



UPPSALA
UNIVERSITET

*Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 1418*

Surgical ablation for the treatment of atrial fibrillation in different patient populations

*A study of clinical outcomes including rhythm,
quality of life, atrial function and safety*

LOUISE BAGGE



ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2018

ISSN 1651-6206
ISBN 978-91-513-0207-2
urn:nbn:se:uu:diva-338097

Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Akademiska Sjukhuset, ingång 50, bv, Uppsala, Friday, 2 March 2018 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Professor Mårten Rosenqvist (Institutionen för kliniska vetenskaper, Danderyds sjukhus).

Abstract

Bagge, L. 2018. Surgical ablation for the treatment of atrial fibrillation in different patient populations. A study of clinical outcomes including rhythm, quality of life, atrial function and safety. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1418. 111 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0207-2.

Patients with atrial fibrillation (AF) have markedly reduced quality of life (QoL) and catheter ablation has become a useful tool in the rhythm control therapy. However, because of the poor outcome for patients with persistent AF, new surgical ablation strategies for rhythm control are emerging.

The aims of this thesis were to evaluate QoL, the main indication for rhythm control, after three different types of surgical ablation for AF, two stand-alone epicardial AF ablation procedures and one concomitant procedure during mitral valve surgery (MVS), and to perform a long-term follow-up of one of the techniques with regard to rhythm outcome, left atrial function, exercise capacity and safety.

As the first center in the Nordic countries to adopt the video-assisted epicardial pulmonary vein isolation and ganglionated plexi ablation combined with left atrial appendage excision (LAA), the freedom from AF at one year follow-up was found to be 71% and associated with improved exercise capacity, QoL and symptoms as well as preserved left atrial function and size. The most common complication was bleeding events (14%). After 10 years, the improved symptoms and QoL remained, reaching comparable levels of the general Swedish population, despite a marked decline in the rate of freedom from AF (36%). 4 strokes appeared during follow-up despite LAA excision in 3 of these patients.

In order to improve the rhythm outcome for patients with longstanding persistent AF a box-lesion was added to the procedure. At one year follow-up, both symptoms and QoL improved and was indistinguishable from those in the Swedish general population.

Finally, concomitant AF ablation during MVS did not improve QoL compared to MVS alone in a double blinded randomized controlled trial. Moreover, no difference was seen between patients in AF or sinus rhythm at one year follow-up, irrespective of the allocated therapy, indicating that their preoperative symptoms were mainly related to their valve disease.

In conclusion, the stand-alone procedures using surgical ablation was found to be effective but at the expense of procedural complications. In contrast, the concomitant surgical AF ablation did not improve QoL, a finding that raises concerns regarding current recommendations for this procedure.

Keywords: Atrial fibrillation, surgical ablation, quality of life, vagal denervation, ganglionated plexi, left atrial function, epicardial, minimally invasive, left atrial ablation

Louise Bagge, Department of Medical Sciences, Cardiology-Arrhythmia, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

© Louise Bagge 2018

ISSN 1651-6206

ISBN 978-91-513-0207-2

urn:nbn:se:uu:diva-338097 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-338097>)

*To the memory of my beloved parents,
Lars Bagge and Harriet Bagge*

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Bagge L, Blomström P, Nilsson L, Einarsson GM, Jidéus L, Blomström-Lundqvist C. (2009) Epicardial off-pump pulmonary vein isolation and vagal denervation improve long-term outcome and quality of life in patients with atrial fibrillation. *J Thoracic Cardiovasc Surg*, 137(5):1265–71.
- II Bagge L, Blomström P, Jidéus L, Lönnerholm S, Blomström-Lundqvist C. (2017) Left atrial function after epicardial pulmonary vein isolation in patients with atrial fibrillation. *J Interv Card Electrophysiol*, 50(2):195-201.
- III Bagge L, Probst J, Jensen SM, Blomström P, Thelin S, Holmgren A, Blomström-Lundqvist C. (2017) Quality of life is not improved after mitral valve surgery combined with epicardial left atrial cryoablation as compared with mitral valve surgery alone: A substudy of the double blind randomized SWEDish Multicentre Atrial Fibrillation study (SWEMAF). Accepted manuscript *Europace*. [Epub ahead of print]
- IV Bagge L, Jansson V, Blomström P, Blomström-Lundqvist C. 10 years follow-up of video-assisted epicardial pulmonary vein isolation and vagal denervation in patients with atrial fibrillation. *Submitted*.
- V Probst J, Bagge L, Blomström P, Jidéus L, Wassberg E, Lönnerholm S, Malmborg H, Blomström-Lundqvist C. A Prospective Study of the Effects of Thoracoscopic Epicardial Left Atrial Ablation on Symptoms and Quality of Life. *Manuscript*

Reprints were made with permission from the respective publishers.

Contents

Introduction.....	11
Background.....	12
Atrial fibrillation	12
Definition and diagnosis	12
Prevalence and epidemiology	12
Symptomatology, quality of life and classification	13
Patophysiology	14
Management of atrial fibrillation.....	17
Non-pharmacological treatment of atrial fibrillation	19
Historical perspective	19
Cox-Maze procedure	20
Concomitant surgical ablation	20
Cather ablation for atrial fibrillation.....	22
Stand-alone epicardial pulmonary vein isolation with or without left atrial ablation	23
Aims.....	25
Methods	26
Patient selection.....	26
Video-assisted epicardial pulmonary vein isolation trial.....	26
SWEDMAF trial.....	26
TELA-AF trial	27
Study design	28
Clinical evaluation prior procedure	29
Investigations (Paper I, II and IV)	29
Anticoagulation and antiarrhythmic drugs (Paper I, II and IV).....	29
Echocardiographic examination (Paper II).....	29
Evaluation of Quality of life and symptoms (Paper I, III-V).....	30
Investigations (Paper III and Paper V)	30
Procedures	32
Video-assisted epicardial pulmonary vein isolation (Paper I, II and IV).....	32
Concomitant surgical ablation (Paper III)	33
Thoracoscopic left atrial ablation (Paper V).....	34

Follow-up	35
Video-assisted epicardial pulmonary vein isolation (Paper I, II and IV).....	35
Concomitant surgical ablation (Paper III)	36
Thoracoscopic left atrial ablation (Paper V).....	36
Statistics	37
Paper I.....	37
Paper II	37
Paper III	37
Paper IV	37
Paper V	37
Main results.....	38
Videoassisted epicardial pulmonary vein isolation (Paper I, II, IV)	38
Paper I.....	39
Paper II	44
Paper IV	47
Concomitant surgical ablation (Paper III)	57
Quality of life.....	57
Thoracoscopic left atrial ablation (Paper V)	64
Quality of life.....	64
Symptoms	68
Discussion.....	69
Stand-alone epicardial pulmonary vein ablation with or without left atrial ablation (Paper I, II and IV-V).....	70
Rhythm outcome (Paper I, IV)	70
Quality of life and symptoms (Paper I, IV-V)	76
Left atrial function and size (Paper II).....	78
Safety (Paper I, IV).....	79
Concomitant AF surgical ablation (Paper III).....	81
Quality of life.....	81
Limitations	84
Paper I, II and IV-V	84
Paper III	84
Conclusions.....	85
Clinical implications and future perspective.....	87
Summary in Swedish (Sammanfattning på svenska).....	89
Acknowledgements.....	93
References.....	96

Abbreviations

AF	Atrial fibrillation
AAD	Antiarrhythmic drug
CA	Catheter ablation
CABG	Coronary artery bypass grafting
ECG	Electrocardiogram
FAC	Fractional area change
GP	Ganglionated plexi
LA	Left atrium
LAA	Left atrial appendage
MVS	Mitral valve surgery
PV	Pulmonary vein
PVI	Pulmonary vein isolation
QoL	Quality of life
RCT	Randomized controlled trial
RF	Radiofrequency
SA	Surgical ablation
SF-36	Short-Form 36-item
SR	Sinus rhythm
SSQ	Symptom Severity Questionnaire
SWEDMAF	SWEDish Multicenter Atrial Fibrillation
TEE	Transesophageal echocardiography
TELA-AF	Thoracoscopic epicardial left atrial-atrial fibrillation

Introduction

The prevalence of atrial fibrillation (AF) in the developed world is approximately 1-2% of the general population and is likely to increase¹⁻³. At diagnosis the patient may present with palpitations, chest pain, dyspnea, and anxiety or be entirely asymptomatic. Apart from symptoms related to the rapid and irregular rhythm, with markedly reduced exercise capacity⁴ and degraded quality of life (QoL)⁵, AF may in some people be fatal due to development of heart failure, stroke and sudden death⁶.

In the management of AF, apart from anticoagulation, rate control and treatment of underlying conditions to prevent complications, the primary goal is to reduce symptoms and thereby ameliorate QoL. The main indication for rhythm control is AF-related symptoms, despite adequate rate control therapy, since no rhythm control strategy including antiarrhythmic drugs (AADs), transvenous catheter ablation (CA) and surgical ablation (SA), has yet been able to prevent cardiovascular outcomes or withdrawal of anticoagulation^{7, 8}.

Antiarrhythmic drugs only have a moderate effect on maintenance of sinus rhythm (SR) over time and are associated with adverse side effects that may negate the inherent advantage of SR⁹. Transvenous CA eliminates AF in a high proportion of cases with paroxysmal AF, 70%^{10, 11}, but pulmonary vein (PV) reconnection is still a recognized problem¹²⁻¹⁴ and the result of such intervention is less successful in patients with non-paroxysmal AF^{11, 15, 16}.

Hence, alternative approaches using SA either as a stand-alone or concomitant procedure during mitral valve surgery has emerged for the treatment of AF. One of the stand-alone procedures is the video-assisted epicardial pulmonary vein isolation (PVI)^{17, 18}. A further development of the technique with a totally thoracoscopic left atrial ablation including a left box lesion has also been introduced¹⁹. There is, however, limited information available about the long-term outcome and QoL of such procedures.

Concomitant SA procedures, for the treatment of AF during mitral valve surgery (MVS), have demonstrated a higher rate of freedom from AF compared with MVS alone^{20, 21} but no significant improvement in terms of all-cause mortality or stroke²². The reduction in symptoms and improvement in QoL is, however, the main indication for rhythm control in patients with AF but the effect of combined MVS and SA on the QoL has not yet been established in adequately designed RCTs.

Background

Atrial fibrillation

Definition and diagnosis

In the heart the sinus node, consisting of a group of cells in the right atrium of the heart, initiate the normal heart rhythm called SR. In AF, other foci initiate an uncoordinated fibrillation of the atrium. Atrial fibrillation is defined as a supraventricular arrhythmia characterized by this chaotic electric activity within the atrium causing the atriums to fibrillate i.e. to contract very rapidly and uncoordinated²³. Since the atrioventricular junction serves as a filter, the ventricular heart rate is slower but still irregular. The diagnosis of AF is based on the findings on the electrocardiogram (ECG) showing an irregular ventricular rhythm with no distinct p-waves and a variable atrial cycle length of less than 200 ms²³. An episode lasting at least 30 s is diagnostic²³.

Prevalence and epidemiology

Atrial fibrillation is the most common sustained heart arrhythmia and the prevalence is likely to increase in the European union²⁴ and in the United States¹. In 2010 the estimated numbers of adults over 55 years who had AF were 8.8 millions in the European Union²⁴. The data on prevalence of AF in Africa, Asia and South-America is, however, scarce²⁵. Moreover, since the AF can be asymptomatic and therefore might remain undiagnosed in the general population²⁶, the prevalence is probably higher worldwide. There is a higher prevalence of AF among men but also in the aged population^{1,2,25}, in the age stratum of 55-59 years, the prevalence of AF was 1.3% in men and 1.7% in women but increased to 24.2% in men and 16.1% in women for those >85 years of age²⁴. The ageing population is probably the main reason for the increasing prevalence in the population¹ but better detection of silent AF^{27,28} and conditions predisposing to AF³ might contribute.

Atrial fibrillation is associated with a more than fivefold increased risk for stroke^{29,30} due to the inadequate contraction of the atria resulting in the formations of blood clots, mainly in the left atrial appendage (LAA)³¹. Even short episodes of AF can also underprop a generalized prothrombotic state because of atrial myocardial damage and the expression of prothrombotic factors on the atrial endothelial surface and activation of platelets and inflammatory

cells^{32, 33}. Moreover, AF is independently associated with a 2 fold increased risk for all-cause mortality in women and a 1.5 fold increased risk in men^{6, 34, 35} and a risk for heart failure^{6, 36}. Death due to stroke can largely be alleviated by anticoagulation, while other cardiovascular deaths, due to heart failure and sudden death for example, remain frequent even in AF patients treated according to the current guidelines³⁷. The rhythm and rate control improve AF related symptoms and may preserve cardiac function, but have not demonstrated a reduction in long-term morbidity and mortality^{38, 39}. Moreover, AF results in a high rate of hospitalization, mainly due to the management of AF, but also due to heart failure, myocardial infarction and treatment related complications^{40, 41}.

Symptomatology, quality of life and classification

Patients with AF may experience palpitations, lack of energy during exercise, chest pain, dyspnea, anxiety, dizziness and fatigue during AF episodes and have a poorer QoL than healthy controls^{5, 42} and reduced exercise capacity⁴. The QoL in patients with AF is worse or comparable to patients with coronary heart disease and congestive heart failure⁴². However, it is estimated that at least one third of the patients are asymptomatic and have silent AF⁴³.

Clinically, five types of AF can be distinguished, based on the clinical presentation, duration of the arrhythmia and therapeutic goals: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF, see Table 1. When the arrhythmia is first diagnosed it may belong to any of the four latter groups. In one individual the pattern can vary but during time the AF tends to progress towards more sustained forms.

Table 1. Classification of AF according to European Society of Cardiology guidelines for the management of AF 2016²³

Classification	Definition
First diagnosed AF	AF that has not been detected before, irrespective of the duration of AF or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating AF episodes within 7 days. AF episodes that are cardioverted within 7 days should be considered paroxysmal.
Persistent AF	AF episodes that lasts longer than 7 days, including episodes that are terminated by cardioversion after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	Continuous AF that is accepted by the patient (and physician). Rhythm control interventions are not applied in patients with permanent AF. If a rhythm control strategy is adopted, the arrhythmia should be re-classified as long-standing persistent AF.

Patophysiology

The pathophysiology of AF is complex and multifactorial with different mechanisms for its initiation and/or its maintenance. The triggers are responsible for AF initiation, the substrate is necessary for AF maintenance and perpetuators underlie the progression of the arrhythmia from paroxysmal to the persistent forms. The pathophysiological changes that promote the different forms of re-entry in the atria that contribute to the perpetuation of AF are also complex and include electrical and structural remodeling of the atrium⁴⁴. Atrial remodeling implies any persistent change in atrial structure or function. It is believed that some degree of structural remodeling must precede electrical remodeling.

Atrial fibrillation can be maintained by sustained rapid ectopic activity or by re-entry, see *Figure 1*. Reentry requires a suitable substrate and a trigger (eg ectopic beat) that acts on the substrate to initiate reentry. Ectopic firing contributes to reentry by providing triggers for reentry induction. Atrial remodeling has the potential to increase the likelihood of ectopic or reentrant activity through several potential mechanisms.

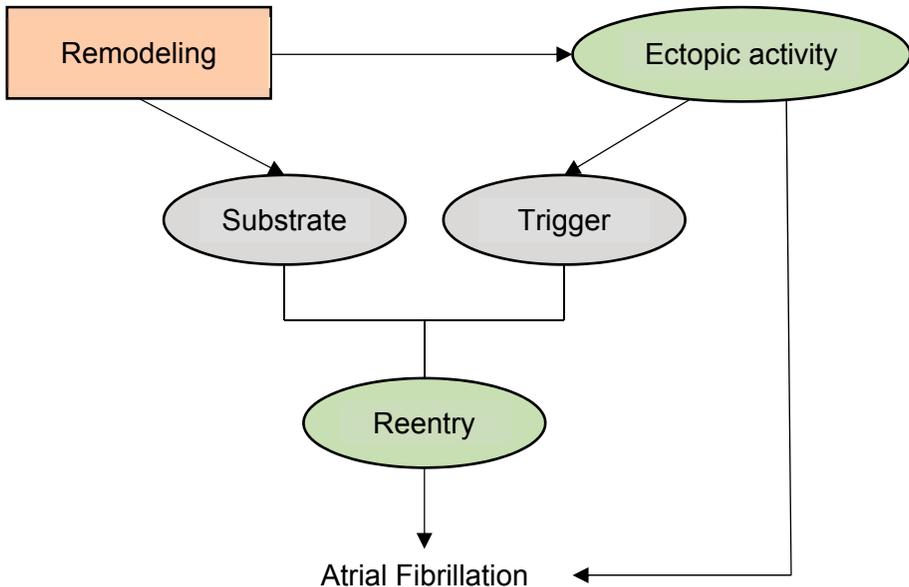


Figure 1. Key mechanisms in AF.

Electrophysiologic mechanisms of atrial fibrillation and electrical remodeling

Sleeves of myocardium extends from the left atrium (LA) into the PV and focal ectopic activity originating from the PVs has been described as a trigger for AF and the isolation of the PVs may suppress recurrent AF⁴⁵. Moreover, multiple sites inside one PV or multiple PVs can harbor the ectopic activity resulting in AF initiation in an individual⁴⁶. The focal activity might involve both triggered activity and localized reentry promoting AF.^{47, 48} The PVs have also been proposed to contribute to the perpetuation of AF⁴⁹.

