated by the Kaplan–Meier method. HF = heart failure.

The unadjusted Cox proportional hazard regression analysis revealed QRS duration (both as a categorical and a continuous variable), coronary artery disease, LVEF < 35 %, left atrial diameter and previous HF to be statistically significant risk factors for HF hospitalization, Table 9. The

relative risk of HF hospitalization increased 30 % with every 10 ms increase in QRS duration.

The adjusted Cox regression revealed a QRS duration ≥ 120 ms as a statistically significant predictor for hospitalization for HF; when adjustment was made for all potential prognostic factors, the association was HR 2.77 (95 % CI: 1.18-6.54), p = 0.02. Left atrial diameter was also a statistically significant predictor in the adjusted Cox regression with HR 1.11 (95 % CI: 1.03-1.19), p = 0.007, and previous HF had a borderline significance of HR 2.81 (95 % CI: 1.00-7.89), p = 0.05.

Table 9. Potential risk factors for hospitalization for HF and all-cause mortality evaluated with Cox regression

	Unadjusted (n=162) HR (95% CI)	**p**	**Adjusted*** (n=157) HR (95% CI)	**p**
Hospitalization for HF				
Age (years)	1.00 (1.00-1.08)	0.07		
Age ≤ 65	1.00		1.00	
Age 66-75	1.17 (0.47-2.87)	0.74	1.44 (0.49-4.24)	0.51
Age ≥ 76	2.60 (1.04-6.51)	**0.04**	1.40 (0.46-4.31)	0.56
Sex, male	1.54 (0.71-3.34)	0.28	1.37 (0.60-3.14)	0.46
Non-paroxysmal AF	1.38 (0.65-2.94)	0.41	1.34 (0.54-3.35)	0.54
QRS duration ≥ 120ms [1]	3.30 (1.55-7.05)	**0.002**	2.77 (1.18-6.54)	**0.02**
QRS duration (ms) [1]	1.03 (1.01-1.04)	**<0.001**		
$CHADS_2 \geq 2$	1.60 (0.73-3.48)	0.24		
CHA_2DS_2-VASc ≥ 2	1.50 (0.67-3.33)	0.32		
Hypertension	0.93 (0.43-2.01)	0.85	1.79 (0.70-4.54)	0.22
Diabetes	0.72 (0.22-2.39)	0.59	0.56 (0.14-2.18)	0.40
Coronary artery disease	3.04 (1.37-6.72)	**0.006**	2.27 (0.82-6.27)	0.11
LVEF < 35%[1]	5.92 (2.37-14.79)	**<0.001**		
Left atrial diameter [5]	1.13 (1.07-1.19)	**<0.001**	1.11 (1.03-1.19)	**0.007**
Previous HF	6.20 (2.93-13.11)	**<0.001**	2.81 (1.00-7.89)	0.05
Previous pacemaker	1.61 (0.77-3.39)	0.21	1.54 (0.66-3.62)	0.32
Centre, Odense	0.64 (0.29-1.41)	0.27	1.09 (0.38-3.11)	0.87
All-cause mortality				
Age (years)	1.06 (1.02-1.09)	**0.004**		
Age ≤ 65	1.00		1.00	
Age 66-75	2.03 (0.93-4.44)	0.07	2.00 (0.85-4.70)	0.11

Age ≥ 76	3.38 (1.42-8.04)	**0.006**	2.30 (0.80-6.63)	0.12
Sex, male	0.91 (0.47-1.78)	0.79	1.18 (0.56-2.48)	0.30
Non-paroxysmal AF	2.18 (1.11-4.28)	**0.02**	2.00 (0.91-4.40)	0.08
QRS duration ≥ 120ms [1]	0.57 (0.20-1.60)	0.28	0.56 (0.19-1.68)	0.30
QRS duration (ms) [1]	0.99 (0.98-1.00)	0.30		
$CHADS_2 \geq 2$	2.99 (1.53-5.86)	**0.001**		
CHA_2DS_2-VASc ≥ 2	3.47 (1.51-8.00)	**0.003**		
Hypertension	2.08 (1.07-4.06)	**0.03**	2.26 (1.08-4.75)	**0.03**
Diabetes	2.29 (1.07-4.89)	**0.03**	1.86 (0.77-4.46)	0.17
Coronary artery disease	1.27 (0.53-3.07)	0.59	0.74 (0.27-2.03)	0.56
LVEF < 35% [1]	1.53 (0.37-6.41)	0.56		
Left atrial diameter	1.07 (1.01-1.13)	**0.02**	1.05 (0.99-1.12)	0.11
Previous HF	2.27 (1.09-4.74)	**0.03**	2.63 (1.01-6.82)	**0.047**
Previous pacemaker	1.30 (0.66-2.54)	0.45	1.43 (0.66-3.11)	0.37
Centre, Odense	0.68 (0.33-1.42)	0.30	1.84 (0.72-4.69)	0.20
0-24 months†	1.42 (0.29-7.05)	0.67		

CI = confidence interval; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke/transient ischaemic attack (doubled); CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 65 or 75 years (doubled), diabetes, prior stroke/transient ischaemic attack (doubled), vascular disease, female sex; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction. [] defines number of missing values. Boldface indicates significance ($p < 0.05$).

** Adjusted for all variables except LVEF < 35 %, $CHADS_2$ and CHA_2DS_2-VASc*

† Evaluated as a time-dependent factor 0–24 months

All-cause Mortality

Thirty-five (22 %) patients, 19 men and 16 women, died at a median time of 47 (IQR 24 – 65) months after AVJA. Their mean age at AVJA was 69 ± 10 years. Among those who died, eight patients had a previous AF ablation (18 %) and 27 (23 %) pharmacological failure. The one-year cumulative incidence for mortality was 1.9 % (95 % CI 0.6 – 5.7) and the two-year cumulative incidence was 5.2 % (95 % CI 2.7 – 10.2), Figure 7.

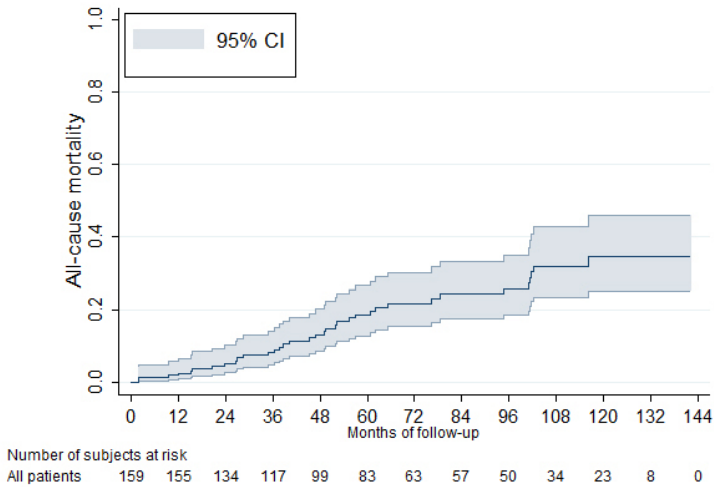

Figure 7. Cumulative incidence of all-cause mortality estimated by the Kaplan–Meier method.

Causes of death were HF (17 %), cancer (17 %), myocardial infarction (14 %), infections (11 %), arrhythmias (9 %), stroke (6 %), respiratory failure (6 %) and other causes (20 %). Other causes comprised of one patient each with ruptured aortic aneurysm, primary biliary cirrhosis, pulmonary hypertension, intestinal ischemia, and neuromuscular disease and two patients with Alzheimer's disease.

Eight statistically significant risk factors of all-cause mortality were identified in the unadjusted Cox proportional hazard regression analysis: age, non-paroxysmal AF, $CHADS_2$ score ≥ 2, CHA_2DS_2-VASc score ≥ 2, hypertension, diabetes, left atrial diameter and previous HF, Table 9. Multiple Cox regression revealed hypertension (HR 2.26 (95 % CI: 1.08-

4.75), p = 0.03) and previous HF (HR 2.63 (95 % CI: 1.01-6.82), p = 0.047) as independent predictors of all-cause mortality.

Baseline Characteristics Papers II-IV

The characteristics of the study population are shown in Table 10. Fifty-four patients completed the 24-month follow-up. Twenty-three (43 %) patients had a reablation procedure a mean of 11 ± 4 months after the first procedure.

Table 10. Baseline characteristics papers II-IV

	n=57
Sex, male	34 (60%)
Age, years (mean ± SD)	57 ± 9
BMI (mean ± SD)	29 ± 5
Paroxysmal AF	50 (88%)
Persistent AF	7 (12%)
Months from first AF episode (median, IQR)	57 (IQR 36-120)
Days from latest perceived AF episode (median, IQR)	29 (IQR 3-116)
EHRA class I, n (%)	20 (35%)
EHRA class II, n (%)	23 (40%)
EHRA class III, n (%)	13 (23%)
EHRA class IV, n (%)	1 (2%)
Concomitant cardiovascular disease	
Heart failure	2 (4%)
Hypertension	24 (42%)
Diabetes	2 (4%)
Coronary artery disease	1 (2%)
Valvular heart disease	1 (2%)
Stroke/TIA	8 (14%)
$CHADS_2$ scores	
0	31 (54%)
1	14 (25%)
≥ 2	12 (21%)
CHA_2DS_2-VASc scores	
0	15 (26%)
1	20 (35%)
≥ 2	22 (39%)

Echocardiogram	
LVEF, % (mean ± SD)	60 ± 5
Left atrial diameter, mm (mean ± SD)	42 ± 7
Medications	
β blockers	37 (65%)
Class I AAD	16 (28%)
Class III AAD	16 (28%)
Warfarin	42 (74%)

Values are n (%), mean ± SD or median (IQR). AAD = antiarrhythmic drugs; AF = atrial fibrillation; BMI = body mass index; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke/transient ischaemic attack (doubled); CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 65 or 75 years (doubled), diabetes, prior stroke/transient ischaemic attack (doubled), vascular disease, female sex; EHRA = European Heart Rhythm Association; IQR = interquartile range; LVEF = left ventricular ejection fraction; SD = standard deviation; TIA = transient ischaemic attack.

Paper II

AF Recurrences

Thirteen (24 %) patients had no AF episodes at all detected by ILR after the end of the blanking period and up to 24 months after ablation (AF burden 0 %), while at least one AF episode was detected by ILR in 41 (76 %) patients. While the proportion of patients without AF recurrence was fairly constant over time (43-48 %), several patients' rhythm varied between AF and sinus rhythm from one six-month period to the other, meaning that the concordance between successive time intervals was 81-87 %.

Using an AF burden cut-off of < 0.5 %, 22 (41 %) patients were responders from the end of the blanking period and up to 24 months after ablation, while AF recurrence was confirmed in 32 (59 %) patients. The proportion of patients with an AF burden < 0.5 % increased significantly from before ablation to six ($p = 0.01$), 12 ($p = 0.01$) and 24 ($p = 0.004$) months after ablation.

The number of AF episodes ($p = 0.02$) and the duration of the longest AF episode ($p = 0.04$) decreased significantly over the two-year follow-up. The median AF burden was 0.9 % (IQR 0-5.3) before ablation and was 0.09 % during the 18-24 month interval.

Recurrences were common during the blanking period (Figure 8A), occurring in 90 % of patients with AF recurrence after the blanking period compared to 15 % of patients without recurrence after the blanking period ($p < 0.001$).

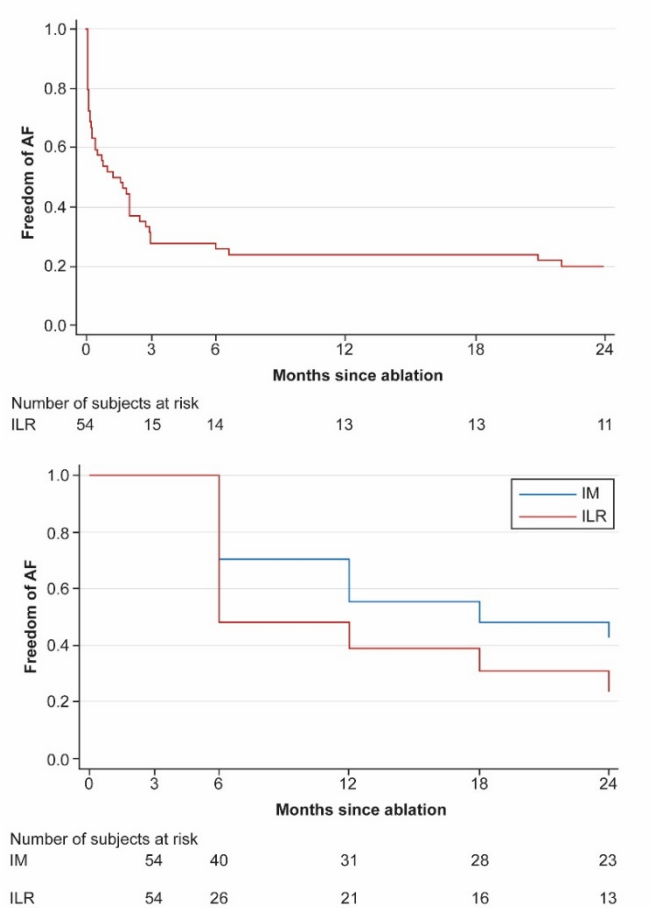

Figure 8A-8B. Kaplan-Meier curves for freedom from AF after AF ablation showing (A) detection by the ILR at exact times 0-24 months, and (B) a comparison between ILR and IM at scheduled visits three to 24 months, excluding the blanking period from analysis, hazard ratio 1.51 (95 % confidence interval: 1.22-1.87), p < 0.001. AF = atrial fibrillation; ILR = implantable loop recorder; IM = intermittent monitoring.

After the blanking period, at least one AF recurrence (AF burden > 0 %) was detected by the ILR in 41 (76 %) patients and by intermittent follow-up in 31 (57 %) patients, Figure 8B. All AF recurrences identified by intermittent monitoring were also detected by ILR. The median AF burden after ablation was significantly lower when AF was only detected by ILR compared with when detected by both intermittent monitoring and ILR (p = 0.001) and ILR detected AF recurrences significantly earlier (p < 0.001).

When automatically detected AF episodes were manually analysed, the most common reason for false positive AF was frequent premature atrial and ventricular complexes, Figure 9. The AF burden was based on manually adjudicated AF episodes.

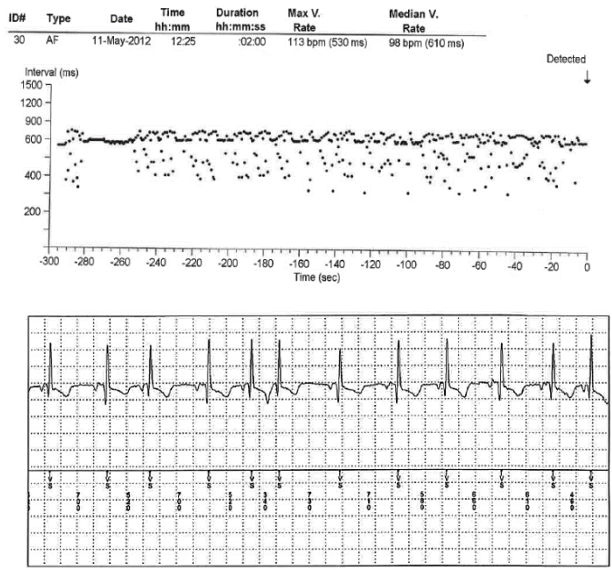

Figure 9. Episode falsely classified as AF due to frequent premature atrial complexes. The episode interval plot displays a graph that plots the RR intervals versus time. AF = atrial fibrillation; V = ventricular.

Predictors of AF Recurrence

Early recurrence detected by ILR and early recurrence combined with symptoms, were, unadjusted, significantly associated with late AF recurrence (OR 50.9 (95 % CI: 8.2-316), p < 0.001 and OR 13.9 (95 % CI: 1.65-117), p = 0.015) but were not included in the multiple regression

analysis. No baseline variables were significantly associated with recurrence in the multiple regression analysis.

In intermittent monitoring, early recurrence combined with patients' symptoms (OR 7.52 (95 % CI: 2.05-27.5), p = 0.002) and AF burden (OR 4.06 (95 % CI: 1.29-12.8), p = 0.02) and AF burden > 0.5 % before ablation (OR 6.8 (95 % CI: 1.9-24.7, p = 0.003) and longest AF (OR 4.52 (95 % CI: 1.66-12.3), p = 0.003) and longest AF > 6 hours (OR 5.24 (95 % CI: 1.50-18.3), p = 0.01) before ablation were, unadjusted, significantly associated with late recurrence. AF burden (OR 4.90 (95 % CI: 1.13-21.3), p = 0.03) and longest AF episode (OR 6.30 (95 % CI: 1.84-21.5), p = 0.003) before the ablation were separately independent predictors of AF recurrence detected by intermittent monitoring.

Symptoms versus Arrhythmia Recurrence

Twenty-six (48 %) patients reported symptoms using the patient activator after the blanking period. Twenty-one (81 %) of them had AF at least once when reporting symptoms, and five (19 %) patients had no AF recurrence during the whole follow-up. Another three patients had AF recurrence but no reported symptoms during AF, although symptoms at other times. Altogether, the 26 patients reported symptoms on 341 occasions, of which 228 (67 %) correlated with AF episodes. Symptoms not correlated with AF were most often due to frequent premature atrial or ventricular complexes, Figure 10. Twenty-five patients did not use the patient activator, but 17 (68 %) of them had at least one ILR detected AF recurrence and one patient underwent reablation. Patients without symptoms were younger (p = 0.02) than symptomatic patients, more often men (p = 0.03) and were treated with AADs to a higher extent at the time of ablation (p = 0.001).