During AF, the atrial myocardium responds to the high atrial rate by shortening of atrial refractoriness and atrial action potential duration⁵⁰. The shortening of the action potential not only preserves viability during AF, but also makes the atria prone to recurrent AF⁵¹. This process is described as electrical remodeling.

In 1959 Moe et al proposed a mechanism for the perpetuation of AF by continuous conduction of several independent propagating through the atrium in a chaotic matter “the multiple wavelet hypothesis”⁵². The arrhythmia is sustained as long as the number of wavefronts does not decline below a critical level. Localized sources of AF, such as ectopic foci, rotors⁵³ or stable re-entry circuits all cause fibrillatory conduction distant from the source, which is hard to distinguish from propagation sustaining AF by multiple wavelets. The functional re-entry resulting from rotors has been described and ablation of the rotors may result in termination of the arrhythmia⁵⁴.

Subsequently, there may be several other triggers than the PVs for AF. Experimental studies have also demonstrated that chemical stimulation⁵⁵ of GP or electric stimulation⁵⁶ of the nerves within the PVs could induce PV firing and AF.

Structural remodeling

The structural remodeling consists of AF induced increased expression of extracellular matrix proteins and increased atrial fibrosis⁵⁷. The fibrosis results in slowed atrial conduction and electrical isolation of atrial cardiomyocytes disturbing the continuous cable-like arrangement of cardiomyocytes⁵⁸, favoring re-entry and perpetuation of the arrhythmia, and is an important contributor to the AF substrate⁵⁹.

Moreover, AF reduces atrial contractile function and increases atrial size⁶⁰ which is a known risk factor for progressing to more sustained AF patterns⁶¹.

Atrial enlargement is also associated with heart failure related remodeling⁶² and heart failure itself further promote atrial tissue fibrosis^{63, 64}. Hence, after full hemodynamic recovery from heart failure, the fibrosis remains and sustained AF is still inducible, despite the absence of atrial dilatation⁶⁴.

In patients, without concomitant conditions, the most likely cause of the first AF episode is focal sources of electrical activity (usually in the PVs). Some of the patients never develop sustained AF⁶⁵ while others present with sustained AF from the start. The number of predisposing conditions (e.g. diabetes⁶⁶, hypertension, obesity or heart failure⁶⁷) is related to the probability of sustained forms of AF in a majority of patients with AF. Many of these conditions are present already at the diagnosis of AF.

Atrial fibrillation and the autonomic nervous system

The heart rate is normally determined by the rate of depolarization of the cardiac pacemaker tissue, normally the sinus node, and is modulated by the autonomic nervous system. The autonomic nervous system is successively modulated by mechanical stress receptors, baro- and chemoreceptors located in the heart and great vessels of the heart and can be divided into the extrinsic and intrinsic cardiac nervous system⁶⁸.

The extrinsic cardiac nervous system consists of both sympathetic and parasympathetic components, including neurons in the brain and spinal cord and nerves directed to the heart. The intrinsic nervous system, however, includes autonomic neurons and nerves located in the GP in the epicardial fat pads outside the heart and along the great vessels⁶⁹. Some of the GPs are located in the epicardial fat pads around the LA and the PVs⁶⁹. The GPs modulate the interactions between the extrinsic and intrinsic nervous system⁷⁰ and contain, predominantly, parasympathetic neurons but also sympathetic neurons⁶⁹.

It has been demonstrated that the GPs may play a role in triggering PV firing^{56, 71-73}. Moreover, the ablation of GP has been reported to reduce recurrence of or eliminate AF⁷⁴⁻⁷⁶.

Ligament of Marshall and left atrial appendage

The ligament of Marshall is an embryologic remnant of the left superior vena cava located between the LAA and the left PVs. In the adult, the Ligament of Marshall contains fibrous tissues, a myocardial sleeve and GPs. The muscle structure can serve as a trigger for AF⁷⁷ and the autonomic innervation may contribute to the initiation of AF⁷⁸. Ablation of the ligament of Marshall has resulted in a reduction of AF episodes⁷⁹.

The LAA has also been identified as a trigger site for AF^{80, 81} and ablation of the LAA resulted in a high degree of freedom from AF⁸¹.

Management of atrial fibrillation

The primary goals with the treatment of AF is to reduce symptoms and to prevent complications associated with AF. The strategies to prevent complications involve anticoagulation to prevent thromboembolic events, rate control to prevent tachycardia-induced cardiomyopathy and treatment of underlying conditions to prevent the progression of AF and reduce morbidity and all-cause mortality. These treatments may alleviate the symptoms per se, but other strategies might also be required, such as rhythm control by cardioversion, AADs, transvenous CA or SA.

Anticoagulation

AF is associated with an increased risk of stroke^{29, 30} but the risk varies across patients dependent on the prevalence of several risk factors. The recommended predictive risk stratification score according to guidelines is CHADS-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, female sex) for evaluation prior to initiation of treatment^{23, 82}. Patients with an increased risk are recommended anticoagulation in absence of contraindications²³. The use of a bleeding risk score, eg. HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly) should also be considered to identify modifiable risk factors for major bleeding^{23, 83}.

Rate control

Rate control regulate the ventricular rate with drugs and results in an improved cardiac efficiency and prevention of tachycardia-induced heart failure^{84, 85}, subsequently, and may be sufficient to reduce AF related symptoms. To achieve acute or long-term rate control beta-blockers, digoxin, the calcium channel blockers diltiazem and verapamil, or combination therapy may be re-

quired²³. Urgent cardioversion is considered if the patient is unstable. However, today a lenient rate control is acceptable, unless symptoms call for a stricter rate control²³.

Treatments of underlying conditions

Several concomitant cardiovascular and non-cardiovascular conditions amplifies the risk of developing AF, the progression of AF and AF-associated complications. Thus, to prevent AF and its disease burden, it is of major importance to identify, prevent and treat such conditions. The conditions includes blood pressure control^{3, 86}, heart failure treatment^{3, 86}, treatment of valvular heart disease^{87, 88}, treatment of diabetes mellitus^{3, 89}, weight reduction^{3, 90}, increasing cardiorespiratory fitness^{91, 92}, and other measures.

Rhythm control

The aim for rhythm control is to restore and maintain SR with electrical cardioversion, AADs and/or transvenous CA and SA. The first line antiarrhythmic therapy is pharmacological agents for the prevention of recurrent episodes of AF in symptomatic patients with AF²³. Unfortunately, the majority of the AADs are only moderately effective in maintaining SR over time and those that are more effective cause significant morbidity and side effects themselves that may negate the inherent advantage of SR⁹. Catheter ablation or combination therapy is often effective when AADs fail⁹³. Until now, the comparison of rhythm control versus rate control have resulted in neutral outcomes regarding cardiovascular events^{7, 8} but whether the modern strategy with CA, combination therapy and early therapy leads to a reduction in cardiovascular events and/or improved survival remains to be seen in ongoing trials such as EAST AFNET 4 (ClinicalTrials.gov identifier NCT01288352) and CABANA (ClinicalTrials.gov identifier NCT00911508). At the moment, rhythm control is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy²³.

Antiarrhythmic drugs

Antiarrhythmic drugs approximately doubles SR maintenance compared with no therapy⁹⁴. The choice of AAD needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and serious side effects, patient preferences, and symptom burden and safety rather than efficacy considerations should primarily guide the choice of AADs²³. The major AADs available to prevent AF in Europe are: amiodarone, dronedarone, flecainide, propafenone and sotalol²³.

Non-pharmacological treatment of atrial fibrillation

The moderate effect of AADs and the finding of triggers of AF in the PVs⁴⁵ led to the development of CA though PVI as a treatment to prevent recurrent AF⁹⁵. However, the first invasive treatment of AF was performed before the introduction of CA.

Historical perspective

The first surgical intervention for AF was the creation of an atrioventricular nodal block with concomitant pacemaker insertion⁹⁶. When the atrioventricular node is destroyed, the ventricle is no longer dependent on the atrium for rate and instead is controlled by the pacemaker. This procedure was invasive and irreversible and still left the atrium fibrillating, so it did not alter the risk for thromboembolic disease and required anticoagulant therapy in addition to a permanent pacemaker. It is no longer in use but a less invasive catheter based ablation of the atrioventricular node, preceded by pacemaker insertion, is considered nowadays for patients when the rate cannot be controlled by pharmacological agents and when AF cannot be prevented by antiarrhythmic therapy.

The Maze procedure was introduced by James Cox for the treatment of AF approximately 30 years ago⁹⁷. It evolved into the Cox-Maze III technique which involves making multiple incisions in the atrium to create scars that can eliminate abnormal electrical conduction since scar tissue does not conduct electrical impulses, hence, eliminate every potential area of re-entry⁹⁸. Although the procedure is effective^{99, 100}, it has failed to achieve widespread adoption because of its complexity and highly invasive nature. However, the Cox-Maze procedure and other simpler variants of AF surgery have mainly been used concomitant to other open heart surgery procedures¹⁰¹.

Less invasive procedures have been developed owing to increased knowledge about the pathophysiology of AF. In 1998, Haissaguerre et al reported spontaneous initiation of AF by ectopic beats originating in the PVs⁴⁵. This resulted in the development of transvenous catheter based treatment strategies to electrically isolate the PVs¹⁰². Thenceforth the PVs is a cornerstone of most existing catheter and SA techniques. Although, fortuitously, it had already been a part of the original Cox-Maze lesions 10 years earlier.

In patients with persistent AF, non-PV triggers for AF are increased as compared to paroxysmal AF¹⁰³. This finding, the poor outcome for patients with persistent AF after PV isolation¹⁰⁴ and also the presence of patients who had failed previous attempts of transvenous CA for PV isolation has led to the development of alternative approaches. One of those is the stand-alone off-pump epicardial PVI first introduced in 2003^{105, 106} and the hypothesis was that a radiofrequency (RF) clamp applied epicardially at the confluence of the veins, without intervening blood, was believed to create more durable and transmural lesions as compared to endocardial RF applications. Moreover,

non-PV triggers could be targeted, eg. GP^{56, 71, 73} and ligament of Marshall⁷⁷ and finally an excision of LAA could be performed to prevent strokes¹⁰⁷. The stand-alone epicardial PV procedure has also evolved to include box lesion and lines towards the mitral annulus^{19, 108-114}.

Recently in 2012, the epicardial and endocardial strategies have also been combined in a hybrid procedure to treat AF¹¹⁵.

Moreover, new strategies to target organized atrial rotors and other extended ablation procedures (beyond PVI) during transvenous CA has been developed for the treatment of persistent AF but does not seem justified in the first procedure^{16, 23, 116, 117}. However, the additional ablation on top of complete PVI may be considered in patients failing the initial ablation procedure²³ but there exists no consensus about what should be included in the additional ablation.

Cox-Maze procedure

The cut-and-saw technique introduced 30 years ago, involved isolation of the posterior LA, a cavotricuspid connection, a cavocaval connection, a connection to the posterior mitral annulus and exclusion of the LAA¹¹⁸. Thus, an electrical labyrinth (maze) of pathways is designed through which the impulse from the sinoatrial node finds a route to the atrioventricular node while preventing fibrillatory conduction.

The Cox-Maze III procedure still presents the most effective method in SR restoration even in long-term¹⁰⁰. Although, as previously mentioned, the Cox-Maze procedure has failed to gain widespread application due to its complexity, technical difficulty and morbidity. During the last decade, the most recent modification, Cox-Maze IV procedure, is performed with bipolar and unipolar RF, cryo-energy or combination of energies for most lesions, making the procedure more easy and safe. The overall freedom from AF at 5 years follow-up is 78% with no difference between stand-alone or concomitant procedure¹¹⁹. The effect of Cox-Maze IV has also been similar to those achieved with earlier Cox-Maze III in a propensity analysis¹²⁰. Currently, the attempt to deploy the devices through minimal access incisions place constraints on the locations and number of ablation lesions that can be performed during a stand-alone procedure. The ESC guidelines although recommend that maze surgery, possibly via minimally invasive approach, should be considered by an AF Heart Team as a treatment option for patients with symptomatic refractory persistent or post-ablation AF to improve symptoms²³.

Concomitant surgical ablation

This refers to patients undergoing cardiac surgery, commonly MVS, aorta valve surgery and/or coronary artery bypass grafting (CABG), along with surgical AF ablation. The concomitant SA can be divided into open concomitant

cardiac surgical operations, in which a left atriotomy is performed for the primary procedure (MVS), and closed concomitant SA, in which a left atriotomy is not otherwise performed (aorta valve replacement and/or CABG).

In approximately 50% of the patients presenting for MVS AF is found preoperatively¹²¹, but in only 6% of patients undergoing isolated CABG¹²², and in 14% of the patients at the time of aorta valve surgery¹²³. Since AF will persist in a majority of patients after such surgery it has led to a more widespread use of concomitant Cox-Maze III surgery or modifications of that procedure including SA.

Conventional Cox-Maze procedure and simplified SA procedures confined to the LA have in previous RCTs and meta-analyses demonstrated an approximately doubled risk of freedom from AF, diagnosed preoperatively, as compared with cardiac surgery alone^{20, 21, 124-134}. Importantly, the meta-analysis including 22 RCTs did not demonstrate any significant improvement of concomitant AF surgery versus cardiac surgery alone in terms of 30-day mortality, all-cause mortality, stroke or thrombo-embolism but found an increased risk for permanent pacemaker implantation and hence up to date there is no scientific evidence of improved clinical outcome after such combined procedures¹³³. However, the reduction in symptoms and improvement in QoL is the most important indication for rhythm control in patients with AF but the effect of combined MVS and epicardial left atrial cryoablation on the QoL has not yet been established in adequately designed RCTs.

Up to date, two non-randomized trials comparing QoL after MVS with versus without concomitant AF SA in patients with persistent AF reported improved QoL^{135, 136} and two RCTs found no significant differences between the treatment groups^{21, 132}. Neither trial was double-blinded though. Hence, the effect of concomitant AF SA during MVS on QoL remains to be seen in double-blinded RCTs. Currently, the ESC guidelines recommend that AF surgery, preferable biatrial, should be considered in AF patients undergoing cardiac surgery to improve symptoms attributable to AF, balancing the added risk of the procedure and the benefit of rhythm control therapy²³. Considering AF type, in PAF, PVI seems to be effective¹³⁷ and in persistent and long-standing persistent AF biatrial lesion patterns may be more effective¹³⁸⁻¹⁴⁰. Concomitant biatrial maze or PVI may even be considered in asymptomatic AF patients undergoing cardiac surgery according to guidelines²³. One of the problems, though, is to evaluate if the patients have symptoms of AF or if the symptoms can be attributed to their valvular disorder. Therefore, RCTs to evaluate QoL after the concomitant AF SA during MVS for these patients is of major importance.

Catheter ablation for atrial fibrillation

The identification by Haissaguerre of triggers that initiate AF within the PVs⁴⁵, resulted in an ablation at the site of origin of the trigger¹⁴¹. This procedure was later abandoned due to the infrequency with which AF initiation could be reproducibly triggered. Instead, an ablation approach was introduced to electrically isolate the PVs⁴⁶. However, the recognition of PV stenosis as a complication of RF within a PV as well as the identification of sites of AF initiation and/or maintenance were commonly located within the PV antrum, resulted in a shift towards ablation of the atrial tissue located in the antrum rather than in the PV itself^{142, 143}.

Complete PVI on an atrial level is the target and can be achievable by either RF or cryoablation with similar outcomes^{144, 145}. The rhythm outcome after CA of AF is difficult to predict depending on patient selection, AF type, time for follow-up and different methods used.

In patients with paroxysmal AF, a single PVI procedure is successful in achieving SR without severely symptomatic recurrences of AF in approximately 70% of the patients and in patients with persistent AF the success rate after PV isolation alone is 50%^{10, 11, 16}. In many patients multiple CAs for AF are necessary¹⁴⁶ possibly due to PV reconnection, reflecting difficulties in achieving transmural lesions^{12, 13}. The addition of a second procedure increases the success rate to 80%¹¹.

According to ESC guidelines CA of AF in patients with PAF, persistent and probably long-standing persistent, is a second-line treatment after failure of or intolerance to AADs²³. In these patients CA is more effective than AADs in maintaining SR^{10, 147-149}. Although, as a first-line treatment in patients with paroxysmal AF, there are only moderate improved rhythm outcome with CA compared to AADs^{150, 151}. There are three trials comparing CA as first line therapy for AF demonstrating that QoL improved with both AAD treatment and CA and significantly more with CA^{150, 152, 153}. Since the complication rates were similar, CA can be justified as first-line treatment in selected patients with PAF who prefer interventional therapy.

Reliable data are lacking for patients with persistent or longstanding AF but all point to improved rhythm outcome for CA compared to AADs^{147, 149}. As previously mentioned, additional ablation beyond complete PVI¹⁵⁴ for patients with persistent AF may be considered after failing the initial ablation procedure but there are insufficient data to guide the use of these at present^{16, 23}. The complications related to CA of AF includes asymptomatic cerebral embolism, vascular complications, cardiac tamponade, persistent phrenic nerve palsy, PV stenosis, periprocedural stroke, esophageal injury and periprocedural death (<0.2%)²³.