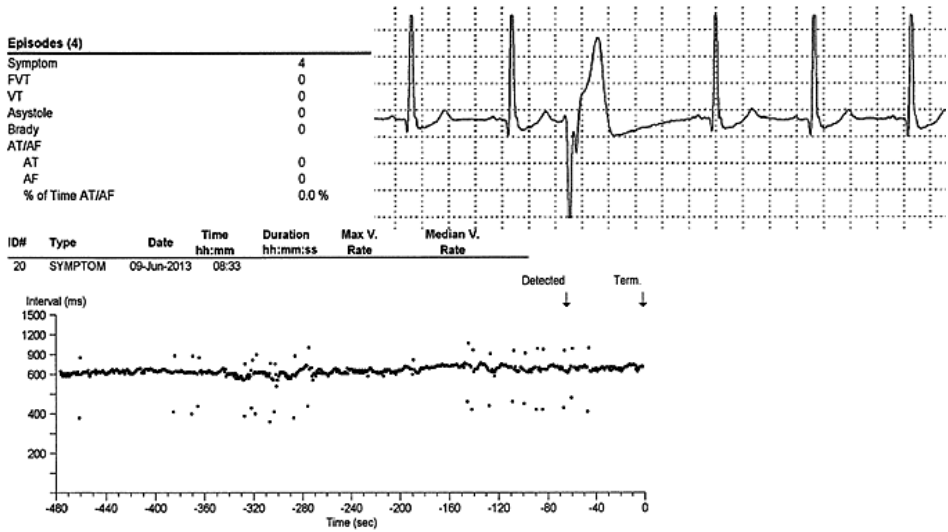

Figure 10. Patient reporting symptoms using the patient activator. Episode correctly not interpreted as AF. ECG shows a premature ventricular complex. AF = atrial fibrillation; AT = atrial tachycardia; FVT = fast ventricular tachycardia; VT = ventricular tachycardia; V = ventricular.

Paper III

Patients' Assessment of Symptoms before and after Ablation

All AF6 items and the sum score improved from before ablation to six months after ablation and further to 12 months for all items and the sum score, except for item 1 (breathing difficulties at rest), and remained at this level at 24 months after ablation, Table 11. The most severe scoring item both before and after ablation was item 5 (tiredness due to AF).

Table 11. Patients and physicians assessment of AF-specific symptoms before and after ablation using the AF6 and European Rhythm Association classification

	Before ablation	**6 months***	**12 months†**	**24 months‡**	**p§**
AF6 item 1, median (IQR)	1 (0-3)	0 (0-2)	1 (0-4)	0 (0-1)	**0.001**
AF6 item 2, median (IQR)	5 (2-8)	3 (0-7)	1 (0-4)	2 (0-6)	**0.004**
AF6 item 3, median (IQR)	5 (2-8)	2 (0-5)	1 (0-3)	1 (0-5)	**0.001**
AF6 item 4, median (IQR)	6 (3-8)	3 (0-6)	1 (0-3)	1 (0-6)	**<0.001**
AF6 item 5, median (IQR)	7 (4-8)	5 (0-8)	2 (0-6)	2 (0-7)	**<0.001**
AF6 item 6, median (IQR)	4 (2-6)	2 (0-5)	0 (0-3)	1 (0-3)	**<0.001**
AF6 sum, median (IQR)	30 (17-38)	17 (2-30)	7 (0-19)	9 (0-27)	**<0.001**
EHRA class I, n (%)	19 (35%)	41 (76%)	38 (70%)	44 (82%)	**<0.001**
EHRA class II, n (%)	22 (41%)	10 (19%)	14 (26%)	7 (13%)	**<0.001**
EHRA class III, n (%)	12 (22%)	3 (6%)	2 (4%)	3 (6%)	**<0.001**
EHRA class IV, n (%)	1 (2%)	0	0	0	**<0.001**

Boldface indicates significance ($p < 0.05$). AF6 item 1 'breathing difficulties at rest', item 2 'breathing difficulties upon exertion', item 3 'limitations in day-to-day life due to AF', item 4 'feeling of discomfort due to AF', item 5 'tiredness due to AF' and item 6 'worry/anxiety due to AF'. A score of 0 (no symptoms) to ten (severe symptoms) is reported for each item and all scores are added to give a single sum score of 0 to 60; EHRA class I (no symptoms), II (mild symptoms), III (severe symptoms) or IV (disabling symptoms). EHRA = European Heart Rhythm Association; IQR = interquartile range.

**1 patient missing*

†5 patients missing

‡1 patient missing

§p Friedmans test

The AF6 sum score at all times after ablation correlated significantly with the AF6 sum score before ablation (r = 0.50 (p < 0.001), n = 50, r = 0.38 (p = 0.008), n = 44, and r = 0.28 (p = 0.04), n = 49, six, 12 and 24 months after ablation, respectively), Figure 11A to 11C.

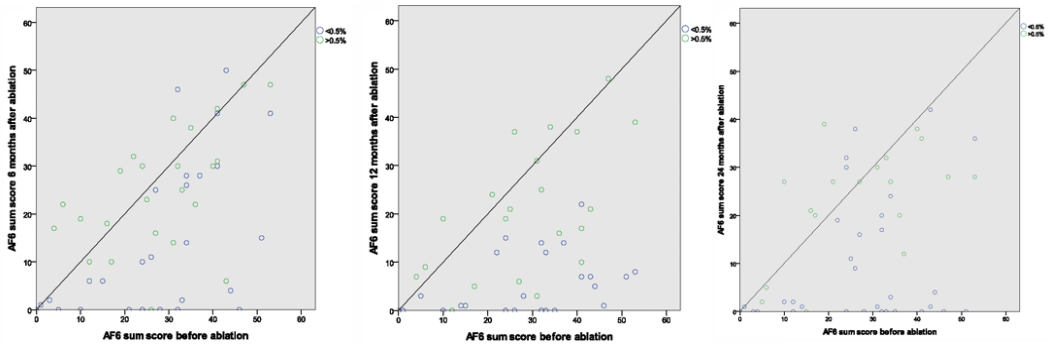

Figure 11A-11C. Scatterplot comparing the AF6 sum score before and (A) six months (B) 12 months and (C) 24 months after AF ablation. Patients above the line of identity had worsened and patients below the line improved scores following ablation. Atrial fibrillation burden is defined as < 0.5 % (blue circles) or > 0.5 % (green circles). AF = atrial fibrillation.

The mean AF6 sum score was 29.5 ± 13.9 before ablation. The mean difference in the AF6 sum score from before ablation was 9.3 (95 % CI: 5.2 to 13.4; p < 0.001) at six months after ablation, 16.6 (95 % CI: 12.2 to 20.9; p < 0.001) at 12 months, and 13.6 (95 % CI: 9.0 to 18.3 (p < 0.001) 24 months after ablation, corresponding to moderate to large effect sizes of 0.67, 1.2, and 0.98, respectively. An improvement of more than 9 points was therefore considered clinically meaningful and was seen in 25 (50 %) patients at six months, 33 (75 %) patients at 12 months, and 30 (61 %) patients at 24 months after ablation.

Physicians' assessment of Symptoms before and after Ablation

EHRA class improved statistically significantly over the two-year follow-up period, with no further improvement after the first six months after ablation, Table 12. The proportion of patients in EHRA class II to IV decreased from 65 % before to 24 %, 30 % and 19 %, respectively, at six, 12 and 24 months after ablation. EHRA class most often improved by one class (from II to I, n = 20; from III to II, n = 1) and less often by two or three classes (from III to I, n = 10; from IV to I, n = 1). Nineteen pa-

tients (35 %) were already categorized in EHRA class I before ablation, and nine of them were also considered to be in EHRA class I at all times after the ablation. The remaining ten patients varied from EHRA classes I to III after ablation; at 24 months, four patients were in EHRA class I, four in EHRA class II, and two in EHRA class III.

Patients' versus Physicians' Evaluation of Symptoms

The AF6 sum score decreased with improving EHRA class, showing a significant correlation at six ($r = 0.48$, $r^2 = 0.23$; $p < 0.001$), 12 ($r = 0.58$, $r^2 = 0.34$; $p < 0.001$), and 24 months after ablation ($r = 0.27$, $r^2 = 0.07$; $p = 0.049$). Patients considered to be improved in EHRA class had statistically significantly lower median AF6 sum scores of 1 (IQR 0 - 4), 6 (IQR 0 - 13) and 5 (IQR 0 - 28) at six, 12, and 24 months after ablation, respectively, compared with patients with unchanged or worse EHRA class with median AF6 sum scores of 40 (IQR 27 - 46; $p = 0.003$), 31 (IQR 12 - 39; $p = 0.001$), and 36 (IQR 28 - 36; $p = 0.02$).

The changes in AF6 sum score and EHRA class from before ablation were visualized with scatterplots at six ($r = 0.31$, $r^2 = 0.10$; $p = 0.02$), 12 ($r = 0.32$, $r^2 = 0.10$; $p = 0.03$) and 24 months ($r = 0.22$, $r^2 = 0.05$; $p = 0.12$) after ablation (Figures 12A to 12C).

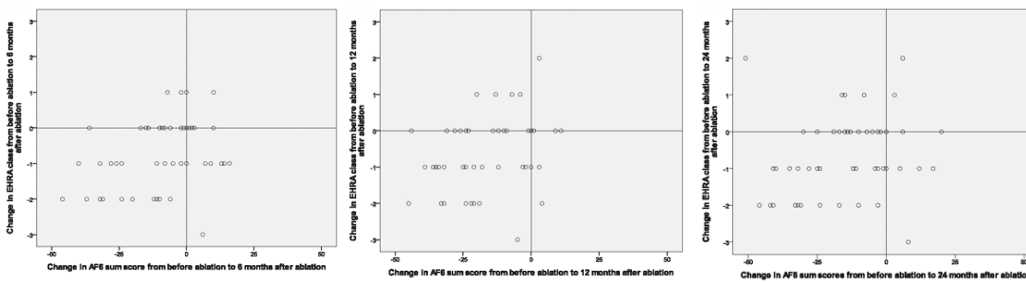

Figure 12A-12C. Scatterplot comparing changes in AF6 sum scores and EHRA class before and after ablation. (A) Six months, (B) 12 months and (C) 24 months after ablation. Negative values indicate improvement and positive values deterioration. Patients in the lower left quadrant show improvement and in the upper right quadrant worsening in both AF6 score and EHRA class, while patients with discordant results are found in the upper left and lower right quadrants. AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

Effect of AF Ablation on Rhythm in Relation to Symptoms

The AF6 sum score was significantly correlated with AF burden at six ($r = 0.37$; $p < 0.01$), 12 ($r = 0.62$; $p < 0.01$) and 24 ($r = 0.52$; $p < 0.01$) months after ablation. EHRA class and AF burden were also significantly correlated at six ($r = 0.35$; $p = 0.01$), 12 ($r = 0.42$; $p = 0.002$) and 24 ($r = 0.44$; $p = 0.001$) months after ablation.

When examining the 14, 23 and 23 patients with AF burden of 0 % at six, 12 and 24 months after ablation, the median AF6 sum score was low, and the IQR showed a relatively wide range (six-month median, 0 (IQR 0 - 27); 12-month median, 0.5 (IQR 0 - 7); 24-month median, 0 (IQR 0 - 11)). The most common AF6 item was item 6 (worry/anxiety due to AF) and the highest ranking item was item 5 (tiredness due to AF). Patients without any AF at any time after ablation were categorized into EHRA class I in 100 %, 91 % and 96 % at six, 12, and 24 months after ablation, respectively.

The AF burden in the subgroup of patients with AF burden > 0.5 % during the period 18 to 24 months after ablation (n = 19) varied between 0.53 % and 100 %. All patients with an AF burden up to 10 % improved in EHRA class (n = 7) compared with before ablation or remained in EHRA class I (n = 4). Six of the patients improved more than 9 points in the AF6 sum score from baseline, compared with 25 patients with AF burden < 0.5 % at 24 months.

Paper IV

Generic HRQoL before and after Ablation and in Responders and Non-responders

All SF-36 domains and the summary scores showed statistically significantly lower values as compared to age- and sex-matched population norms, except for bodily pain, Figure 13, Table 12. The effect size between patients and matched population norms was interpreted as large in vitality and role-physical but small to moderate in most domains. The mean difference in summary scores between patients and norms corresponded to moderate effect sizes (PCS 0.64 and MCS 0.65).

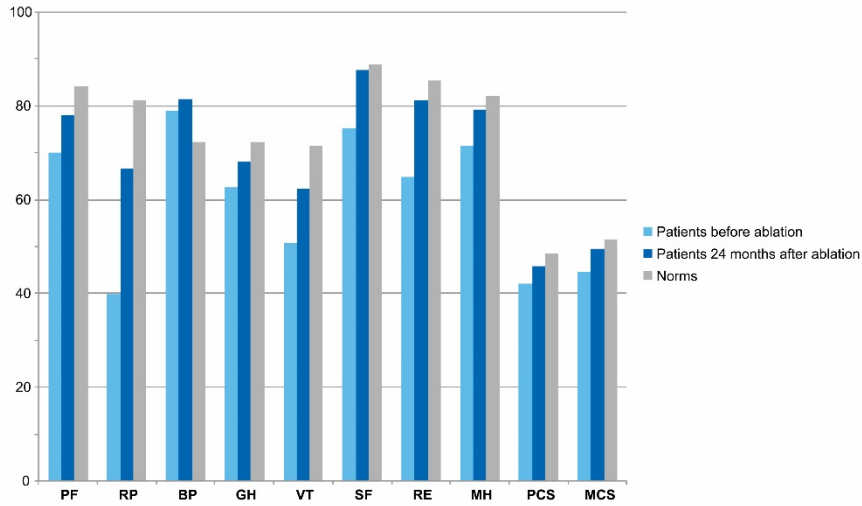

Figure 13. SF-36 domain and summary scores before and 24 months after AF ablation compared to Swedish age- and sex-matched population norms (n = 742). BP = bodily pain; GH = general health; MCS = mental component summary; MH = mental health; PCS = physical component summary; PF = physical functioning; RE = role-emotional; RP = role-physical; SF = social functioning; VT = vitality. *Data from one patient missing*

The role-physical, vitality, social functioning and mental health domains and the summary scores improved significantly two years after ablation with moderate effect sizes for role-physical and social functioning but otherwise small effect sizes, Table 13. The improvement occurred mainly during the first six months after ablation. Two years after ablation, the mean of the summary scores, physical functioning, general health, social functioning, role-emotional and mental health, did not differ significantly from that of the general population, but the patients scored slightly but significantly lower than norms on role-physical and vitality, Table 12.

Responders showed statistically significantly improved scores two years after ablation in physical functioning, role-physical and PCS. The effect sizes were large in physical functioning (0.86), role-physical (0.83) and role-emotional (0.90), and moderate in general health (0.55), vitality (0.54), social functioning (0.63), mental health (0.53) and both summary scores (PCS 0.63 and MCS 0.64). The non-responders showed significant

improvement in role-physical (ES 0.58) and social functioning (ES 0.47). Responders reached the HRQoL of general population norms in all domains and both summary scores while non-responders only reached norms in social functioning and MCS. Responders showed significantly greater improvement in physical functioning and PCS than non-responders from before to two years after ablation, Table 13.

AF-specific AF6 in Responders and Non-Responders

All AF6 items and the sum score showed statistically significant improvement at 24 months after ablation, with moderate to large effect sizes, Table 13. Before ablation, item 1 (breathing difficulties at rest) scored significantly lower in subsequent responders than non-responders ($p = 0.01$), while there were no significant differences in the other items or the AF6 sum score. In responders, items 2 to 6 showed statistically significant improvements, all with large effect sizes (ES 1.0 to 1.7), but item 1 (breathing difficulties at rest) still had a moderate effect size of 0.58. All items and the AF6 sum score improved significantly in non-responders; item 2 (breathing difficulties upon exertion) showed a large effect size (0.84), and all others moderate effect sizes (0.50 to 0.75). Responders showed significantly greater improvement in all items except items 1 (breathing difficulities at rest) and 6 (worry/anxiety due to AF) than non-responders from before to two years after ablation, Table 13.

Table 12. SF-36 mean scores in patients at baseline and six, 12 and 24 months after AF ablation compared to general Swedish population norms

SF-36 domains	Norm data	Baseline			6 months			12 months			24 months		
	Mean ± SD (n=742)	Mean difference (95% CI) (n=54)	p*	ES	Mean difference (95% CI) (n=53)	p*	ES	Mean difference (95% CI) (n=48)	p*	ES	Mean difference (95% CI) (n=53)	p*	ES
PF	84.1 ± 20.9	-14.0 (-19.9 to -8.1)	**<0.001**	0.61	-6.5 (-12.5 to -0.56)	0.03	0.29	-7.4 (-13.6 to -1.3)	0.02	0.34	-6.1 (-11.9 to -0.23)	0.04	0.29
RP	81.3 ± 33.0	-41.5 (-50.7 to -32.2)	**<0.001**	1.1	-13.0 (-22.3 to -3.7)	**0.006**	0.39	-5.7 (-15.4 to 3.9)	0.25	0.17	-14.8 (-24.1 to -5.4)	**0.002**	0.40
BP	72.3 ± 27.4	6.6 (-0.89 to 14.1)	0.08	0.26	2.7 (-5.0 to 10.4)	0.48	0.10	5.7 (-2.3 to 13.6)	0.16	0.22	9.1 (1.5 to 16.7)	0.02	0.35
GH	71.6 ± 22.7	-9.8 (-16.1 to -3.5)	**0.002**	0.41	-4.2 (-10.6 to 2.1)	0.19	0.19	-5.0 (-11.6 to 1.5)	0.13	0.24	-4.2 (-10.5 to 2.1)	0.19	0.19
VT	71.6 ± 23.4	-20.7 (-27.2 to -14.3)	**<0.001**	0.90	-11.7 (-18.3 to -5.0)	**0.001**	0.47	-10.0 (-16.9 to -3.1)	**0.004**	0.41	-9.2 (-15.8 to -2.6)	**0.006**	0.36
SF	88.9 ± 21.1	-13.7 (-19.6 to -7.7)	**<0.001**	0.56	-6.2 (-12.2 to -0.24)	0.04	0.29	-1.4 (-7.5 to 4.7)	0.66	0.01	-1.4 (-7.3 to 4.5)	0.64	0.07
RE	85.3 ± 29.2	-20.5 (-28.9 to -12.1)	**<0.001**	0.57	-7.7 (-16.1 to 0.59)	0.07	0.24	-2.7 (-11.2 to 5.9)	0.54	0.09	-4.2 (-12.5 to 4.1)	0.32	0.13
MH	82.3 ± 19.2	-10.6 (-16.0 to -5.3)	**<0.001**	0.57	-6.4 (-11.9 to -1.0)	0.02	0.33	-5.4 (-11.0 to 0.15)	0.06	0.29	-3.0 (-8.3 to 2.4)	0.28	0.16
PCS	48.4 ± 9.9	-6.4 (-3.7 to -9.2)	**<0.001**	0.64	-2.6 (-5.5 to 0.19)	0.07	0.25	-2.2 (-5.1 to 0.7)	0.14	0.21	-2.6 (-5.4 to 0.23)	0.07	0.25
MCS	51.5 ± 9.7	-7.0 (-4.3 to -9.8)	**<0.001**	0.65	-4.0 (-6.7 to -1.2)	**0.005**	0.38	-2.4 (-5.3 to 0.5)	0.10	0.25	-1.8 (-4.6 to 0.90)	0.19	0.18