At the moment there is no indication for CA to prevent cardiovascular outcomes or withdrawal of anticoagulation or to reduce hospitalization³⁸ but there are trials underway such as Catheter Ablation versus Anti-arrhythmic Drug

Therapy for Atrial Fibrillation Trial (CABANA) (ClinicalTrials.gov identifier NCT00911508) which is a prospective RCT of ablation versus medical management of AF. Several studies have demonstrated improved QoL after AF ablation in patients with symptomatic AF or compared to AADs as a second line treatment¹⁵⁵⁻¹⁵⁷ but more RCTs comparing CA versus AADs are ongoing (CABANA) or have reported preliminary data (CAPTAF, ClinicalTrials.gov identifier NCT02294955), with QoL as a primary endpoint, supporting the ablation therapy for patients who had failed one drug either for rate or rhythm control.

Stand-alone epicardial pulmonary vein isolation with or without left atrial ablation

In 2005, Wolf et al performed bilateral epicardial PV isolation with bipolar RF energy on a beating heart and also added exclusion of the LAA through bilateral mini thoracotomies with video assistance¹⁷. The addition of the exclusion of the LAA was included to reduce the risk for future thromboembolic events. The epicardial approach for isolation of the PVs with a RF clamp applied at the confluence of the veins, without intervening blood, is believed to create more durable and transmural lesions as compared to transvenous RF ablation catheters applied endocardially.

Several groups have also incorporated GP mapping and ablation into the procedure^{18, 158-160} since GPs have been demonstrated to play a role in AF induction^{56, 71-73} and the ablation of them may reduce AF recurrences⁷⁴⁻⁷⁶. Since AF also has been shown to originate from the ligament of Marshall^{77, 78}, a division of the ligament has been added to the procedure¹⁵⁸⁻¹⁶⁰.

One of the most common energy sources during SA is using RF energy during these procedures to perform PVI which may potentially cause scar tissue in the LA¹⁶¹ which in turn can deteriorate the mechanical function and result in an enlargement of the atrium. This is important since a decrease in function may promote thromboembolic events because of the inadequate contraction of the atria resulting in the formations of blood clots even in the absence of AF and an increase in left atrial size may promote AF recurrence^{162, 163}. There is limited information about the effect on left atrial function and size after SA for AF.

The technologies used to perform lesions, the lesion sets and the patient selection vary between operators and there is an absence of a comparator group in most studies which makes the rhythm outcomes difficult to compare.

Since it is believed that persistent and long-standing persistent AF require a more extensive lesion set and therefore divergent linear lesions and left atrial box lesion set and lines towards the mitral annulus has been introduced^{19, 108-114, 164}. The number of patients subject to these procedures in studies are still small and the data are insufficient to draw any conclusions from.

Recently there has been at least three RCTs conducted comparing SA and CA. Surgical AF ablation in patients with mainly paroxysmal AF reported 66-89 % freedom from AF after epicardial PVI with/or without additional lines, GP ablation and LAA excision, at one year follow-up, as compared to 36-75 % in patients after endocardial CA of AF¹⁶⁵⁻¹⁶⁷. A meta-analysis concluded that SA was more effective than CA in achieving freedom from atrial arrhythmia in mixed AF populations but had a higher rate of immediate post-procedural complications¹⁶⁸. Long-term follow-ups after SA are limited to 5 years reporting freedom from AF in 38-69% of the patients^{162, 163, 169-171}, while effects on QoL are lacking. Despite the limited knowledge of long-term efficacy, the technique has slowly but steadily increased in use.

Aims

The overall aim of this thesis was to evaluate the clinical outcome of three types of surgical ablation for AF in different patient populations.

Specifically, focusing on the following questions:

- I What are the long-term results of video-assisted epicardial PVI combined with GP ablation for the treatment of AF with regard to QoL, symptoms, exercise capacity, safety and freedom from AF?
- II Does the video-assisted epicardial PV isolation combined with GP ablation for the treatment of AF affect the left atrial size and function at 6 months follow-up?
- III Does concomitant SA for AF during MVS improve QoL in patients with longstanding persistent AF compared to MVS alone?
- IV What is the 10-year outcome of video-assisted epicardial PV isolation combined and GP ablation for the treatment of AF with regard to QoL, symptoms, safety and freedom from AF?
- V Does the QoL improve after thoracoscopic left atrial ablation for AF in patients with mainly long-standing persistent AF? Is the QoL comparable to the levels in the Swedish general population in the same age range after surgery?

Methods

Patient selection

The patients included in these studies all had AF documented and verified on 12-lead ECG prior to inclusion, but the AF type and presence of symptoms related to AF varied between the studies.

Video-assisted epicardial pulmonary vein isolation trial

This trial resulted in three papers (**Paper I, II and IV**). In **Paper I**, 43 patients with symptomatic paroxysmal, persistent or permanent AF who either had failed CA or had chosen SA as first alternative undergoing video-assisted epicardial PVI combined with GP ablation from November 2005 until March 2008 were included. All patients had failed at least one Class I or III AADs. At the time for long-term follow-up (**Paper IV**), two patients had been excluded, one because of premature termination of the procedure and one was lost to follow-up. On the other hand, two other patients had been referred a few months later for the procedure and were also included in **Paper IV** for long-term follow-up, in total 43 patients (*Figure 10*). The AF types at baseline were reclassified according to the new 2016 ESC guidelines²³ in **Paper IV**.

The study population in **Paper II** (27 patients) consisted of a subgroup of the patients included in **Paper I**, all of which had SR at baseline and 6 months following the video-assisted epicardial PV isolation combined with GP ablation and were available for appropriate echocardiographic examination (*Figure 9*)

SWEDMAF trial

The data, design of the study, rhythm outcome and safety have been detailed elsewhere²⁰. **Paper III** is a substudy of this trial evaluating the quality of life after the procedure.

In brief, patients aged 18–80 years with permanent AF and mitral valve disease requiring MVS were randomly assigned double-blind to MVS combined with epicardial left atrial cryoablation or to MVS alone (controls) during 2003 to 2005. Patients were eligible irrespective of symptoms from AF since it was too difficult to distinguish symptoms related to AF versus those related to the mitral valve condition. The main exclusion criteria were heart failure in

New York Heart Association function class IV, previous cardiac surgery except for CABG surgery, planned concomitant surgery except CABG, conditions that would impose an increased risk for prolonged surgical procedure, and permanent pacemaker secondary to AV block. After hospital discharge the patients were evaluated with regards to clinical events, medical history, patient diary (date for AF recurrence, cardioversions, change in medication), rhythm, clinical examination, medications, 12-lead ECG, and complications at 1, 2, 3, 6 and 12 months after surgery, all of which were compared with baseline values. Electrocardiogram recordings and cardioversions performed in between or at follow-up visits, whenever such recordings were done and when patients had symptoms, were also documented. The type of AF was defined according to generally accepted criteria as paroxysmal, persistent, or permanent AF. The primary end-point was regained SR. At 12 months follow-up there was a higher rate of regained SR in the patients who had underwent concomitant AF cryoablation (73.3%) compared with patients, who underwent MVS alone (42.9%).

In **Paper III**, the study population consisted of the 65 patients with permanent AF randomized in the SWEDMAF trial and who had reached the primary end-point in the main study, rhythm outcome at 12 months follow-up, and replied to QoL questionnaires at baseline, 6 months and 12 months.

TELA-AF trial

The rhythm outcome and safety of TELA-AF procedure has been reported previously¹⁰⁹. **Paper V** is a substudy of this trial evaluating the quality of life after the procedure.

Sixty patients with severely symptomatic AF were referred for the procedure. The patients had either failed conventional CA for PVI or had chosen the procedure as first alternative. All patients had failed or been intolerant to at least one Class I or III AADs. The TELA-AF procedure consisted of a combined thoracoscopic, epicardial PVI, left atrial roof- and bottom ablation lines (“box-lesion”) as well as partial vagal denervation. The major exclusion criteria were prior cardiac surgery (including minimal invasive ablation), left ventricular ejection fraction $\leq 30\%$, thrombus in the LAA, significant pulmonary disease and left atrial transverse diameter > 6.0 cm. The patients were followed with clinical evaluations and 12-lead electrocardiograms at 3, 6, and 12 months after the surgical intervention and a 7-day Holter monitoring after 6 and 12 months.

At 12 month follow-up, 93% of the patients were free from AF, while 12% suffered from recurrent LA tachycardia.

In **Paper V**, the 50 patients with symptomatic AF undergoing thoracoscopic epicardial left atrial ablation (TELA-AF) from 2008 to 2010 who replied to

QoL and symptom questionnaires at baseline and 12 months were included in a substudy of the TELA-AF procedure.

Study design

Four papers (**I, II, IV and V**) are descriptive studies of our initial experience of new surgical techniques for the treatment of AF, video-assisted epicardial PVI combined with GP ablation (**Paper I, II and IV**) and thoracoscopic epicardial left atrial ablation (**Paper V**).

Paper III is a substudy of the double blinded multicenter SWEDMAF trial, where patients were randomized in a 1:1 manner to MVS with concomitant left atrial cryoablation or MVS alone. Patients, personnel, and all physicians (excluding the operating team) involved in the study and follow-ups were blinded to the allocated surgery, which was recorded separately from the patient's surgical notes.

The time for follow-up and main outcome measures are listed in Table 2.

Table 2. Overview of designs and methods in Paper I-V

	Paper I	Paper II	Paper III	Paper IV	Paper V
Design	Descriptive	Descriptive, substudy	Double-blinded, randomized, substudy	Descriptive, substudy	Descriptive, substudy
Procedure	Stand-alone epicardial PVI and GP ablation	Stand-alone epicardial PVI and GP ablation	Concomitant epicardial left atrial cryoablation	Stand-alone epicardial PVI and GP ablation	Stand-alone epicardial left atrial ablation
Follow-up	1 year	6 months	1 year	10 years	1 year
Main outcome measures	Rhythm outcome, QoL, symptoms, exercise capacity, safety.	Left atrial size and mechanical function.	QoL	Rhythm outcome, QoL, symptoms, safety.	QoL and symptoms.

Clinical evaluation prior procedure

Investigations (Paper I, II and IV)

The clinical evaluation at baseline prior video-assisted epicardial PVI and GP ablation included medical history, physical examination, 12-lead ECG, 2-dimensional echocardiography, coronary angiography (if age above 50 years or if symptoms suggested ischemic heart disease), spirometry (if symptoms of lung disease), 24-hour Holter recording, and contrast tomography (CT) for PV anatomy. Coronary artery disease was defined as previous myocardial infarction, coronary artery revascularization, or documented significant coronary artery stenosis on angiography.

In **Paper I and IV**, symptoms were also evaluated by symptom severity questionnaire (SSQ) and QoL by Short Form 36-item (SF-36) questionnaire at baseline. To evaluate physical capacity in **Paper I**, an exercise bicycle test was also included at baseline. In **Paper II**, the echocardiographic examination at baseline included measurements of the left atrial size and mechanical function, apart from the measurements according to clinical routine, which is discussed further in the section. Evaluations of the left atrial size and function was also related to the extensiveness of the procedure. The procedure was considered extensive if there were either six or more PV applications and/or more than ten GP ablations.

Anticoagulation and antiarrhythmic drugs (Paper I, II and IV)

In **Paper I, II and IV**, all patients were treated with warfarin with the international normalized ratio level for at least 1 month prior to the procedure. Thrombus formation in the LAA was excluded by transesophageal echocardiography (TEE) the day before the operation. Warfarin was replaced by low-molecular-weight heparin for bridging during the surgery. It was then withdrawn 3 months after the operation except for patients with a history of stroke or transient ischemic attack or with CHADS2 score above 2. Heparin (5000 IU) was administered intravenously during surgery.

After discharge, AADs were continued for at least 3 months after surgery, at which time they were withdrawn in patients who remained in SR. Amiodarone was prescribed if AF recurred more than once during the first 3 months postoperatively.

Echocardiographic examination (Paper II)

The echocardiographic examinations and measurements were made by an experienced technician supervised by a cardiologist (S.L). The LVEF was measured by Simpson's method in the 4 chamber view. The LA anterior posterior

diameter was measured by M-mode in the parasternal long-axis view and valve function was evaluated by Doppler flows.

Maximal LA cavity areas were obtained by planimetry in the apical 4-chamber view at the end of ventricular systole, defined as the last frame before mitral valve opening. Minimal LA cavity areas were obtained at end diastole at the time of the R-wave on the ECG. The mean values were calculated from 2-3 consecutive beats. The atrial fractional area change (FAC) of the LA was calculated using the formula below.

$$FAC = \frac{\text{Maximum area} - \text{Minimum area}}{\text{Maximum area}} \times 100$$

Pulsed Doppler echocardiography was used to assess the transmitral flow velocities from an apical 4-chamber view with a sample volume for the tip of the mitral leaflets during diastole. Peak velocities of the early filling deceleration time of the E-wave, were measured and averaged over two beats and the E/A ratios were calculated.

Evaluation of Quality of life and symptoms (Paper I, III-V)

The QoL in **Paper I, III-V** was evaluated using SF-36 which is a validated questionnaire^{172, 173} and has been widely used in a number of disease states and health conditions⁴², including in a number of studies of AF^{156, 157}. There is also an opportunity to compare improvements in QoL with other medical interventions. It has also been translated in to Swedish. The results of the 36 questions (items) are converted in to 8 subscales (Table 3) and also two component scores (physical and mental) with a score ranging from 0-100, with at higher score representing better QoL. The questionnaire takes 5-10 minutes to answer. There are standard rules to record the items and handle missing data which was applied in the studies.

There is comparative data for the general Swedish population by different age groups available¹⁷².

The symptoms in **Paper I, IV and V** were assessed by five variables in SSQ, which also has been used in AF studies and was developed by Pappone et al¹⁷⁴, and were each scored with regard to severity on a 5-point scale with a higher value representing more pronounced symptoms. The 5 variables in the SSQ includes palpitations, fatigue, dizziness, lack of energy and dyspnea all representing AF related symptoms.

Investigations (Paper III and Paper V)

In **Paper III and V**, the details of the clinical evaluation at baseline of the main studies SWEDMAF study (**Paper III**) and TELA-AF study (**Paper V**)

has already been mentioned. In the substudies the QoL at baseline was evaluated by SF-36 (**Paper III and V**) and symptoms by SSQ (**Paper V**).

Table 3. Summary of information about SF-36.

Scale	Label	Number of		Definition of lowest possible score	Definition of highest possible score
		Items	Levels		
Physical Functioning	PF	10	21	Limited a lot in performing all physical activities including bathing or dressing due to health	Performs all types of physical activities including the most vigorous without limitations due to health
Role-Physical	RP	4	5	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
Bodily Pain	BP	2	11	Very severe and extremely limiting pain	No pain or limitations due to pain
General Health	GH	5	21	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality	VT	4	21	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
Social Functioning	SF	2	9	Extreme and frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role-Emotional	RE	3	4	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
Mental Health	MH	5	26	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time

Procedures

Video-assisted epicardial pulmonary vein isolation (Paper I, II and IV)

The video-assisted off-pump procedure through mini-thoracotomies, included epicardial PVI using a bipolar RF clamp, left atrial GP identification using high-frequency electrical simulation and ablation, division of the ligament of Marshall, and left atrial excision using a stapler.

The general anesthesia was administered with a double-lumen endotracheal tube to be able to deflate one lung at a time. To ensure that electrical isolation could be completed for all veins, in case the excision of the LAA would result in any complication, the procedure started on the right side.

The procedure was initiated, with the patient in a left lateral recumbent position and the right lung deflated, by inserting the thoracoscope at the level of the xiphoid process. In the third intercostal space, a small thoracic incision was made to approach the right PVs. Through the incision, the pericardium was opened parallel and anterior to the phrenic nerve from the superior vena cava down to the inferior vena cava. A lighted dissector was used for blunt dissection around the PVs entering into the oblique sinus and passing out above the superior PV. The dissector was then replaced by rubber band.

The predominantly vagal GP were identified by high-frequency electrical simulation (800 pulses per minute, pulse-width 9.9 ms) applied at 10 sites according to a map (*Figure 2*) adapted from Warren Jackman, University of Oklahoma.

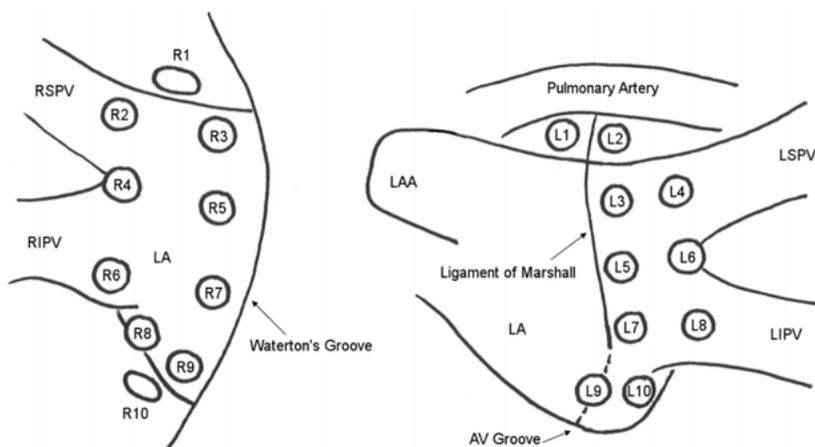


Figure 2. Sites of high-frequency stimulation of ganglionated plexi (GP). In every patient 10 sites on the right side (R1–R10) and 10 on the left side (L1–L10) of the left atrium were mapped. RSPV, Right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; LA, left atrium; LAA, left atrium appendage; AV, atrioventricular; R, right; L, left.