SF-36 scores ranging between 0 and 100 where higher scores indicate better health. Negative mean differences calculated with unpaired t-test indicate lower mean in patients than norms. BP = bodily pain; GH = general health; MCS = mental component summary; MH = mental health; PCS = physical component summary; PF = physical functioning; RE = role-emotional; RP = role-physical; SF = social functioning; VT = vitality; CI = confidence interval; ES = effect size; SD = standard deviation.

** Uncorrected P values are stated and boldface indicates significant results after Bonferroni correction for multiple testing of the eight SF-36 domains*

Table 13. Patient-reported outcomes at baseline and 24 months after ablation in responders and non-responders

	All n=54					**Responders** n=22		**Non-responders** n=32		**Responders vs non-responders**	
	Base-line Mean ± SD	24 months* Mean ± SD	Mean difference (95% CI)	P†‡	ES	Baseline Mean ± SD	24 months Mean ± SD	Baseline Mean ± SD	24 months* Mean ± SD	Mean difference 24 months* (95% CI)	p†‡
SF-36											
PF	70.1 ± 25.3	78.0 ± 20.6	8.1 (2.1 to 14.0)	0.009	0.35	67.0 ± 29.8	86.8 ±16.2	71.9 ± 22.5	72.7 ± 21.3	15.9 (7.3 to 24.6)	**0.001**
RP	39.8 ± 39.3	66.5 ± 40.4	26.7 (15.5 to 38.0)	**<0.001**	0.67	41.3 ± 44.6	76.3 ± 40.1	39.0 ± 36.5	60.6 ± 40.0	14.7 (-5.7 to 35.1)	0.15
BP	78.9 ± 23.8	81.4 ± 25.1	2.6 (-5.9 to 11.1)	0.55	0.10	79.6 ± 27.2	83.4 ± 23.3	78.5 ± 22.0	80.2 ± 26.4	2.3 (-12.2 to 16.9)	0.75
GH	62.5 ± 21.2	68.0 ± 20.6	5.7 (-0.6 to 12.1)	0.08	0.26	63.7 ± 25.3	75.9 ±18.8	61.7 ± 18.7	63.3 ± 20.4	11.2 (0.6 to 21.8)	0.04
VT	50.8 ± 23.0	62.4 ± 27.1	11.4 (5.2 to 17.6)	**0.001**	0.46	52.5 ± 27.9	67.3 ± 27.3	49.9 ± 20.0	59.4 ± 27.0	6.4 (-6 to 18.7)	0.31
SF	75.2 ± 27.1	87.5 ± 20.4	12.5 (5.8 to 19.3)	**<0.001**	0.51	72.5 ± 32.8	88.8 ±19.0	76.8 ± 23.5	86.7 ± 21.4	3.2 (-7.0 to 13.4)	0.53
RE	64.8 ± 41.7	81.1 ± 35.5	16.6 (3.0 to 30.3)	0.02	0.42	58.3 ± 45.7	90.0 ± 24.4	68.6 ± 39.3	75.8 ± 40.2	15.8 (-3.9 to 35.5)	0.11
MH	71.6 ± 18.1	79.3 ± 18.2	7.7 (2.9 to 12.5)	**0.002**	0.42	70.8 ± 20.8	81.2 ±18.8	72.1 ± 16.7	78.2 ± 18.1	3.7 (-5.1 to 12.6)	0.40
PCS	42.0 ± 10.1	45.9 ± 10.6	3.9 (1.2 to 6.6)	**0.005**	0.38	42.3 ±12.2	49.3 ±10.2	41.9 ± 8.8	43.8 ± 10.4	5.2 (0.3 to 10.0)	**0.04**
MCS	44.5 ± 11.7	49.6 ± 10.5	5.2 (2.0 to 8.5)	**0.002**	0.46	43.4 ±14.0	50.5 ± 8.5	45.1 ± 10.4	49.1 ± 11.7	5.0 (-0.5 to 10.5)	0.07

AF6											
AF6 item 1	2.0 ± 2.6	0.8 ± 1.5	-1.2 (-2.0 to -0.6)	**<0.001**	0.57	0.90 ±1.7	0.20 ± 0.7	2.7 ± 2.8	1.1 ± 1.8	-0.5 (-1.4 to 0.3)	0.22
AF6 item 2	4.9 ± 3.3	2.9 ± 3.1	-2.0 (-2.9 to -1.1)	**<0.001**	0.62	4.0 ± 3.5	1.1 ± 2.3	5.5 ± 3.1	4.0 ± 3.1	-2.2 (-3.7 to -0.7)	**0.005**
AF6 item 3	4.8 ± 3.2	2.1 ± 2.5	-2.8 (-3.9 to -1.8)	**<0.001**	0.94	5.0 ± 3.7	0.7 ±1.8	4.9 ± 3.0	3.0 ± 2.5	-2.4 (-3.6 to -1.0)	**0.001**
AF6 item 4	5.5 ± 3.0	2.7 ± 3.3	-2.8 (-3.9 to -1.7)	**<0.001**	0.89	5.0 ± 3.4	0.7 ±1.7	5.9 ± 2.7	3.9 ± 3.4	-3.1 (-4.7 to -1.5)	**<0.001**
AF6 item 5	5.9 ± 3.2	3.2 ± 3.5	-2.7 (-3.7 to -1.6)	**<0.001**	0.81	5.1 ± 4.0	1.1 ± 2.3	6.4 ± 2.5	4.5 ± 3.5	-3.0 (-4.7 to -1.2)	**0.001**
AF6 item 6	4.3 ± 3.0	2.1 ± 2.8	-2.2 (-3.1 to -1.3)	**<0.001**	0.76	4.1 ± 3.3	0.9 ± 1.3	4.4 ± 2.8	2.9 ± 3.2	-1.9 (-3.3 to -0.5)	0.01
AF6 sum score	29.5 ±13.9	13.6 ± 14.3	-13.8 (-18.3 to -9.0)	**<0.001**	0.99	24.1 ± 15.3	4.6 ± 9.1	29.7 ± 12.7	19.3 ± 14.1	-13.0 (-20.1 to -6.0)	**0.001**

SF-36 scores ranging between 0 and 100, where higher scores indicate better health. Positive mean differences calculated with the linear mixed model indicate improvement at 24 months compared to baseline or greater improvement for responders compared to non-responders from baseline to 24 months. AF6 item 1 = breathing difficulties at rest, item 2 = breathing difficulties upon exertion, item 3 = limitations in day-to-day life due to AF, item 4 = feeling of discomfort due to AF, item 5 = tiredness due to AF and item 6 = worry/anxiety due to AF. A score of 0 (no symptoms) to 10 (severe symptoms) is reported for each item, and all scores are added to give a single AF6 sum score of 0 to 60. Negative mean differences calculated with the linear mixed model indicate improvement at 24 months compared to baseline or greater improvement for responders compared to non-responders from baseline to 24 months. BP = bodily pain; GH = general health; MCS = mental component summary; MH = mental health; PCS = physical component summary; PF = physical functioning; RE = role emotional; RP = role physical; SF = social functioning; and VT = vitality; CI = confidence interval; ES = effect size; SD = standard deviation.

** Data from one patient missing*

† Uncorrected P values are stated, and boldface indicates significant results after Bonferroni correction for multiple testing of the eight SF-36 domains

‡ Uncorrected P values are stated and boldface indicates significant results after Bonferroni correction for multiple testing of the six AF6 items

Prognostic Variables for PROs 24 Months after Ablation

No baseline variables were significantly associated with AF6 sum score at 24 months or change in AF6 sum score using linear regression. A log unit increase in AF burden three to 24 months after ablation was significantly associated with 10.7 (95 % CI: 4.7 to 16.6) higher mean AF6 sum score at 24 months adjusted for age and sex, and 11.5 (95 % CI: 4.3-18.7) adjusted for all variables. Higher AF burden was also significantly associated with a larger increase in AF6 sum score from baseline, adjusted for age and sex 10.5 (95 % CI: 4.7-16.3) and adjusted for all variables 11.4 (95 % CI: 4.3-18.5).

A log unit increase in AF burden three to 24 months after ablation was significantly associated with -5.0 (95 % CI: -9.7 to -0.3) lower mean PCS when adjusted for age and sex and -7.0 (95 % CI: -12.2 to -1.7) when adjusted for all variables. A log unit increase in AF burden was also significantly associated with a negative mean change from baseline PCS -5.9 (95 % CI: -9.8 to -2.0) adjusted for age and sex and -6.7 (95 % CI: -11.4 to -2.0) adjusted for all variables. Persistent AF before ablation was significantly associated with -9.8 (95 % CI: -18.7 to -0.9) lower mean MCS at 24 months after ablation adjusted for age and sex and -10.1 (95 % CI: -20.0 to -0.3) adjusted for all variables. Persistent AF was significantly associated with a negative change in MCS score from baseline to 24 months of -9.4 (95 % CI: -18.8 to -0.1) adjusted for all variables. Higher age was significantly associated with higher MCS when adjusted for all variables with 0.4 (95 % CI: 0.0 to 0.8) higher mean MCS for every year increase.

DISCUSSION

Main Findings

In therapy refractory AF, long-term RV pacing was not harmful in the majority of patients after AVJA and remains a valuable treatment option in selected patients. Prolonged QRS duration and left atrial diameter were identified as independent predictors of hospitalization for HF, and hypertension and previous HF as predictors of all-cause mortality.

AF ablation led to long-lasting symptom relief and improvement of HRQoL to the level of the general population, accomplishing the current goal of the procedure. The AF-specific AF6 instrument was more sensitive than the generic SF-36 and the physician-assessed EHRA class. However, there was often a discrepancy between patient-reported AF6 sum scores and physician-assessed EHRA class. Continuous rhythm monitoring using an ILR was superior to intermittent monitoring in detecting AF recurrences, in particular in patients with a low AF burden and/or asymptomatic AF. Complete freedom from AF did not preclude that patients felt some symptoms, but one third of ILR recordings due to symptoms did not show AF. Conversely, patients with an AF burden up to 10 % at 24 months indicated symptomatic improvement after ablation.

Heart Failure after AVJA

One fifth of the patient cohort had at least one hospitalization for HF at a median time of four years after the AVJA and half of these patients had known HF before the AVJA, consistent with a previous study[15]. Prolonged QRS duration was an independent predictor of hospitalization for HF, suggesting that prolonged QRS duration before AVJA could predict deterioration or development of new HF.

The LVEF decreased slightly but significantly in our study one year after as compared to before the AVJA but the LV end-diastolic diameter did not change. A meta-analysis of five studies by Chatterjee et al. showed that, compared to pharmacological therapy alone, AVJA was associated with a modest but significant improvement in LVEF for patients with reduced systolic function (LVEF < 45 %). There was no significant change in LVEF in patients with normal systolic function[127]. The meta-analysis also showed significantly greater improvement in symptoms and HRQoL after

AVJA when compared to pharmacological therapy alone. Part of this improvement in PROs can probably be explained by a reduction of rate control medications after AVJA, as seen in our study.

Current guidelines recommend that CRT instead of RV pacing should be considered in patients with reduced LVEF to reduce hospitalization and improve HRQoL based on small randomized trials[76]. However, there is insufficient evidence to support that all patients undergoing AVJA should receive CRT[75]. Based on the present study it can be speculated that even patients with a normal LVEF but prolonged QRS could benefit from CRT, but this needs to be examined in further studies. Left atrial diameter was also an independent predictor of HF hospitalization and could stand for a more advanced heart disease, and has previously been identified as a marker of cardiovascular risk[128].

Interestingly, 43 % of patients had previous pacemaker or ICD treatment for other reasons than the AVJA and were therefore subjected to longer RV pacing than patients who were implanted with a pacemaker weeks to months before the AVJA. However, previous pacemaker treatment was not a predictor for either mortality or HF.

All-cause Mortality after AVJA

Thirty-five (22 %) patients died at a median time of four years after the AVJA, men and women to a similar extent, but the mortality was higher in the group with failed pharmacological treatment compared with the group with previous AF ablation. The diseased patients were in their 60s and 70s at the time of the AVJA, and cardiovascular disease and cancer were the most common causes of death, which is consistent with the general population. The all-cause mortality was similar to that of previous studies[15, 129]. Ozcan et al. showed that long-term survival after AVJA was comparable to that in patients with pharmacological therapy for AF and, when adjusted for underlying heart disease, survival was similar to the expected survival in the general population[129]. In a meta-analysis of 21 studies by Wood et al., the one-year total mortality rate was 6.3 % compared to 1.9 % in our study but included heterogeneous studies of patients with atrial tachyarrhythmias undergoing AVJA (97 % AF)[70].

Hypertension and previous HF were independent predictors of all-cause mortality in the present cohort, showing what seems to be intuitive, that comorbidities entail an increased risk of mortality. Previous HF has in

several studies been found to be an independent predictor of mortality after AVJA[129, 130]. A higher prevalence of coronary artery disease in the group with failed pharmacological treatment might explain the slightly higher mortality in this group compared to the group with previous AF ablation.

An increased risk of sudden death after AVJA has been described as being due to ventricular arrhythmias[73, 131]. This risk can be largely eliminated by programming the pacemaker to a higher basic rate the first weeks after the procedure[73]. In the present patient cohort, only one patient with prior ICD treatment had ventricular arrhythmias during the two-day hospitalization after the procedure and there were no early sudden deaths. A total of 9 % of patients died of arrhythmias during the nearly five-year long follow-up, but the one-year and two-year cumulative incidence for mortality was low, 1.9 % and 5.2 %, respectively.

Continuous versus Intermittent Rhythm Monitoring

Continuous monitoring using an ILR has several advantages, predominantly the extended monitoring, compared to intermittent rhythm monitoring and can accurately measure AF duration, frequency, burden and ventricular rate. Furthermore, continuous monitoring could potentially be used within a rhythm control strategy to guide therapy and select patients for AF ablation and possibly ablation strategy in the individual patient.

Based on a conventional intermittent rhythm monitoring strategy, one fourth of patients in the present study would have been falsely classified as AF-free and success rates overestimated. Not surprisingly, mostly short paroxysmal AF episodes failed detection by intermittent monitoring. This is in line with the ABACUS study of 38 patients who underwent AF ablation and where, in 29 % of patients, AF recurrences were detected by ILR but not by transtelephonic monitors[132]. The delay in detection of AF recurrences could lead to progression of AF and postpone further treatment with AADs or reablation, rendering the patient less responsive to rhythm control therapy. Moreover, detection of early AF recurrences may identify patients at higher risk of late recurrences, as early recurrences are strong predictors of late recurrences, shown in ours and previous studies[133]. Indeed, a study by Pokushalov et al. using continuous monitoring found that an AF burden ≥ 4.5 % during the first two months after ablation could predict the success rate at 12 months[134]. Another study by Pokushalov et al. used ILRs to identify potential triggers of early AF recurrences in indi-

vidual patients after AF ablation[135]. In 286 patients who underwent AF ablation because of paroxysmal AF, patients with AF recurrences during the three-month blanking period were randomized to treatment with either AADs for six weeks and reablation or AADs if recurrences after the blanking period, or treated according to the onset mechanism with AADs if no trigger was found and early reablation if recurrences were triggered by premature atrial complexes, AT or atrial flutter. At 12 months after the first ablation, patients in the group treated with reablation if AF onset had been triggered had significantly fewer AF recurrences than patients without early reablation (20 % compared to 67 %). Furthermore, unacknowledged AF recurrences with high ventricular rates could potentially lead to tachycardia-induced HF. According to current guidelines, anticoagulation should be managed according to underlying stroke risk, regardless of ablation outcome, and patients at high risk would therefore not have discontinued OAC therapy even if they were considered AF-free. There is, however, some evidence that AF duration is important for the risk of stroke[111] and extensive continuous monitoring could in the future possibly select patients who could discontinue OAC therapy after ablation. Finally, reliable rhythm assessment is of paramount importance when comparing different rhythm control treatments in clinical trials.

Another advantage of the ILR is that it enables patients to record ECG during symptoms that can be manually inspected by physicians. In the present study, only two thirds of symptoms correlated with AF episodes, highlighting the unreliability of symptoms to identify patients with and without AF recurrences and stress the importance of extended monitoring. Symptoms not correlated with AF were most often caused by frequent atrial or ventricular premature complexes, consistent with other studies[105, 132]. Patients who did not activate the device due to symptoms were younger, more often men and were treated with AADs to a higher extent at the time of ablation but may still have felt symptoms. However, in the DISCERN AF study, AF ablation was the strongest independent predictor of asymptomatic AF[11]. A major strength of our study is that we used the manually adjudicated AF burden to determine the accurate AF burden, excluding false-positive AF episodes and determining the true AF episode duration. Limitations of ILRs include the limited memory and the inability to detect AF episodes shorter than two minutes.