A bradycardia with a doubling of the R-R interval was defined as a positive response. To introduce the bipolar RF ablation clamp around the PV pair the rubber band was used. Prior to ablation, PV conduction was assessed for each PV pair. The clamp was closed proximal to the confluence of the veins and ablation was performed according to an algorithm that automatically stopped the ablation when the impedance change indicated that a transmural lesion was achieved between the jaws. Conduction block was then confirmed by pacing or, if AF was present, by the absence of fibrillation potentials on the distal or PV side of the ablation line. In case conduction block was not achieved after the first 3 consecutive applications, 1 or 2 additional RF applications were given until PV conduction block occurred. The high-frequency stimulation scheme (*Figure 2*) was then repeated, and if GP activity was still present, it was abolished by electrocautery or by an RF ablation pen, until no vagal response could be provoked. A thoracic drain was inserted, the lung inflated, and the incisions closed.

To approach the left PVs for isolation and GP ablation, the patient was then repositioned in a right lateral recumbent position and the procedure repeated as described above. If a ligament of Marshall could be identified, it was divided. Finally, the LAA was excised using a stapler (Autosuture, United States Surgical, Norwalk, Conn), if judged feasible and safe (absence of a wide base or thin wall). Intercostal analgetic blockade was given on both the right and left sides.

Concomitant surgical ablation (Paper III)

The SA included cryoablation lines that were applied by a cryosurgical probe epicardially resulting in left atrial posterior linear lesions and a lesion to the LAA (*Figure 3*). After cold cardioplegic arrest, the LA was opened and the valve procedures were performed according to routine. Epicardial electrical cardioversion was performed after surgery in patients with ongoing AF.

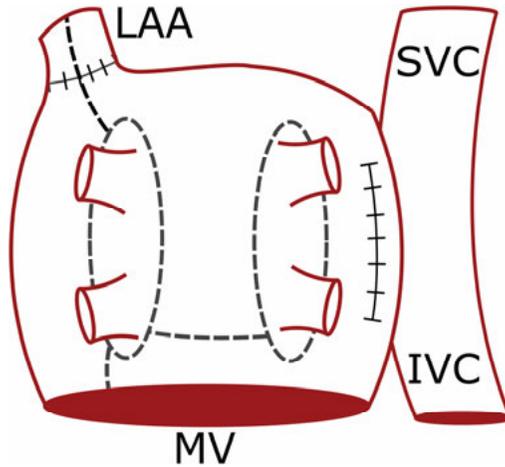


Figure 3. A schematic drawing of the left atrium, in a postero-anterior view, visualizing the cryoablation lesions (hatched lines) and the suture lines. LAA, left atrium appendage; SVC, superior vena cava; IVC, inferior vena cava; MV, mitral valve.

Thoracoscopic left atrial ablation (Paper V)

The totally thoracoscopic off-pump procedure included epicardial PVI using a RF clamp, partial vagal denervation using the same technique for identification of GPs by high-frequency electrical simulation as described previously for **Paper I, II and IV**, left atrial box lesion set by a 30 mm long irrigated CoolRail Linear Pen, division the ligament of Marshall and exclusion of the LAA using a stapler (*Figure 4*).

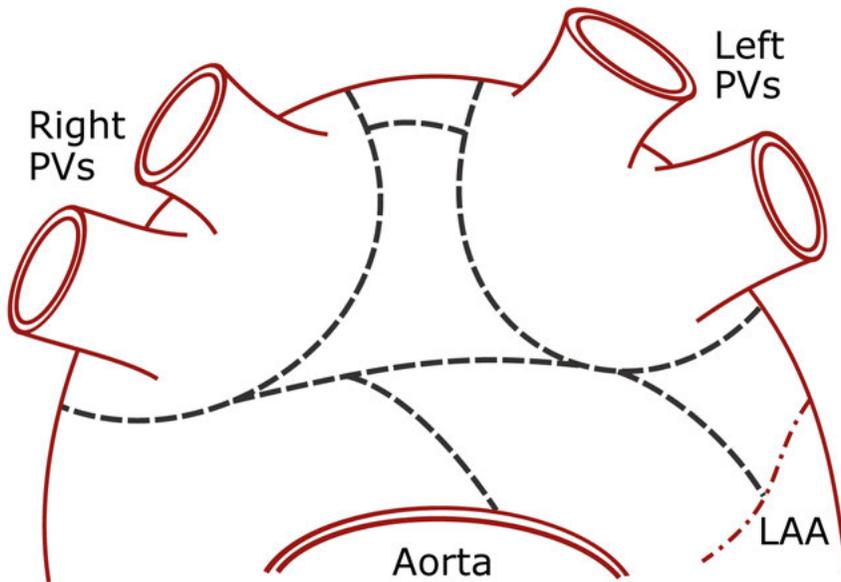


Figure 4. Schematic drawing in a superior view of the left atrium showing ablation lines (hatched lines). PV, pulmonary vein; LAA, left atrial appendage.

Follow-up

Video-assisted epicardial pulmonary vein isolation (Paper I, II and IV)

The patients were followed with regard to symptoms of AF and 12-lead ECG at 3, and 6 months after surgery in **Paper I, II and IV**. In **Paper II**, the echocardiographic examination and measurements were repeated and the follow-up completed to evaluate left atrial size and mechanical function.

In **Paper I and IV**, the patients were followed with regard to symptoms of AF at least another 6 months. An exercise bicycle test to assess physical capacity, echocardiography, CT (to exclude PV stenosis), 24-hour Holter recording, an evaluation of symptoms by SSQ and QoL by SF-36 were performed after 6 months, and the latter three (24-hour Holter recording, SSQ, and Short Form-36) and 12 lead ECG were repeated at 12-month follow-up in **Paper I**. A successful outcome in **Paper I** was defined as no documented symptomatic AF episodes or left atrial tachycardias after 12 months of follow-up, excluding the initial 3 months postoperatively, according to 12-lead ECG, 24-hour Holter recording, and spot ECG recorded when symptoms dictated. The perioperative and late complications up to 12 months after hospitalization were documented in **Paper I**. A comparison in QoL was also performed between the patients at 12 months follow-up and the general Swedish population.

In Paper IV the follow-up was extended to 10 years follow-up and included medical history, the SSQ, SF-36, 12-lead ECG and 24-h Holter ECG. AF/AT recurrences were searched for by interviewing patients, reviewing medical records and 12-lead ECG's during the 10 years follow-up, by spot ECG recorded when symptoms and by a 24-hour Holter recording at 10 years. The original follow-up data was updated regarding outcome, since more patients had completed a 12 months follow-up. Late complications, including strokes were recorded during 10 years follow-up.

The primary endpoint was freedom from AF episodes or left atrial tachycardias (AT) of >30 seconds duration, excluding cavotricuspid isthmus (CTI) dependent atrial flutter, during 10 years. A 3 months postoperative blanking period was used.

The secondary endpoints were symptoms and QoL using the SSQ and SF-36 at 10-years follow-up. The QoL values were adjusted according to age for the normal population during the 10 years follow-up and a comparison with the Swedish general population in the same age range was performed.

Concomitant surgical ablation (Paper III)

The present analysis focused on the patients who reached the primary endpoints at 6 and 12-months follow-up. Quality of life was assessed using the SF-36 at 6 and 12-months follow-up and the result compared between baseline and 6 and 12-month follow-up. Moreover, a comparison was made between patients undergoing combined MVS with cryoablation as compared with those undergoing MVS alone at 6 and 12-month follow-up. A corresponding comparison was also conducted between patients in SR and those in AF at the 6 and 12-month follow-up visits, regardless of whether cryoablation had been performed or not. Finally, the patients undergoing combined MVS with cryoablation and those undergoing MVS alone were compared with the Swedish general population in the same age range at baseline and 12 months. Patients in SR and AF at 12 months, irrespective of the allocated therapy, was also compared with the general Swedish population.

Thoracoscopic left atrial ablation (Paper V)

All patients were asked to fill out the SF-36 and SSQ at 12 months after the procedure and the results were compared between baseline and 12 months. Comparisons in QoL were also made between the patients at baseline and 12 months follow-up with the Swedish general population. Finally at baseline, the QoL of the patients were compared to patients with congestive heart failure, hepatitis, major depression and patients in hemodialysis.

Statistics

Descriptive statistics are presented as means and standard deviations for continuous variables and as counts and percentages for categorical variables unless otherwise stated. All p-values were two-sided and differences were considered statistically significant at a p-value less than 0.05.

Paper I

Continuous variables, when appropriate, were compared with the use of Student *t* test or otherwise Mann–Whitney *U* test. Tukey HSD test was used for the comparison of QoL. Wilcoxon matched-paired test or, when appropriate, the analysis of variance test was used for the evaluation of symptom scores.

Paper II

Continuous variables for each patient at different time periods were compared with the use of Wilcoxon matched-paired test. To analyze differences in LA function between patients with enlarged LA and those with normal-sized LA, the ANOVA test was used. The ANOVA test was also used to analyze differences in LA function between patients with extensive PV and/or GP ablations (either six or more PV applications and/or more than ten GP ablations) compared with patients with less extensive PV and GP ablations. Statistica was used for the analyses.

Paper III

Continuous variables are reported as 95% confidence interval (95% CI) and were compared with the use of Student's *t*-test. The power calculation is described elsewhere.

Paper IV

Continuous variables such as the QoL and SSQ score were compared with the use of paired or independent two-sample *t*-test. A Kaplan-Meier analysis was performed.

Paper V

Effect sizes were considered medium or large according to Cohen¹⁷⁵. Probability of score changes before and after intervention was tested by paired Student's *t*-tests for SF-36 scores. SSQ scores were pooled and the null-hypotheses was tested using unpaired *t*-tests.

Main results

Video-assisted epicardial pulmonary vein isolation (Paper I, II, IV)

The patient demographics at baseline are listed in Table 4.

Table 4. The patient demographics in Paper I, II and IV.

Characteristics	Paper I n = 43	Paper II n = 27	Paper IV n = 43
Age (years) mean±SD	57.1±8.6	57.7±8.5	57±8.5
Sex (male)	29 (67)	17 (63)	29 (67)
History of AF (years) mean±SD	8.1±5.5	8.1±4.9	8.4±5.5
AF classification			
Paroxysmal AF	28 (65)	22 (81)	33 (77)
Persist AF	6 (14)	5 (19)	9 (21)
Long-standing persistent AF		0	1 (2)
Permanent AF	9 (21)	0	0
Comorbidities			
Hypertension	13 (30)	9 (33)	13 (30)
History of stroke/TIA	8 (19)	8 (30)	8 (19)
Diabetes Mellitus	1 (2)	1 (0)	1 (2)
Coronary artery disease	3 (7)	1 (4)	4 (9)
Heart failure	6 (14)	2 (7)	6 (14)
Valvular heart disease	4 (9)	3 (11)	4 (9)
Sleep apnea syndrome	2 (5)	1 (4)	2 (5)
Asthma	4 (9)	4 (15)	4 (9)
Left atrial diameter (cm) mean±SD	4.5±0.7	4.4±0.72	4.5±0.7
LVEF <0.50	6 (14)	2 (7)	6 (14)
CHADS-VASc			17 (40)

Figures denote numbers and percentages in parenthesis unless otherwise stated. *AF*, atrial fibrillation; *LVEF*, Left ventricular ejection fraction; *SD*, standard deviation, *TIA*, transient ischemic attack.

Paper I

Procedural results

The results are based on the 42 patients in whom PV isolation could be performed. One patient was excluded because of premature termination of the procedure before PV isolation due to bleeding from the PV during dissection. The flowchart is depicted in *Figure 5*. The procedural results are presented in Table 5.

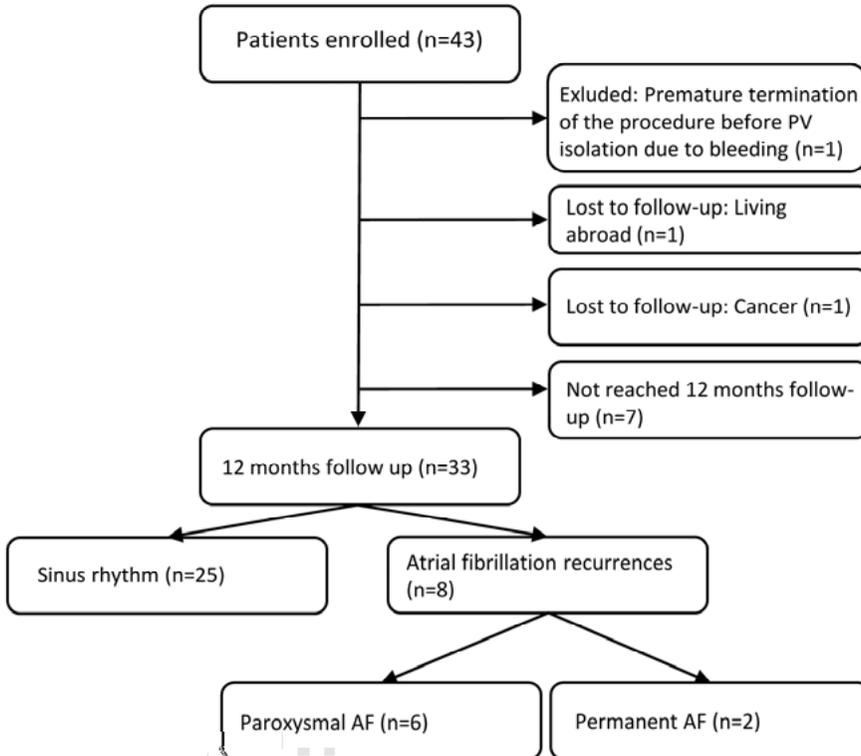


Figure 5. Flowchart of outcome after video-assisted epicardial pulmonary vein isolation in Paper I.

Table 5. Procedural result n=42.

	n (%)
Vagal activity prior PVI	40 (95)
PVI	37 (88)
Uncomplete elimination of active GPs	16 (38)
Division of the ligament of Marshall	40 (95)
Excision of LAA	32 (76)
Surgical procedure time, min, median (range)	227.5 (185-410)
Hospital stay, days, median (range)	11 (6-34)
Intensive care unit length of stay	4 (2-17)

PVI, pulmonary vein isolation; GP, ganglionated plexi; LAA, left atrial appendage; min, minutes.

Active GP at baseline were identified on both the left and right side in 23 of 42 (55%) patients but on the right side only in 17 of 42 (40%) patients. There were significantly more active GP sites on the right than on the left side (4.0 ± 2.4 versus 1.4 ± 1.7 , $p < .001$), and the greatest concentrations of vagal GP activity were found around the Waterton's groove on the right side and the ligament of Marshall on the left side (Figure 6). Patients who previously had transvenous catheter-based AF ablation had significantly fewer active vagal GP sites (mean 4.0 ± 2.2) at baseline than those who had not (mean 6.4 ± 3.5 , $p = .01$). The number of active vagal GP sites in patients with paroxysmal AF was not significantly different from those in patients with persistent or permanent AF (mean 4.9 ± 3.1 v s 6.2 ± 2.0 , $p = .23$).

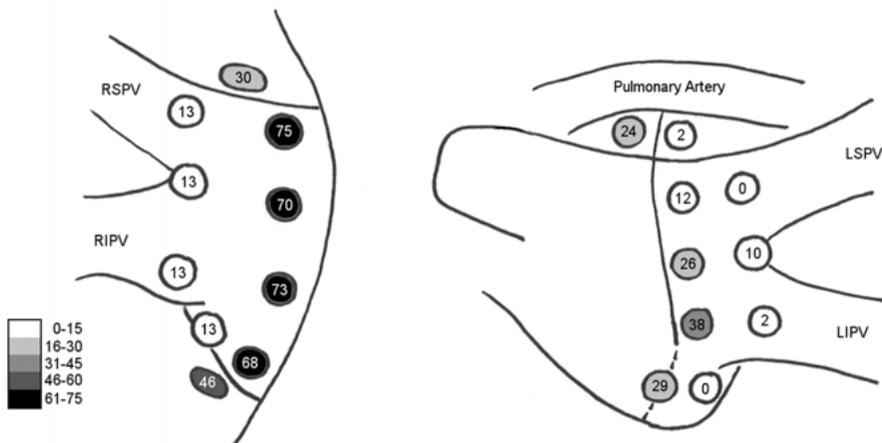


Figure 6. Results of epicardial GP mapping. High-frequency stimulation map showing distribution of active GP sites displayed as percentages as well as by grayscale. RSPV, Right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; LA, left atrium; LAA, left atrium appendage; AV, atrioventricular; R, right; L, left.

Rhythm outcome

Forty one of the 42 patients who completed the procedure were followed after surgery. One patient living abroad was excluded from follow-up. The flowchart of outcome is depicted in *Figure 5*.

Twenty-five of the 33 patients (76%) who had completed the 12-month follow-up schedule were free from AF episodes. When success rate was related to the type of AF, the corresponding figures were 79% (19 of 24) for patients with paroxysmal AF, 100% (2 of 2) for those with persistent AF, and 57% (4 of 7) for patients with permanent AF, although the differences did not reach statistical significance.

The rate of freedom from AF was 69% in patients who had a previous catheter-AF ablation compared with 81% in those who had not ($p=.46$). The number of active GP sites at baseline did not differ between patients who remained free from AF (5.1 ± 3.3) and those with AF recurrence at last follow-up (5.2 ± 1.9 , $p=.864$).

No patient suffered from left atrial tachycardias. Two patients had tricuspid isthmus ablation for atrial flutter. Another 2 patients required pacemaker implantation for chronotropic incompetence and bradycardia.

Among the 25 patients clinically free from AF at 12-months follow-up, 8 (32%) were still on AADs and 6 were still on warfarin related to earlier stroke/transient ischemic attack/thromboembolic event in 4 patients and for unknown reason in 2 patients.

Of the remaining 7 patients who had not reached 12-months follow-up, 3 of 4 patients followed for 6 months and 2 out of 3 patients who completed 3 months of follow-up had no documented episodes of AF.

Quality of life, symptoms and exercise capacity

Health-related QoL was significantly improved at 6 and 12 months on all scales except for bodily pain, as compared with baseline before surgery (*Figure 7A*).

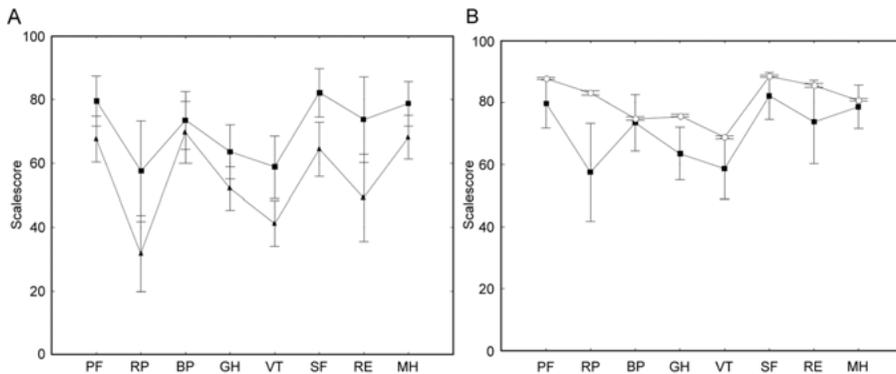


Figure 7. Comparison of quality of life assessed by the Short Form-36 questionnaire for QoL. A, Baseline (n = 42) versus 12 months following surgery (n = 33). Error bars show 95% confidence limits of the mean. ▲, Baseline; ■, 12-month follow-up; PF, physical functioning; RP, role limitation due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitation due to emotional problems; MH, mental health. PF: P = .0019; RP: P = .0078; BP: P = .39; GH: P = .0070; VT: P = .00014; SF: P = .00014; RE: P = .00059; MH: P = .00036. B, Twelve months after surgery (n = 33) versus the general Swedish population. ■, 12-month follow-up; ○, Swedish general population. PF: P = .038; RP: P = .0023; BP: P = .78; GH: P = .0065; VT: P = .046; SF: P = .096; RE: P = .080; MH: P = 0.53.

At 12-months follow-up, QoL reached the values of a general Swedish population for 4 of the scales (*Figure 7B*). The QoL prior to surgery was significantly lower than for the Swedish general population, with the exception of bodily pain.

Overall, SSQ improved significantly at 12 months after surgery (10.7 ± 4.8 points) compared with baseline (15.2 ± 4.0 points, $p = .02$). All symptoms except for dizziness and palpitations improved at 12-month follow-up as compared with baseline (Table 6).

Patients who remained in SR had significantly lower SSQ score at 12-month follow-up (mean 10.2 ± 5.0 points) compared with baseline (mean 15.8 ± 4.7 points, $p = .036$), but only dyspnea ($p = .018$) and fatigue ($p = .015$) improved significantly. In patients with recurrences of AF, the SSQ score did not differ between 12-month follow-up and baseline (mean 13.4 ± 3.2 points versus 15.0 ± 1.6 points, $p = .42$), and nor did the separate symptoms.

The physical capacity on exercise test was significantly improved at 6 months compared with baseline (165.2 ± 64.8 Watt versus 155.9 ± 56.7 Watt, $P = .02$).

Table 6. Symptoms at baseline and 12 months after video-assisted epicardial pulmonary vein isolation.

SSQ	Baseline (n = 37), mean (95% CL)	12 months (n = 37), mean (95% CL)	P-value
Palpitations	2.6 (2.1–3.1)	2.2 (1.7–2.6)	.28
Fatigue	3.6 (3.2–4.1)	2.2 (1.7–2.7)	.004
Dizziness	2.1 (1.7–2.5)	1.8 (1.4–2.3)	.67
Lack of energy	3.9 (3.5–4.3)	2.5 (2.0–3.0)	.006
Dyspnea	2.9 (2.5–3.4)	2.0 (1.5–2.4)	<.001

SSQ, symptom severity questionnaire; CL, confidence limits

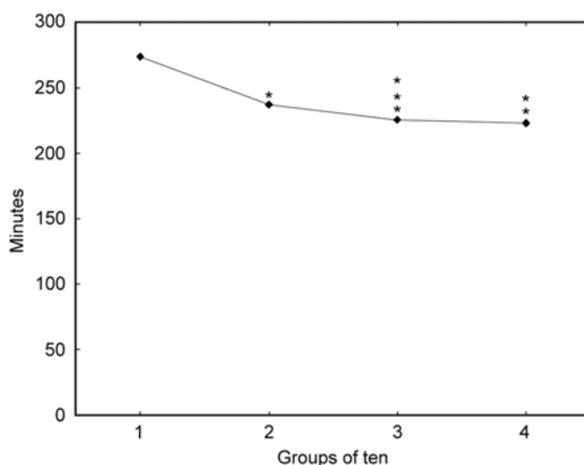


Figure 8. Learning curve with procedure time averaged per group of 10 consecutive patients. *The time at which major bleeding occurred.

Safety

The first 40 procedures were divided into groups of 10 to analyse the learning curve with regard to procedure time and bleeding events (Figure 8).

The procedure time was significantly reduced from 274±42 minutes for the first 10 procedures to 224±26 minutes for the last 10 procedures (p=.0070).

There were no perioperative or late deaths after surgery. Major bleeding, defined as bleeding requiring transfusion or surgical intervention and/or leading to treatment cessation, occurred in 6 patients (Table 7).

Table 7. *Complications after surgery.*

	n (%)
Perioperative* (n=43)	
Haemorrhage	6 (14)
Pleural effusion/haemothorax	2 (5)
Ventricular tachycardia	1 (2)
Transient confusion	1 (2)
Rib fracture	1 (2)
Infections	4 (9)
Ischemic stroke	1 (2)
Postcardiotomy syndrome	1 (2)
Late † (n = 42)	
Postpericardiotomy syndrome	1 (2)
Infections	2 (5)
Esophagitis and gastritis	1 (2)
Incisional hernia	1 (2)

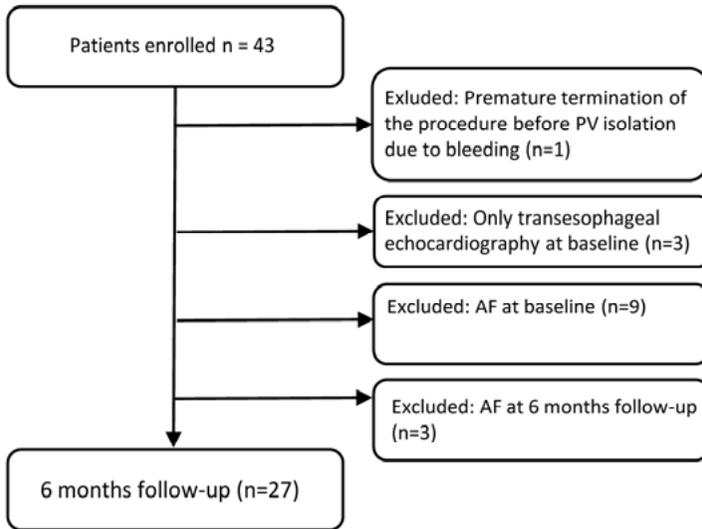
*During hospitalization; † Up to 12 months after hospitalization

The reasons for bleeding were rupture of the staple line when the LAA was extirpated (1), rift of a right PV (2), rift of the tissue around the right inferior PV and the inferior vena cava (1), rift of the pulmonary artery during dissection (1), and bleeding from an intercostal artery (1), which required reoperation twice. In 4 of these cases, an extension of the incision was made, and in 2, the heart-lung machine was required. In the first patient requiring heart-lung machine, the femoral nerve was damaged during the acute dissection for cannulation in the groin, and in the other, the operation could not be completed. The time, at which bleeding events occurred, is depicted in the learning curve (*Figure 8*). One patient with permanent AF suffered from a stroke 2 days after the operation. Warfarin had been discontinued 4 days before surgery but by mistake was not replaced by low-molecular-weight heparin until the day before operation. No patient developed PV stenosis according to CT performed 5 to 12 months after surgery in 31 patients.

Paper II

The 27 patients included in **Paper II** consisted of a subgroup of the patients derived from **Paper I**, all of which had SR at baseline and 6 months following the procedure and were available for appropriate echocardiographic examination (*Figure 9*). The patient demographics is listed in Table 4.

Figure 9. Flowchart for Paper II.



Left atrial dimension

At baseline, median LA diameter was of 4.3 cm (2.6-5.9 cm), and 5 out of 27 patients had enlarged LA, as defined by an equation for predicting normal echocardiographic measurements from body weight and age by Henry et al.¹⁷⁶ At six months follow-up after surgery, the LA diameter decreased or normalized in 3 of the 5 patients with enlarged LA at baseline and became enlarged in 2 of the 22 other patients, with normal LA diameter prior to surgery.

The LA max and min areas recorded by echocardiography at 6 months follow-up did not differ significantly from those obtained at baseline (Table 8).

Table 8. Left atrial areas, fractional area change, and transmitral pulsed-Doppler velocities in patients with sinus rhythm at baseline and 6 months after the procedure.

	Baseline	6 months	p-value
Max area cm ^{2*}	18.7 ± 5.3	17.1 ± 4.6	0.110
Min area cm ^{2*}	13.4 ± 4.7	12.5 ± 3.8	0.248
FAC*	28.7 ± 10.6	27.4 ± 8.2	0.670
E-wave [‡]	54.3 ± 13.5	53.5 ± 13.7	0.869
A-wave*	39.4 ± 11.5	37.3 ± 10.1	0.584
E/A ratio*	1.54 ± 0.67	1.49 ± 0.47	0.855

*n =23; [‡]n=26. FAC, fractional area change

A significant decrease in LA maximal area was, however, observed after surgery for patients with enlarged LA at baseline as opposed to patients with normal sized LA (Table 9).

Table 9. Effects of surgery on left atrial areas, fractional area change, and E/A ratio from baseline to 6 months follow-up in patients with enlarged left atrium compared with patients with normal-sized atrium at baseline.

	Normal preop LAd (n =18)			Enlarged preop LAd (n=5)			p-value
	Baseline	6 months	Δ	Baseline	6 months	Δ	
Max area cm ²	17.0±2.8	16.4±3.9	-0.55±3.0	25.0±7.8	19.8±6.4	-5.15±6.4	.029
Min area cm ²	12.1±3.3	11.8±3.2	-0.25±3.7	18.4±6.1	14.8±5.1	-3.6±3.5	.082
FAC	29.4±11.6	28.1±8.1	-1.31±12.9	26.4±6.2	24.7±8.7	-1.69±11.5	.952
E/A ratio*	1.49±0.7*	1.44± 0.5*	-0.04±0.8*	1.90±0.7 [±]	1.82±0.5 [±]	-0.08±0.8 [±]	.931

The p-value is tested whether the differences from baseline to 6 months differ significantly between those with normal preop LAd versus those with enlarged LAd. *FAC*, fractional area change; *LAd*, left atrial diameter; *preop*, preoperatively; *n=20; [±]n=3

The LA maximal and minimal area change in patients with extensive PV and/or GP ablation lesions did not differ from those in patients with less extensive PV and/or GP ablations (Table 10).

Table 10. Left atrial areas and fractional area changes, at baseline and 6 months follow-up, in patients with non-extensive pulmonary vein isolation and ganglionated plexi ablation as compared with those with extensive pulmonary vein isolation and ganglionated plexi ablation after surgery

	Non-extensive ablation (n=12)			Extensive ablation (n=7)			p-value
	Baseline	6 months	Δ	Baseline	6 months	Δ	
Max area cm ²	18.8±3.1	18.9± 3.6	0.07±3.5	19.2±8.7	16.4±5.7	-2.79±3.4	.097
Min area cm ²	13.3±4.0	13.7±3.4	0.34±4.2	14.8±6.5	11.9±4.8	-2.89±1.9	.073
FAC	30.5±11.5	28.3±8.6	-2.14±13.9	22.7±6.5	27.8±8.2	5.09±7.9	.227

The p value is tested whether the differences from baseline to 6 months differ significantly between those with normal non-extensive ablation versus those with extensive ablation. *FAC*, fractional area change.

Left atrial mechanical function

Overall, the measurements of FAC, E-wave and A-wave velocities, and E/A ratio recorded at 6-month follow-up were not significantly different from those at baseline (Table 8). The FAC and E/A ratio changes in patients with enlarged LA at baseline and 6 months did not differ from those in patients with normal-sized LA at baseline and 6 months (Table 9). The FAC change after surgery did not differ in patients with extensive PV and/or GP ablations

as compared with those in patients with less extensive PV and GP ablation (Table 10).

Paper IV

Rhythm outcome

Of the 43 patients entering long-term follow-up (Table 4), 2 patients were excluded at 6 months because of lack of consent and 2 died, leaving 39 patients for complete evaluations at 10 years follow-up (Figure 10). The comorbidities appearing during follow-up include pacemaker implantation in 8 patients (18.6%) and biventricular pacing in one of those (Table 11).

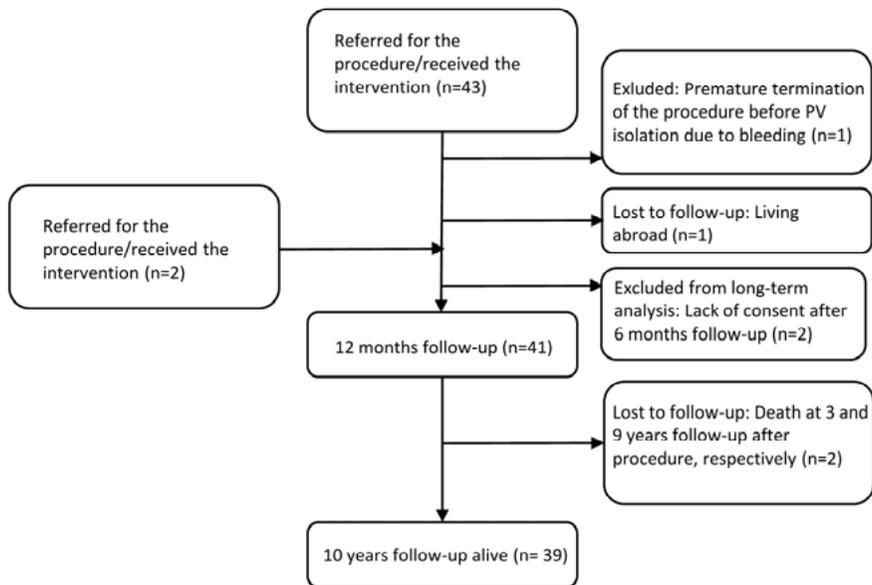


Figure 10. Flowchart for the long-term follow-up after video-assisted epicardial pulmonary vein isolation in Paper IV.

Table 11. Patient demographics at follow-up (n=43).