Patient-Reported and Physician-Assessed Outcomes

Since symptoms and impaired HRQoL are the main reasons for AF ablation and ablation has no impact on long-term OAC therapy, it could be argued that success rates should be based solely on PROs. However, as asymptomatic AF recurrences are common and symptoms unreliable, the absence of symptoms should therefore not be interpreted as absence of AF recurrences. Nevertheless, PROs are important, to assess both symptom severity and the impact of a treatment, in patients with AF. We have shown that both patient-reported AF6 and SF-36 scores and physician-assessed EHRA class improved following ablation, probably due to a reduction in AF burden. The AF6, in contrast to the SF-36 and the EHRA class, showed continued improvement from six to 12 months after ablation, indicating that the AF-specific instrument was the most sensitive for assessment of clinical outcome after AF ablation. The role-physical and vitality domains showed the greatest improvement of SF-36 domains during follow-up but were still lower than age- and sex-matched general population norms 24 months after ablation. However, both summary scores reached normative levels. In a study of 323 patients undergoing AF ablation by Wokhlu et al., all SF-36 domains reached norm values, but norms were not matched for age and sex and the authors used the same mean score for every domain for norms, which may have affected their results[119]. Responders improved to the level of the general population in all domains while non-responders only reached norm level in social functioning and MCS, further indicating that a reduction of the AF burden is important. Furthermore, a higher AF burden after ablation was independently associated with poorer physical but not mental health.

There were discrepancies between patients' and physicians' assessment of the patient's symptoms after ablation. Both most often agreed when symptoms were improved after ablation, whereas there was a relatively poor correlation between the two when either party felt that there was no change or a worsening of symptoms, as pointed out by and Dorian and Angaran in an editorial comment to paper III[139]. In some cases, patients perceived worsened symptoms but physicians had a more positive interpretation of symptom relief. This is in line with another study of the EHRA classification and the Atrial Fibrillation Effect on Quality of Life questionnaire in patients with AF, although not ablation patients, where patients assessed as asymptomatic by physicians reported AF-specific symptoms[136]. Possible explanations for these discrepancies could be treatment

expectations or limitations in the EHRA classification, which takes only symptoms and no other factors into consideration. The physician may also have a bias toward maximizing the clinical benefit of the procedure, while a patient may under-report symptoms when being directly questioned, but not when completing a questionnaire, as suggested by Morady in a summary of paper III[140].

The EHRA class and AF6 scores correlated with AF burden but, interestingly, there was a wide range of AF6 scores in patients with extremely low AF burden after ablation, whereas some patients with a higher AF burden had few symptoms following ablation, indicating that more factors besides AF burden affect PROs and that symptom improvement can occur despite little or no effect on AF burden. There are several possible explanations for this finding, including a higher proportion of asymptomatic AF episodes, left atrial denervation or increased AAD effectiveness or possibly a placebo effect or regression towards the mean after ablation. PROs are known to not only be affected by symptoms of AF but also by multiple factors including patient factors, side effects from medications, comorbidities, the memory of symptoms and anxiety about their recurrence. In addition, pre-procedural expectations and caregiver reassurance in a clinical trial can affect improvement in PROs in patients undergoing AF ablation. The use of an AF-specific instrument could possibly exclude some of these factors.

Patient Involvement in Treatment Decisions

Recent guidelines and EHRA consensus documents advocate more patient involvement in decisions about how to treat AF, both when selecting drugs for rhythm and/or rate control and when deciding for or against AF ablation[9, 137, 138]. This shared decision-making approach puts each patient at the center of the care process. Patients with AF need repeated, individually tailored education about their condition, treatment options and possible outcomes to make informed choices[138]. Decisions regarding rhythm (and/or rate) control, including ablation, are based on symptomatology in relation to the type of AF and its duration as well as benefits and risks in individual patients. Complex management decisions should be supported by a multidisciplinary AF Heart Team[9, 137]. Symptoms are most often what bring patients to their physicians, and the way they verbally express and explain their symptoms may differ a great deal. A short, informative and validated symptom score may add significant information and be of help in the selection of treatment.

Limitations

Paper I

The study was retrospective in design, which carries inherent limitations. The study parameters are based on hospital medical records and the quality of the data depend on the accuracy of the medical records. Echocardiography was not performed in all patients after the AVJA, and the time of the imaging varied among patients. Nearly half of the patients had previous pacemaker treatment for other reasons than the AVJA, but the treatment was not a predictor of either mortality or HF.

The study included two centres and, while the criteria for AVJA were the same, the selection still turned out somewhat differently. This did not, however, result in any relevant statistical differences. During the first years of the enrolment period, AVJA was also offered to younger patients, and even patients with paroxysmal AF, in whom AF ablation became a preferred treatment later in the enrolment period.

Papers II-IV

The study population was small, but patients were followed in great detail for two years after AF ablation and strengths of the study are the use of an AF-specific instrument in combination with a complete and accurate measure of AF burden by the use of ILRs. The ILRs were implanted only a few weeks before ablation, and the AF burden before ablation may therefore not be entirely representative. ILR data were downloaded at each follow-up visit and when patients experienced symptoms of AF, but in occasional patients with frequent and/or long-lasting AF recurrences, memory overflow occurred. However, all episodes defined as AF by the ILR appeared in the arrhythmia episode log, and the missing recordings contributed minimally to the AF burden.

The AF6 and the SF-36 have different recall periods, while no such period has been indicated for the EHRA classification, which may have influenced the results. The latest available national norm data, used in our study, were validated in 1991-92, and the HRQoL of the general population may have changed since then. The AF6 was validated in symptomatic patients undergoing electrical cardioversion for short-lasting persistent AF, while patients in the present study had paroxysmal and persistent AF.

Due to the low power, we have likely failed to detect some existing associations, but the associations we have found are probably valid. Our conclusions should be considered hypothesis generating.

CONCLUSIONS

AVJA is still a valid option in selected patients with high ventricular rates resistant to other treatment modalities and not suitable for AF ablation or AADs, especially in the elderly or in patients with severe comorbidities.

The AF burden was low during two-year follow-up after AF ablation. Continuous rhythm monitoring with ILR was superior to intermittent monitoring in detecting AF recurrences, especially short episodes, and one fourth of patients would have been falsely classified as AF-free using only intermittent follow-up. Symptoms were commonly reported by activation of the ILR but one third of recordings did not show AF and symptoms alone were therefore not a good indicator of AF recurrence.

The AF-specific PRO instrument AF6 was more sensitive than the SF-36 and the EHRA class for assessment of clinical outcome after AF ablation. There were frequent discrepancies between the patient-reported AF6 and the physician-assessed EHRA class. Complete freedom from AF and a low AF burden resulted most often in a reduction of symptoms, but symptom relief also occurred despite little effect on AF burden.

Clinical implications

The QRS duration is an important ECG parameter that should be considered when choosing pacing modality for patients undergoing AVJA.

Focusing on PROs, both when selecting AF ablation candidates and when measuring outcomes after ablation, is reasonable as symptoms and impaired HRQoL are what brings the patients to the physician and are currently the main indications for AF ablation. A simple, short, validated AF-specific instrument such as the AF6 may give a better understanding of which patients can derive the greatest subjective improvement of AF ablation or other interventions and be a tool for involving patients. However, it is well known that reliance on patients' perception of AF following ablation results in an underestimation of AF recurrence and a reliable assessment of rhythm outcome is therefore also essential in outcome assessment. In current practice of AF ablation, ILRs have only been used in clinical trials. It could be reasonable to provide all patients scheduled for AF ablation with an ILR, definitely all patients included in clinical trials.

Future Perspectives

There is a need for future randomized trials to assess whether CRT is superior to RV pacing in all patients undergoing AVJA, not just patients with reduced LVEF prior to AVJA.

AF ablation usually generates lower success rates in patients with persistent AF in terms of arrhythmia reduction. A study focusing on PROs might show higher success rates and better demonstrate the benefit for patients. Additional studies may show the value of AF-specific instruments that meet the standard of the FDA PRO guidance, in other AF patient populations and/or after other interventions than AF ablation.

Rhythm monitoring with an ILR might have a relevant impact on patient management but the clinical impact has to be evaluated in future clinical trials. Since the present study, smaller ILR devices have been developed, and remote monitoring may overcome the issue with limited memory.

AF causes considerable morbidity, particularly due to stroke and HF, and up to doubles the mortality rate. Most complications associated with the arrhythmia occur after some time in AF, while symptoms and impaired HRQoL generally appear immediately after the onset of the arrhythmia and are what bring the patient to the physician. Inclusion of PROs as outcome measures is therefore of great importance when assessing the success of an intervention.