Characteristics	Results	
	During Follow-up	At follow-up
Age (years), mean±SD		67±8.4
Sex, male		29 (67)
AF classification		
Paroxysmal AF		13 (30)
Persistent AF		1 (2)
Longstanding persistent AF		0 (0)
Permanent		11 (26)
Failed class I AADs		
Failed class III AADs		
LAd, cm, mean±SD		
Pulmonary vein isolation	15	29 (67)
CTI-dependent atrial flutter ablation	10	20 (47)
Permanent pacemaker	8	14 (33)
Comorbidities		
Hypertension	5	18 (42)
Stroke/TIA	4	11 (26)
Diabetes	2	3 (7)
Coronary artery disease	3	7 (16)
Heart failure	7	10 (23)
HFpEF	4	4
HFmrEF or HFrEF	3	6
Valvular heart disease	2	5 (12)
Sleep apnea syndrome	1	3 (7)
Asthma	1	5 (12)
CHADS-VASc ≥2	10	27 (63)
Medications		
Anticoagulants		28 (65)
AADs		10 (23)
AADs class I		5
AADs class III		5
ACEIs/ARBs		16 (37)
Diuretics		12 (28)

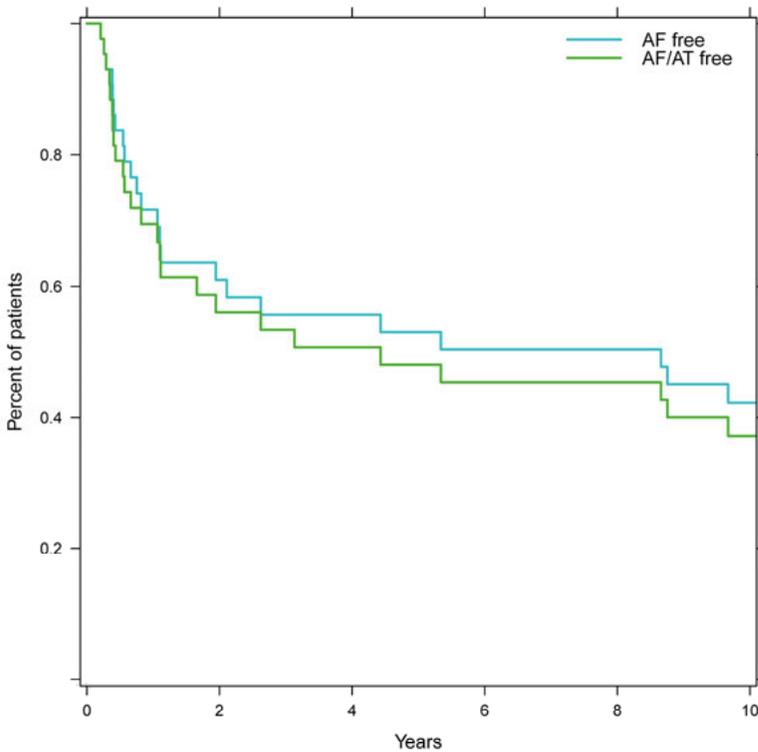
Figures denote numbers and percentages in parenthesis unless otherwise stated. AAD, anti-arrhythmic drugs; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, Angiotensin receptor blocker; CTI, Cavotricuspid isthmus; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAd, left atrial diameter; LVEF, left ventricular ejection fraction; SD, standard deviation.

The AF/AT free survival during follow-up in the 43 patients is depicted in the Kaplan Meier curve (Figure 11). At long-term follow-up (mean±1SD) 10.8±0.7 years, 36% (14/39) of the patients were free from AF/AT episodes compared to 71% (29/41) at 12 months follow-up (Figure 12). The freedom from AF/AT was 45.2% (14 out of 31) for patients with paroxysmal AF, which was significantly higher than 0% (0 out of 8) for those with persistent or longstanding persistent AF (p = 0.034) at 10 years follow up. The freedom

from AF/AT was 47.1% (8/17) in patients who had undergone a previous CA compared with 27.3% (6/22) in those who had not ($p= 0.314$).

Patients without AF/AT recurrences

None of the 14 patients who were free from clinical recurrent AF/AT episodes according to medical record had any episodes of AF/AT on Holter recordings, but 69% (9/12) of the patients had supraventricular extrasystoles or non-sustained regular supraventricular tachycardia on the recording. In two of these 14 patients, only the right PVs or the left PVs, respectively, had been completely isolated during surgery. One of the 14 patients had CTI-dependent atrial flutter, later subject to ablation. Three of these 14 patients (21%) were on AADs which had been continued since surgery for unknown reason or related to extra systoles in 2 patients, and in another patient initiated last month because of palpitations.



AF free	43	23	21	19	19	14
AF/AT free	43	21	19	17	17	13

Figure 11. Kaplan-Meier curve of atrial fibrillation and atrial tachycardia free survival during follow-up. Number of patients free from atrial fibrillation and free from atrial fibrillation /atrial tachycardia after 0, 2, 4, 6, 8 and 10 years. *AF*, atrial fibrillation; *AT*, atrial tachycardia.

Patients with AF/AT recurrences

There were 25 patients with recurrences; AF in 23 and AT in 2, and 10 of these patients had both AF/AT. Five were still on AADs during follow-up. The AF was paroxysmal in 12/23 (52%) patients, persistent in 1/23 (4%) and permanent in 10/23 (43%) patients, while the ATs were paroxysmal in one and permanent in the other patient (*Figure 12*). In two of these patients only the left PVs and in one only the right PVs had been completely isolated during surgery. Nine of 25 patients underwent CTI-dependent atrial flutter ablation during follow-up.

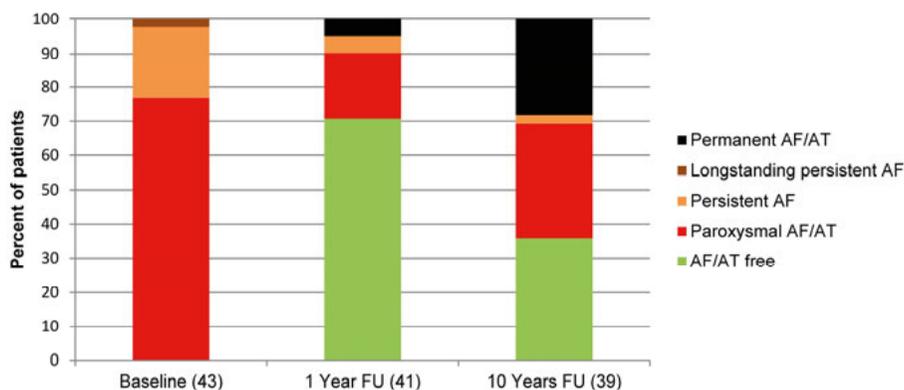


Figure 12. Heart rhythm and type of atrial fibrillation/atrial tachycardia at baseline and follow-up. Figure in brackets denote number of patients. *AF*, atrial fibrillation; *AT*, atrial tachycardia; *FU*, follow-up.

Fifteen of the 25 (60%) patients with recurrences underwent CA for AF at mean 4.1 ± 2.8 years after the surgical procedure.

Pulmonary vein gaps were present in 12/15 (80%) patients while complete PVI was found in the other 3 patients (20%). The PV re-conductions were located to the left inferior PV in 83% (10/12) of the patients, left superior PV in 67% (8/12), right superior PV in 36% (4/11, excluding a failed right superior PVI by SA) and right inferior PV in 27% (3/12) of the patients. A second CA for AF was performed in 4/25 patients and a third in one patient. In two other patients left ATs were not inducible for ablation during a separate intervention.

AV node ablation was required in 3/25 patients with AF recurrences; despite repeated CA for AF in 2 patients or because of failed PVI during epicardial PVI in one patient.

Another patient underwent Cox-Maze III cut-and-saw procedure after failing CA for AF after SA.

Quality of life

Three out of 8 subscales were still improved compared to baseline; role limitation due to physical problems (RP), vitality (VT) and role limitation due to emotional problems (RE) at 10 years follow-up (Figure 13). The Mental Component Score (MCS) was still improved at 10 years as compared to baseline (48.19 ± 12.22 versus 40.44 ± 12.32 , $n = 31$, $p = 0.011$), while the Physical Component Score (PCS) almost reached statistical significance (43.44 ± 12.31 versus 39.41 ± 9.40 , $p = 0.053$).

Quality of life did not differ between the 13 patients free from AT/AF and the 22 patients with AF/AT, at 10 years follow-up, in any of the subscales (Figure 14), nor in the MCS (51.71 ± 11.35 versus 46.43 ± 12.55 $p = 0.223$) or

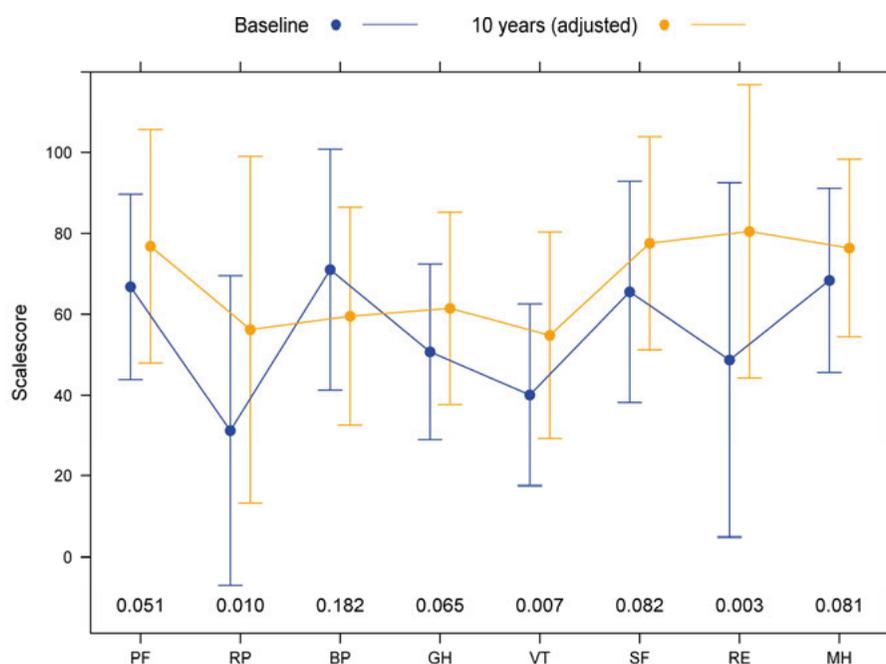


Figure 13. Comparison of quality of life by SF-36 questionnaire at baseline and 10 years follow-up (adjusted for age according to the Swedish general population) after surgery ($n = 34$). Error bars show mean \pm standard deviation and p-values are typed at each subscale. *PF*, physical functioning, *RP*, role limitations due to physical problems, *BP*, bodily pain, *GH*, general health, *VT*, vitality, *SF*, social functioning, *RE*, role limitations due to emotional problems, *MH*, mental health.

in the PCS (37.50 ± 13.52 versus 39.78 ± 11.79 , $p = 0.604$). Likewise, there were no significant differences in the changes from baseline to 10 years follow-up between the AF/AT free patients ($n = 11$) and patients with AF/AT ($n = 20$) in the MCS (9.78 ± 10.70 versus 4.45 ± 13.45 , $p = 0.268$) or in the PCS (0.71 ± 15.12 versus -0.50 ± 10.76 , $p = 0.798$) or in any of the subscales.

The QoL at baseline prior to surgery for the patients was significantly lower than for the Swedish general population in the same age range, with the exception of bodily pain (*Figure 15*).

The QoL levels at 10 years follow-up, were comparable with a Swedish general population in the same age range for a majority of the subscales (5 out of 8) (*Figure 16*), and also for the MCS (48.39 ± 12.22 versus 50.90 ± 11.20 , $p=0.196$) and the PCS (38.94 ± 12.31 versus 42.30 ± 12.00 , $p=0.105$).

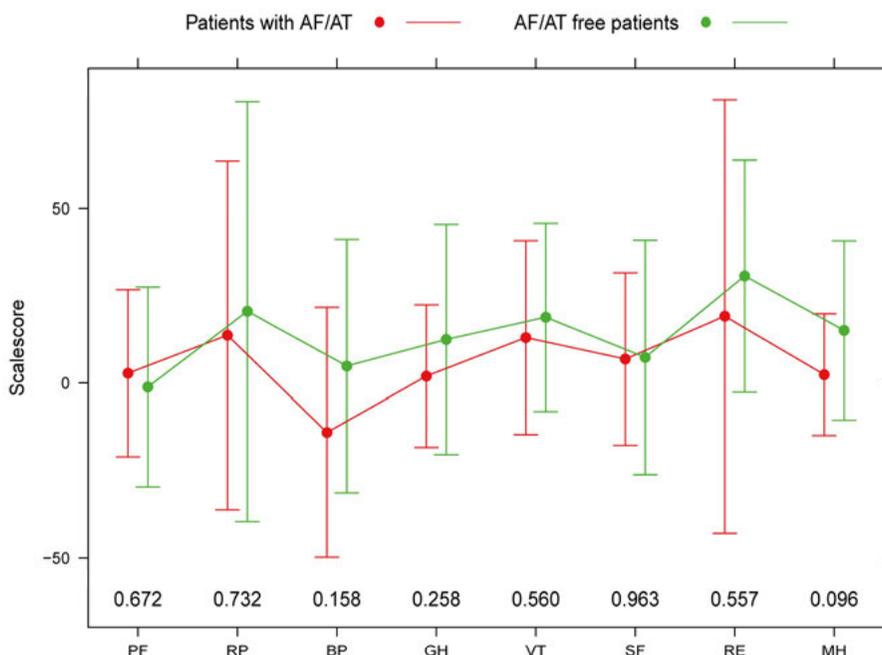


Figure 14. Comparison of quality of life by SF-36 questionnaire at 10 years follow-up after surgery for atrial fibrillation/atrial tachycardia free patients and patients with atrial fibrillation/atrial tachycardia recurrences. Error bars show mean \pm standard deviation and p-values are typed at each subscale. *PF*, physical functioning, *RP*, role limitations due to physical problems, *BP*, bodily pain, *GH*, general health, *VT*, vitality, *SF*, social functioning, *RE*, role limitations due to emotional problems, *MH*, mental health. *AF*, atrial fibrillation, *AT*, atrial tachycardia.

Symptoms

The SSQ scores were still significantly improved 10 years after surgery compared to baseline (12.89 ± 4.27 versus 15.19 ± 4.01 , $n = 31$, $p = 0.036$). All separate symptoms except for palpitations and dizziness were still significantly improved (*Figure 17*). There was no difference in the total SSQ score between the 13 AF/AT free patients and the 22 patients with AF/AT at 10 years follow-up (11.69 ± 4.15 versus 13.59 ± 4.27 , $p = 0.208$), nor were there any differences in individual symptoms (*Figure 18*). Likewise, the changes in total SSQ score from baseline to 10 years follow-up did not differ significantly between

AF/AT free patients (n=10) and patients with AF/AT (n=21) (-3.70 ± 6.25 versus -1.05 ± 4.94 , $p = 0.261$) and only palpitations improved significantly in AF/AT free patients (-1.40 ± 1.07 versus 0.75 ± 1.80 , $p = <0.001$).

Safety

Four strokes occurred at 18 months, 5, 7 and 9 years after the procedure (Table 11). Three of these patients had their LAA excised during surgery of whom two were on aspirin (CHA₂DS₂-VASc 3 and 5, respectively) while the other had no anticoagulant/antiplatelet therapy (CHA₂DS₂-VASc 1). The fourth patient did not have the LAA excised due to TEE diagnosed thrombus during surgery, was on continuous warfarin and had CHA₂DS₂-VASc score 2. At long-term follow-up, one patient died of cancer at 3 years and another died 10 years after surgery due to cardiac arrest for unknown reason.

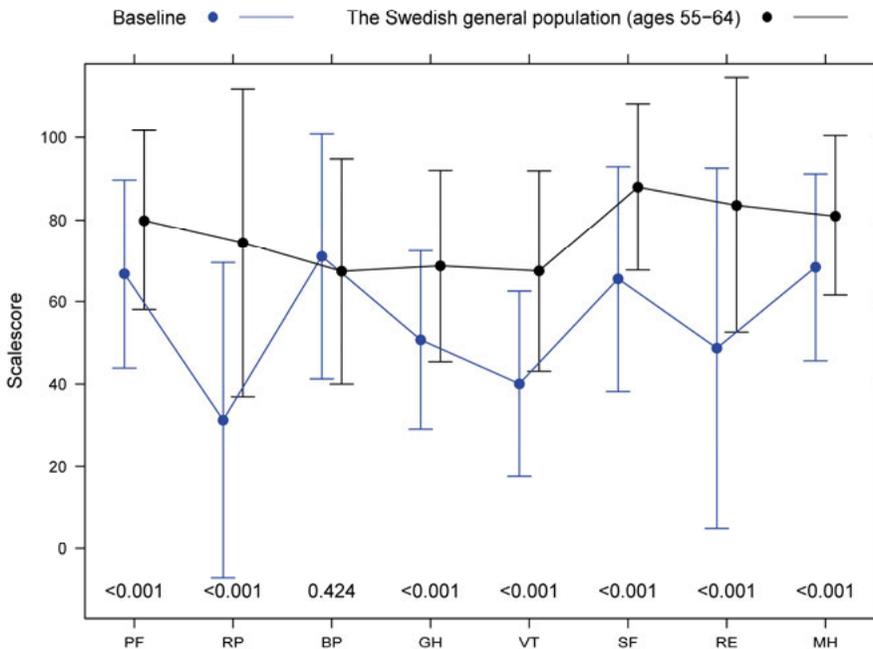


Figure 15. Comparison of quality of life by SF-36 questionnaire between the patients at baseline (n = 34) and a subgroup of the Swedish general population in the same age range (n= 941, aged 65-74 years). Error bars show mean \pm standard deviation and p-values are typed at each subscale. PF, physical functioning, RP, role limitations due to physical problems, BP, bodily pain, GH, general health, VT, vitality, SF, social functioning, RE, role limitations due to emotional problems, MH, mental health.

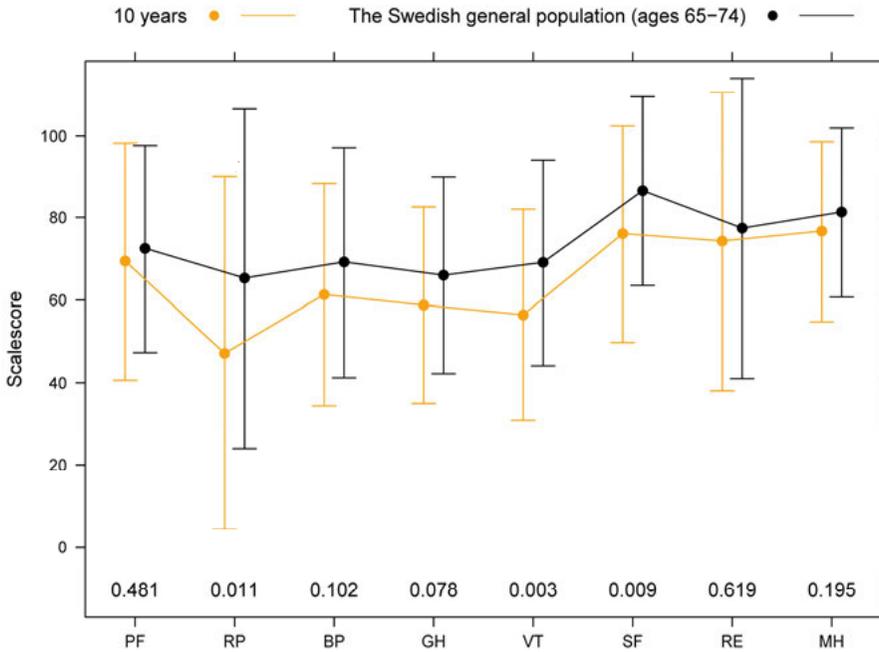


Figure 16. Comparison of quality of life by SF-36 questionnaire between the patients at 10 years follow-up after surgery (n = 35) and a subgroup of the Swedish general population in the same age range (n = 941, aged 65-74 years). Error bars show mean \pm standard deviation and p-values are typed at each subscale. *PF*, physical functioning, *RP*, role limitations due to physical problems, *BP*, bodily pain, *GH*, general health, *VT*, vitality, *SF*, social functioning, *RE*, role limitations due to emotional problems, *MH*, mental health.

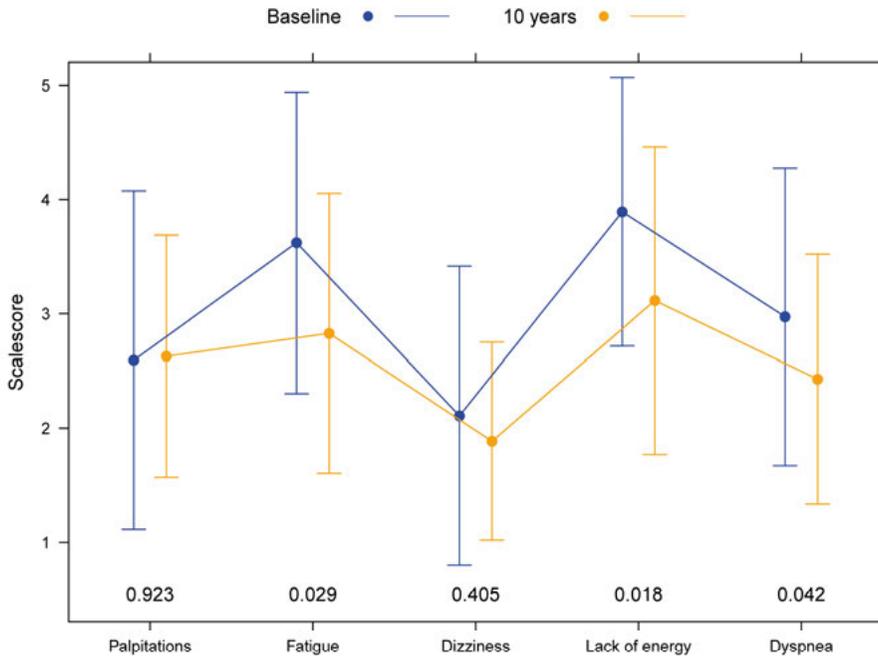


Figure 17. Comparison of symptoms by Symptom Severity Questionnaire at baseline and 10 years follow-up after surgery. Error bars show mean \pm standard deviation and p-values are typed at each symptom.

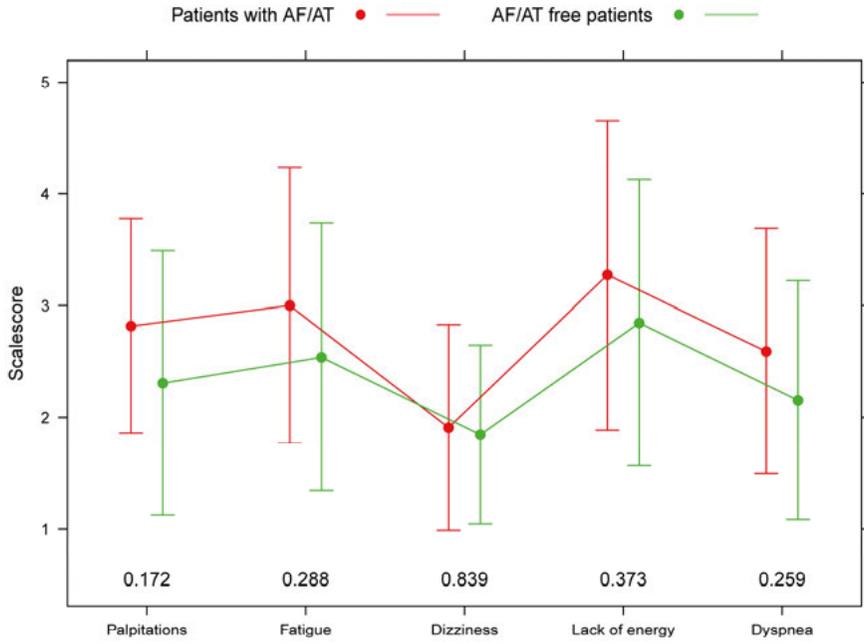


Figure 18. Comparison of symptoms by Symptom Severity Questionnaire between atrial fibrillation/atrial tachycardia free patients and patients with atrial fibrillation/atrial tachycardia recurrences at 10 years follow-up after the procedure. Error bars show mean \pm standard deviation and p-values are typed at each symptom. AF, atrial fibrillation; AT, atrial tachycardia.

Concomitant surgical ablation (Paper III)

Combined left atrial cryoablation and MVS was performed in 30 patients and MVS alone in 35 patients. Patient demographics is listed in Table 12.

Table 12. Patient demographics at baseline in Paper III. Figures denote numbers and percentages in parenthesis unless otherwise stated.

Characteristics	Paper III (n=65)	
	Cryoablation + MVS (n=30)	MVS (n=35)
Sex (male)	25 (83.3)	26 (74.3)
Age (years), mean±SD	69.5±7.9	65.6±8.8
AF duration, ECG verified (months), mean±SD	26±33	33±54
History of stroke/TIA	1 (3.3)	3 (8.6)
Left atrial diameter (cm), mean±SD	6.1±1.1	5.8±0.7
LVEF (%)	53.6±9.1	57±12
LVEF ≤ 40%	5 (16.7)	2 (5.7)
Comorbidities		
Preoperative heart failure	8 (26.7)	3 (8.6)
NYHA function class		
I	2 (6.7)	1 (2.9)
II	8 (26.7)	10 (28.6)
III	20 (66.7)	24 (68.6)
Coronary artery disease	6 (20.0)	9 (25.7)
Hypertension	9 (30.0)	11 (31.4)
Diabetes	2 (6.7)	6 (17.1)
Lung disease	2 (6.7)	6 (17.1)
CHADS-VASc	18 (60.0)	18 (51.4)
Medication		
Rhythm control therapy	0	3 (8.6)
Rate control therapy	29 (96.7)	32 (91.4)

Figures denote numbers and percentages in parenthesis unless otherwise stated. *ECG*, electrocardiogram; *LVEF*, left ventricular ejection fraction; *MVS*, mitral valve surgery; *NYHA*, New York heart association functional classification; *SD*, standard deviation; *TIA*; transient ischemic attack

Quality of life

Concomitant AF cryoablation versus MVS alone

For patients undergoing the combined MVS (n = 26), the baseline physical component score (PCS) and the mental component score (MCS) improved significantly after surgery from mean 36.9 (95% CI 32.9–40.9) and mean 41.8 (95% CI 35.9–47.7), respectively, to mean 43.3 (95% CI 38.7–47.9) (P= 0.0046) and mean 52.7 (95% CI 49.3– 56.1) (P= 0.0017), respectively, at 12

months follow-up. In patients undergoing MVS alone ($n = 34$), the baseline PCS and MCS also improved significantly after surgery from mean 35.5 (95% CI 32.4– 38.6) and mean (43.1 (95% CI 39.6–46.7), respectively, to mean 44.0 (95% CI 40.2–47.7) ($P = 0.000532$) and mean 48.4 (95% CI 44.6– 52.2) ($P = 0.0492$), respectively, at 12 months follow-up.

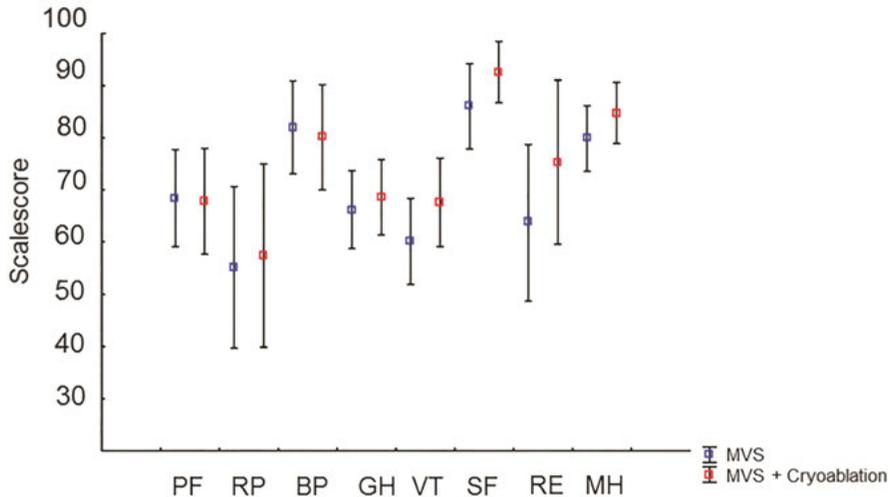


Figure 19. Comparison of QOL by SF-36 questionnaire at 12 months in patients undergoing combined mitral valve surgery (MVS) and cryoablation ($n = 27$) versus MVS alone ($n = 34$). Figure dots are mean values with error bars showing 95% confidence limits of the mean. P -values for each comparison of subscale are given in brackets. PF, physical functioning (0.929); RP, role limitations due to physical problems (0.844); BP, bodily pain (0.768); GH, general health (0.647); VT, vitality (0.207); SF, social functioning (0.209); RE, role limitations due to emotional problems (0.285); MH, mental health (0.264).

The QoL did not differ in any of the subscales at 12 months follow-up, respectively, between patients undergoing combined MVS with cryoablation as compared with those undergoing MVS alone (*Figure 19*). Furthermore, there were no significant differences in improvements of QoL from baseline to 12 months follow-up for patients undergoing MVS with cryoablation compared with MVS alone (*Figure 20*).

Sinus rhythm versus atrial fibrillation

A significantly higher proportion of patients (73.3%) who underwent MVS with cryoablation, maintained SR as compared with patients treated with MVS only at 6 months (45.7%, $P = 0.024$) and at 12 months follow-up (42.9%, $P = 0.013$). Of the patients in SR, 72.7% of patients in the cryoablation group and 53.3% of patients in the MVS group were without AAD therapy at 12 months. When comparing QoL in patients irrespective of the allocated procedure but

according to their heart rhythm at 12-month follow-up versus baseline, both the MCS and PCS significantly improved for patients achieving SR but only the MCS for patients with AF. The SR group ($n = 37$) improved their baseline PCS from mean 35.3 (95% CI 32.1–38.5) to mean 45.4 (95% CI 42.0–48.7) ($P = 0.000003$) at 12 months and their baseline MCS from mean 44.1 (95% CI 39.9–48.2) to mean 51.0 (95% CI 48.0–54.1) ($P = 0.0094$) at 12-months follow-up. In the AF group ($n = 23$), PCS at baseline mean 37.4 (95% CI 33.4–41.3) did not differ from mean 40.9 (95% CI 35.7–46.1) at 12 months ($P = 0.171$), but MCS improved from mean 40.1 (95% CI 35.1–45.2) at baseline to mean 49.0 (95% CI 44.0–54.1) ($P = 0.0134$) at 12-months follow-up. There were no significant differences in PCS or MCS when comparing patients in SR with those in AF at 12 months (Table 13). The subscales of the SF-36 at 12 months did not differ either, except for PF that was worse in patients with AF compared with patients in SR (Table 13).

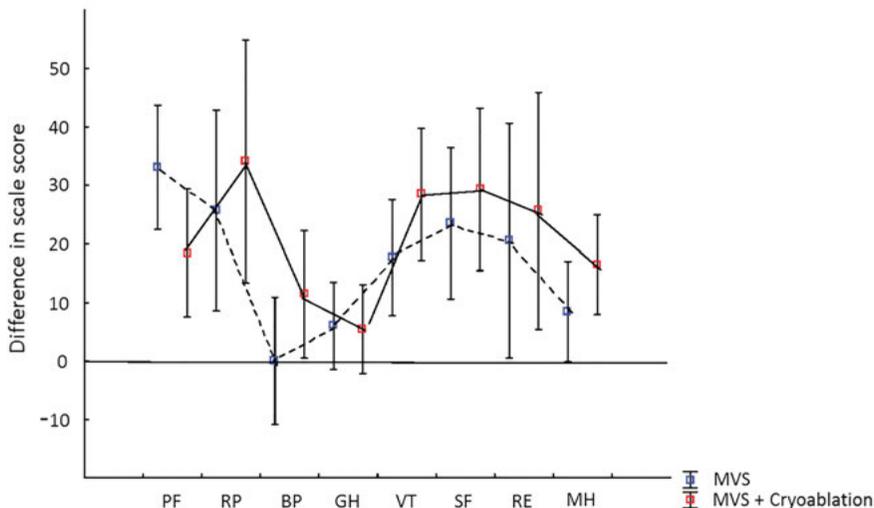


Figure 20. Differences in improvements of QoL by SF 36 questionnaire from baseline to 12 months follow-up for patients undergoing mitral valve surgery (MVS) with cryoablation ($n = 26$) compared with MVS alone ($n = 34$). Error bars show 95% confidence limits of the mean. The following P -values for each comparison of subscale are given in brackets; PF, physical functioning (0.058); RP, role limitations due to physical problems (0.524); BP, bodily pain (0.144); GH, general health (0.915); VT, vitality (0.146); SF, social functioning (0.537); RE, role limitations due to emotional problems (0.723); MH, mental health (0.189).

When comparing the changes from baseline to 12 months in the Physical and Mental Component Summary between patients in SR ($n = 37$) and those in AF ($n = 23$), the PCS change was greater for patients in SR, mean 10.1 (95% CI

6.3–13.8) than those in AF, mean 3.5 (95% CI -1.7 to 8.7) ($P = 0.037$). The corresponding changes for MCS did not differ between patients in SR, mean 7.0 (95% CI 1.8–12.1) and those in AF, mean 8.9 (95% CI 2.9–15.8), ($P=$

Table 13. Comparison of QoL by short-form 36 questionnaire in patients with sinus rhythm versus those with atrial fibrillation, at 12-month follow-up.

Scale	SR 95% CI n=37	AF 95% CI n=24	p-value
PF	73.6 (65.4-81.9)	59.6(48.3-70.8)	0.038
RP	58.1(43.8-72.4)	53.1(33.6-72.6)	0.669
BP	84.8(77.7-91.8)	75.6(62.7-88.5)	0.172
GH	70.6 (63.6-77.7)	62.0(54.8-69.2)	0.096
VT	67.7(60.3.7-75.1)	56.9(47.4-66.3)	0.069
SF	90.2(84.2-96.2)	87.0(77.1-96.9)	0.546
RE	70.3(56.7-83.8)	66.7(48.1-85.2)	0.744
MH	84.5(79.6-89.5)	78.2(70.2-86.2)	0.148
PCS	45.4(42.0-48.7)	40.5(35.5-45.6)	0.096
MCS	51.0(48.0-54.1)	49.6(44.6-54.5)	0.581

SR, sinus rhythm; AF, atrial fibrillation; 95% CI, 95% confidence limits of the mean, PF, physical functioning; RP, role limitation due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitation due to emotional problems; MH, mental health.

0.641), respectively. Furthermore, there were no differences in the changes in subscales of the SF-36 between patients in SR and AF except for bodily pain, which improved more in patients in SR mean 11.2 (95% CI 2.0–20.4) than in those with AF, in whom there was a worsening, -5.2 (95% CI -18–8.2), ($P = 0.037$), respectively.