SAMMANFATTNING PÅ SVENSKA

Bakgrund
Förmaksflimmer är den vanligaste hjärtrytmrubbningen och drabbar ca 3 % av den vuxna befolkningen. Förekomsten ökar med stigande ålder och vid annan hjärt-kärlsjukdom och förväntas öka ytterligare på grund av ökad förekomst av riskfaktorer i den åldrande befolkningen. Förmaksflimmer är förknippat med en betydande sjuklighet (framförallt på grund av stroke och hjärtsvikt) och död samt ofta symptom och försämrad livskvalitet. Hos patienter med förmaksflimmer väljer man behandling med antingen *rytmkontroll* som syftar till att behålla patienten i normal sinusrytm, eller *frekvenskontroll* då man accepterar förmaksflimret men sänker frekvensen. Behandling med *antikoagulantia* bör ges till alla patienter med förmaksflimmer och riskfaktorer för stroke enligt CHA_2DS_2-VASc-skalan, för att minska stroke och död oavsett rytm- eller frekvenskontroll.

Kateterablation, elektrisk isolering av lungvenerna vilka mynnar i vänster förmak, är effektiv för att förhindra förmaksflimmeråterfall för utvalda patienter med symptomgivande förmaksflimmer då patienten har terapisvikt av ett eller flera antiarytmiska läkemedel och i enstaka fall som förstahandsbehandling vid rytmkontroll. Det är dock svårt att definiera vad som är en lyckad förmaksflimmerablation. Uppföljningen genomförs ofta med enstaka EKG, patientens uppgivna symptom och intermittenta långtids-EKG. Vid minst ett EKG-verifierat återfall räknas proceduren som misslyckad trots att många patienter har minskat antal förmaksflimmerepisoder och ofta upplever sig förbättrade. Förmaksflimmerepisoder helt utan symptom förekommer dessutom i ökad utsträckning efter ablationen, vilket ytterligare försvårar bedömningen av vilken procedur som lyckats och vilken som inte lyckats. Det är heller inte ovanligt att patienten har kvarstående symptom efter ablationen som inte är relaterade till förmaksflimmer.

Hos patienter med förmaksflimmer där läkemedelsbehandling varit otillräcklig eller inte tolererats eller kateterablation misslyckats, är pacemakerimplantation och *His-ablation* en palliativ behandling för frekvenskontroll. His-ablation innebär att man bryter förbindelsen mellan förmak och kammare genom kateterburen teknik och har visats minska symptom och vårdtillfällen samt öka livskvaliteten. Dock blir patienten livslångt pacemakerberoende efter ingreppet, och långvarig pacemakerbehandling kan

orsaka försämrad hjärtsvikt och till och med nyupptäckt hjärtsvikt hos vissa patienter. Det finns också en mycket liten ökad risk för kammarrytmrubbningar och plötslig död tidigt efter His-ablation.

Syftet med avhandlingen var att undersöka:

- Andelen ny eller förvärrad hjärtsvikt samt död samt prediktorer för dessa, hos patienter som har genomgått His-ablation och pacemakerbehandling p.g.a. behandlingsresistent förmaksflimmer.
- Andelen återfall i förmaksflimmer med både kontinuerlig och intermittent rytm-monitorering (konventionell) upp till två år efter kateterablation och dess relation till symptom.
- Symptombörda och livskvalitet före och upp till två år efter kateterablation genom såväl läkares symptomskattning som patientens egen uppfattning uttryckt i ett förmaksflimmerspecifikt instrument samt ett livskvalitetinstrument, i förhållande till kontinuerlig EKG-monitorering.
- Livskvalitet före och två år efter kateterablation för förmaksflimmer jämfört med en ålders- och könsmatchad normalbefolkning.

Metoder och resultat

Det *första delarbetet* beskriver andel hjärtsvikt som lett till inläggning på sjukhus samt död hos 162 konsekutiva patienter som His-abladerats i Örebro och Odense åren 2001 till 2011. Andelen patienter som vårdats inneliggande för hjärtsvikt var 20 % under den i median fem år långa uppföljningen och vårdtiden skedde i median 53 (IQR 20-102) månader efter His-ablationen. Hälften av dessa hade känd hjärtsvikt före HIS-ablationen. QRS-duration ≥ 120 ms och förstorat vänster förmak var oberoende riskfaktorer för inläggning för hjärtsvikt. Trettiofem patienter (22 %) avled 47 (IQR 24-65) månader efter His-ablationen och de vanligaste dödsorsakerna var hjärtsvikt och cancer. Hypertoni och tidigare känd hjärtsvikt var oberoende prediktorer för död.

Delarbetena två till fyra baseras på en patientpopulation bestående av 54 patienter med dokumenterat symptomatiskt förmaksflimmer som var planerade för kateterablation i Örebro eller Odense från april 2009 till januari 2013. Samtliga patienter erhöll en implanterbar hjärtmonitor (ILR) minst två veckor före ablationen för automatisk kontinuerlig rytmövervakning i två år och uppmanades att manuellt spela in hjärtrytmen vid symptom. Dessutom genomgick alla patienter EKG samt 48-96 timmars

intermittenta långtids-EKG tre, sex, 12, 18 och 24 månader efter ablationen. Patienterna fyllde i formulär för förmaksflimmerspecifika symptom (AF6) och livskvalitet (SF-36 hälsoenkät) och läkare uppskattade symptomens svårighetsgrad (EHRA-klass) före och vid uppföljande besök upptill två år efter ablationen.

Delarbete två visade att kontinuerlig monitorering detekterade förmaksflimmeråterfall hos en högre andel patienter upptill två år efter ablationen (76 % vid kontinuerlig monitorering, 57 % vid intermittent monitorering) och dessutom tidigare än intermittent monitorering. Flimmerbördan, dvs. den procentuella tiden i förmaksflimmer mellan återbesöken, var signifikant lägre när återfall bara detekterades med kontinuerlig monitorering jämfört med detektion med båda modaliteterna. Andelen patienter utan flimmeråterfall var relativt konstant efter ablationen men rytmen varierade mellan förmaksflimmer och sinusrytm mellan återbesöken hos 13-19 % av patienterna. Hälften av patienterna angav symptom vid minst ett tillfälle men en tredjedel av symptomen motsvarades inte av förmaksflimmer. Patienterna som inte uppgav några symptom via patientaktivatorn var yngre, oftare män och hade oftare antiarytmikabehandling vid ablationen.

I *delarbete tre* sågs att både patientskattade (AF6) och läkarskattade symptom (EHRA-klass) förbättrades signifikant efter ablation. Den största symptomförbättringen sågs sex månader efter ablationen men AF6 visade fortsatt förbättring upptill 12 månader efter ablationen i motsats till EHRA-klass. Överensstämmelsen mellan patientskattad AF6 och läkarbedömd EHRA-klass var låg, i allmänhet var patienter och läkare ense vid förbättrade symptom men i många fall upplevde patienterna ingen förbättring medan läkarna upplevde att patienterna förbättrats eller tvärtom. Både AF6 och EHRA-klass var signifikant korrelerade till flimmerbördan, men vid låg flimmerbörda var spridningen i AF6-poäng stor mellan enskilda patienter och omvänt hade en del patienter med högre flimmerbörda få symptom. En förbättring på mer än nio poäng i AF6 mosvarade en kliniskt meningsfull symptomförbättring.

I *delarbete fyra* noterades att livskvaliteten enligt SF-36 var sämre hos patienter planerade för förmaksflimmerablation jämfört med en ålders- och könsmatchad normalbefolkning. Båda huvuddimensionerna fysisk och psykisk hälsa förbättrades dock till normalnivå efter ablationen. Patienter med låg flimmerbörda (< 0,5 %) förbättrades till normalnivå i samtliga

livskvalitetskalor medan patienter med högre börda bara förbättrades till normalnivå i social funktion och psykisk hälsodimension. Däremot förbättrades alla skalor i AF6 hos både patienter med hög och låg flimmerbörda men förbättringen var större hos patienter med lägre flimmerbörda (förutom andningsbesvär i vila). Högre flimmerbörda var också oberoende associerat med sämre fysisk hälsa och sämre AF6.

Slutsatser

His-ablation är ett bra behandlingsalternativ vid långvarigt behandlingsresistent förmaksflimmer och långvarig pacemakerbehandling var inte skadlig för majoriteten av patienterna. QRS-bredden bör tas i beaktande inför His-ablation och sviktpacemaker istället för en konventionell pacemaker kan övervägas vid QRS-bredd ≥ 120 ms.

Förmaksflimmerbördan var låg de första två åren efter kateterablation för förmaksflimmer. Kontinuerlig monitorering av hjärtrytmen var överlägsen intermittent monitorering i att detektera förmaksflimmeråterfall, framförallt korta återfall, och en fjärdedel av patienterna skulle felaktigt ha kategoriserats som flimmerfria om bara intermittent monitorering använts. Symptom var vanliga även efter ablation men var i en tredjedel av fallen inte korrelerade till förmaksflimmer. Ablation ledde till minskade symptom, både enligt patienten själv och uppskattat av läkare, samt förbättrad livskvalitet. Ett förmaksflimmerspecifikt instrument var dock känsligare än både EHRA-klass och SF-36 i att uppskatta förändring efter ablation. Dessutom sågs ofta en diskrepans mellan patientens och läkarens uppfattning om patientens symptom efter ablationen. Avsaknad av förmaksflimmeråterfall och en låg flimmerbörda resulterade oftast i minskade symptom men symptomförbättring sågs också trots liten effekt på flimmerbördan.

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