Study population versus the Swedish general population

The QoL at baseline prior to surgery was significantly lower for our patients than for an age-matched Swedish general population except for general health which did not differ and for bodily pain which was less (higher) in patients undergoing MVS alone (*Figure 21*). At 12-month, the subscales of the SF-36 questionnaire showed comparable values to a general Swedish population except for a worse vitality (lower) in patients undergoing MVS alone and less bodily pain (higher) in patients undergoing MVS alone (*Figure 22*). Both the SR group and the AF group reached the same health related QoL at 12 months as the general population for a majority of the scales. The SR group had less bodily pain while the AF group ranked lower on physical function and vitality at 12 months follow-up than the general population (*Figure 23*).

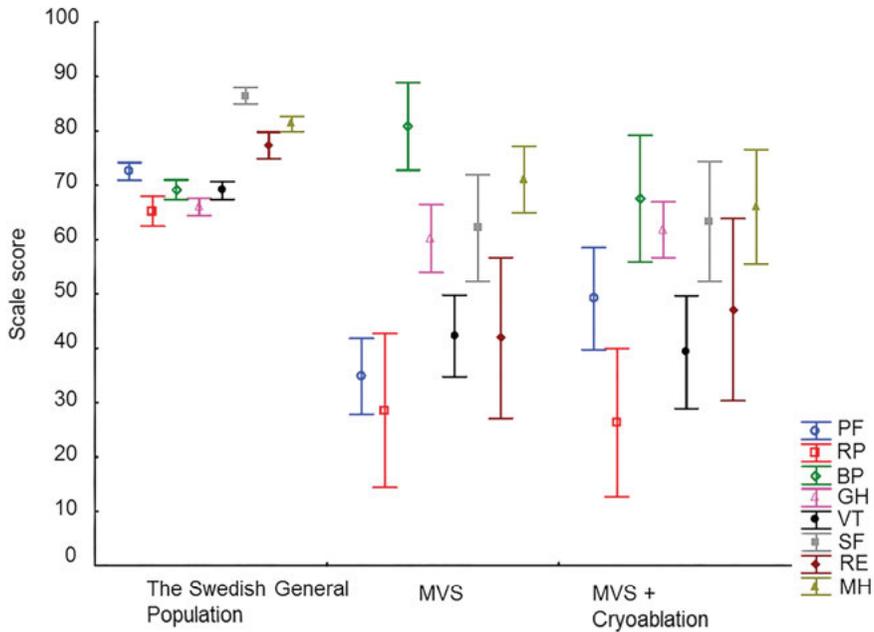


Figure 21. Comparison of quality-of-life by SF-36 questionnaire preoperatively at baseline in patients planned for combined mitral valve surgery (MVS) and cryoablation (n=29) or MVS alone (n=35) with the Swedish general population. Error bars show 95% confidence limits of the mean. P values for each comparison of subscale are given in brackets in patients planned for combined MVS and cryoablation and in those planned for MVS alone, respectively, compared with the general population. *PF*, physical functioning (0.000012/0.000000); *RP*, role limitations due to physical problems (0.000001/0.000008); *BP*, bodily pain (0.517/0.00588); *GH*, general health (0.0764/0.0678); *VT*, vitality (0.000001/0.000000); *SF*, social functioning (0.000099/0.000015); *RE*, role limitations due to emotional problems (0.000462/0.000025); *MH*, mental health (0.00324/0.0017).

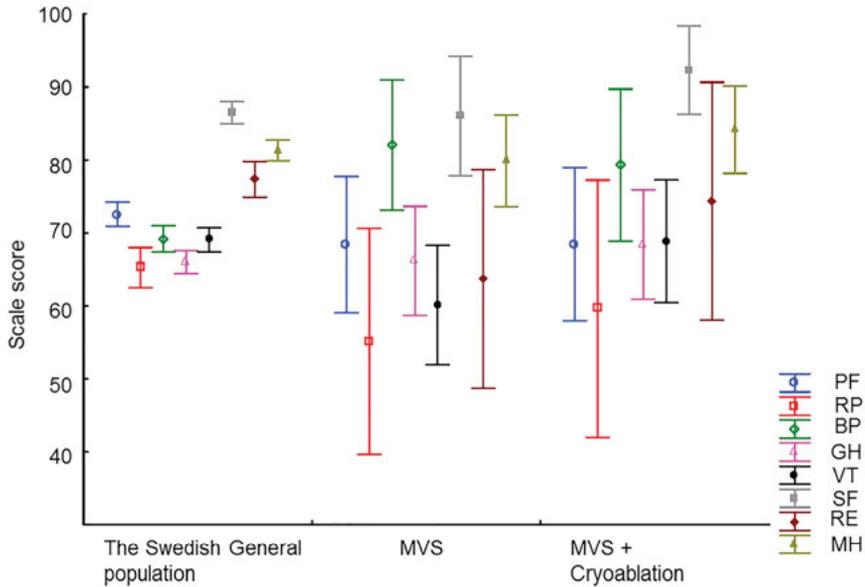


Figure 22. Comparison of quality-of-life by SF-36 questionnaire at 12 months follow-up in patients undergoing mitral valve surgery (MVS) and cryoablation (n=26) or MVS alone (n=34) with the Swedish general population. Error bars show 95% confidence limits of the mean. P values for each comparison of subscale are given in brackets in patients who underwent combined MVS and cryoablation and in those who underwent MVS alone, respectively compared with the general population. *PF*, physical functioning (0.436/0.377); *RP*, role limitations due to physical problems (0.513/0.190); *BP*, bodily pain (0.0565/0.00613); *GH*, general health (0.512/0.962); *VT*, vitality (0.951/0.0335); *SF*, social functioning (0.0600/0.907); *RE*, role limitations due to emotional problems (0.704/0.0722); *MH*, mental health (0.335/0.650).

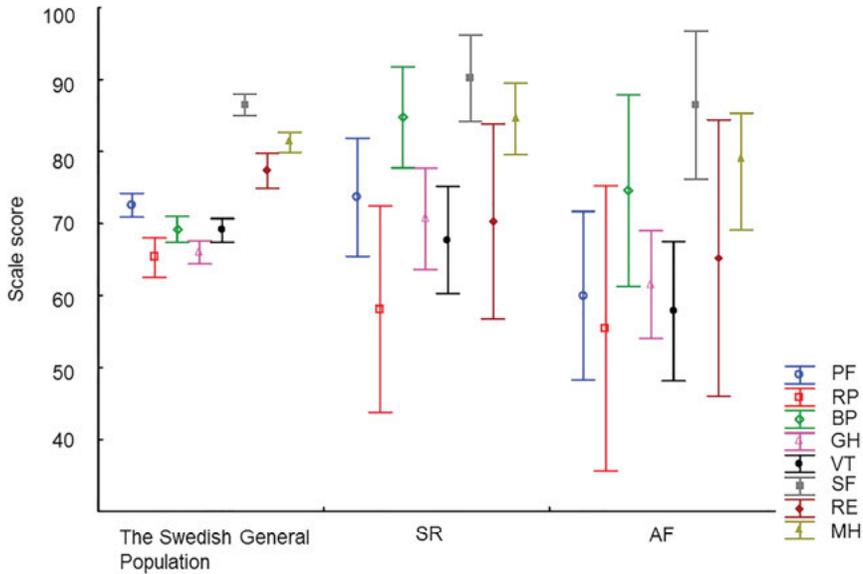


Figure 23. Comparison of quality-of-life by SF-36 questionnaire at 12 months follow-up in patients with sinus rhythm (SR) (n = 37) or atrial fibrillation (AF) (n= 23), with the Swedish general population. Error bars show 95% confidence limits of the mean. P values for each comparison of subscale are given in brackets in patients with SR versus the general population and in patients with AF versus the Swedish general population. *PF*, physical functioning (P = 0.778/0.0373); *RP*, role limitations due to physical problems (P = 0.315/0.313); *BP*, bodily pain (P=0.00070/0.412); *GH*, general health (P = 0.189/0.228); *VT*, vitality (P=0.705/0.0242); *SF*, social functioning (P = 0.218/0.986); *RE*, role limitations due to emotional problems (P = 0.293/0.201); *MH*, mental health (P = 0.195/0.307).

Thoracoscopic left atrial ablation (Paper V)

Fifty of the 60 patients in the TELA-AF study replied to the SF-36 at baseline and at 12 months follow-up. One patient was lost to follow-up and in seven patients evaluation of SF-36 was missing at baseline and in another 2 patients data regarding SF-36 was missing at 12 months follow-up. The patient demographics is listed in Table 14.

Table 14. Patient demographics at baseline in Paper V. Figures denote numbers and percentages in parenthesis unless otherwise stated.

Characteristics	Paper V (n = 50)
Age (years), mean±SD	61±7.8
Sex (male)	39 (78)
AF Classification	
Paroxysmal	6 (12)
Persistent	13 (26)
Longstanding persistent	31 (62)
AF duration (years), min-max	7.8 (1-31)
Comorbidities	
Atrial flutter	4 (8)
Hypertension	24 (48)
History of heart failure	6 (12)
Coronary heart disease	3 (6)
History of stroke/TIA	7 (14)
Chronic pulmonary disease	5 (8)
Diabetes Mellitus	1 (2)
CHADS-VASc ≥2	19 (38)
LVEF<0.50	6 (12)
Left atrial diameter (cm), mean±SD	4.8±0.5
BMI (kg/m ²), mean±SD	28±4

Figures denote numbers and percentages in parenthesis unless otherwise stated. *AF*, atrial fibrillation; *BMI*, body mass index; *LVEF*, left ventricular ejection fraction; *SD*, standard deviation; *TIA*, transient ischemic attack.

Quality of life

At baseline the SF-36 scores were considerably and significantly lower than a normative national cohort in the same age range, in all subscales except for

BP (Figure 24). The PCS at baseline was significantly lower, 37.9 ± 9.2 , compared to Swedish normal population 46.8 ± 10.6 ($p < 0.001$); as was the MCS, 39.8 ± 13.5 versus 50.7 ± 10.6 , $p < 0.001$.

All SF-36 subscales except BP demonstrated a significant increase at 12-months follow up after the procedure compared to baseline (Figure 24). The PCS improved from baseline to 12-months follow-up (37.9 ± 9.2 versus 46.8 ± 9.5 , $p < 0.001$), and the MCS increased from 39.8 ± 13.5 to 49.1 ± 11.3 $p < 0.001$). All subscales except for bodily pain and general health improved more than 20 points from baseline to 12 months.

After 12 months, all subscales except for BP, had improved significantly and were now statistically indistinguishable from Swedish normative data (Figure 24).

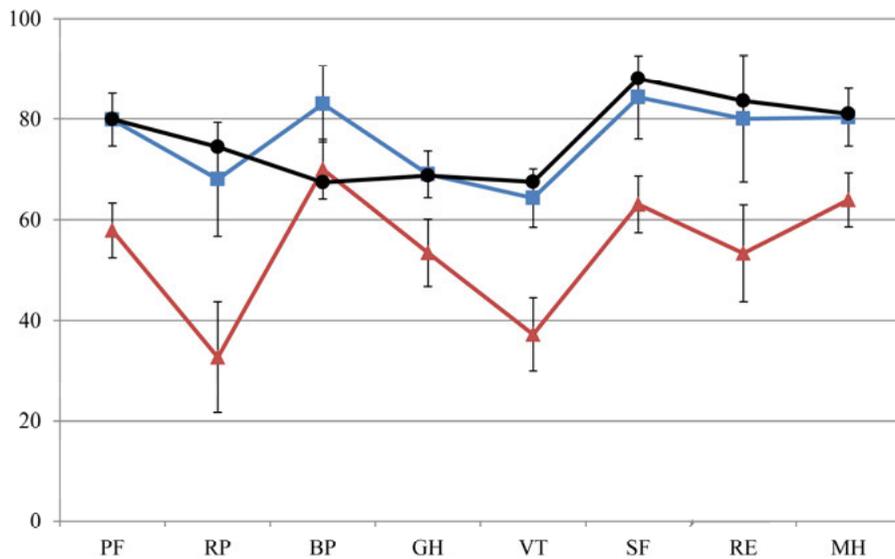


Figure 24. Quality of life according to the SF-36 eight scale scores before thoracoscopic epicardial ablation compared to 12 months follow-up and compared to Swedish normative data. (▲) = before surgery, (■) = after 12-month follow-up in 50 patients, (●) Population standards. Error bars represent mean values with 95 % CI. P-values, are < 0.001 when comparing baseline to follow-up and population standard scale scores, except for BP ($p = 0.002$ versus follow-up and 0.512 versus population standards). Differences between follow-up and population standard were non-significant in all scores except for BP: PF ($p = 0.9875$); RP ($p = 0.243$); BP ($p < 0.001$); GH ($p = 0.936$); VT ($p = 0.352$); SF ($p = 0.202$); RE ($p = 0.425$); MH ($p = 0.803$). Abbreviations; PF, physical functioning; RP, role limitation owing to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitation owing to emotional problems; and MH, mental health.

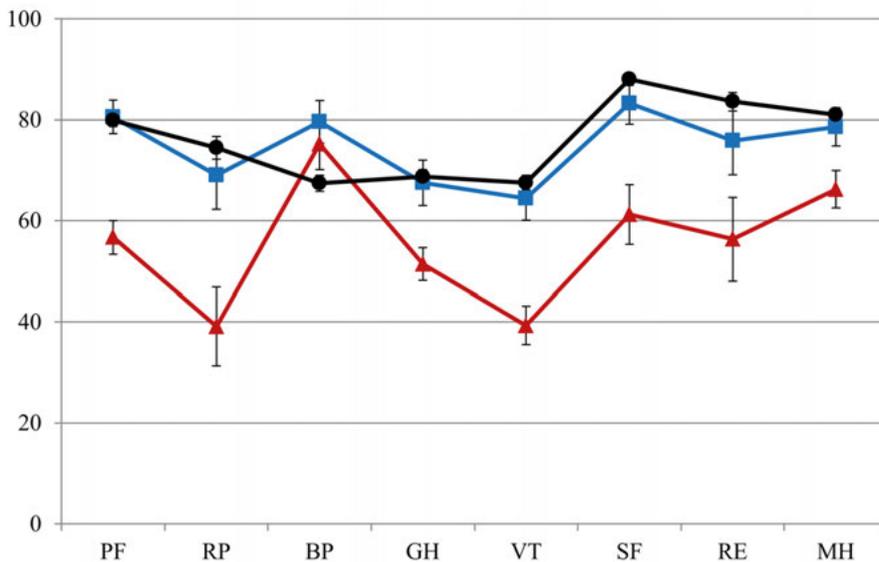


Figure 25. Quality of life according to the SF-36 eight scale scores before surgery for patients with LPAF compared to 12 months follow-up and Swedish normative scores. (▲) Before surgery for patients with LPAF, n=29 (■) 12-month follow-up for patients with LPAF (●) Population standards. Error bars represent mean values with 95 % CI. P-values, are < 0.001 when comparing baseline to follow-up, except for BP p = 0.361. LPAF, longstanding persistent atrial fibrillation. All other abbreviations are identical to figure 1.

In the LPAF-group (29 patients) the scale scores were not significantly different from our main findings (Figure 25). The PCS improved from baseline to 12 months follow-up (38.3 ± 10.1 versus 46.9 ± 8.7 , $p = 0.001$) and so did the MCS (40.6 ± 13.5 versus 47.9 ± 12.0 , $p = < 0.001$).

The QoL at baseline was comparable to the quality of life in a subset of patients with congestive heart failure in 6 of 8 subscales¹⁷⁷, hemodialysis in 6 of 8 subscales¹⁷⁸, hepatitis C in 5 of 8 subscales¹⁷⁹ and major depression in 4 of 8 subscales^{180, 181} (Figure 26).

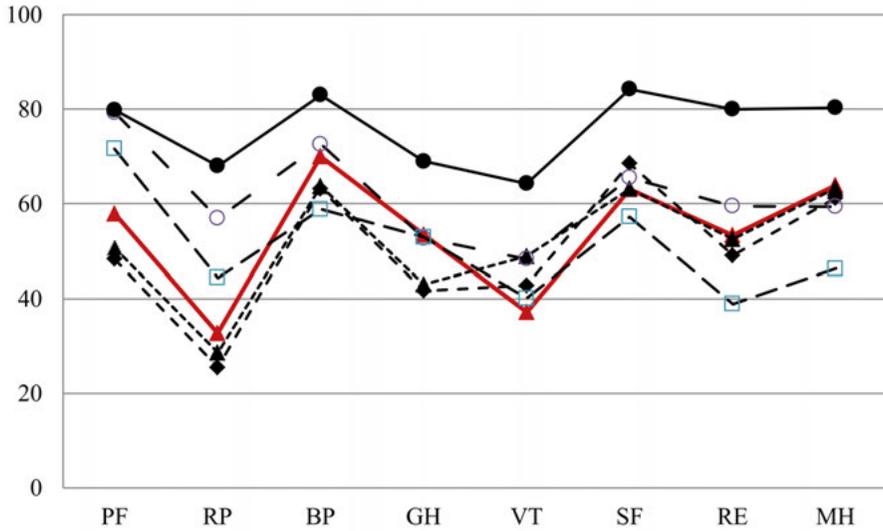


Figure 26. Quality of life at baseline for the TELA-AF patients compared to four unrelated chronic diseases and population standard. ■ Swedish general population; ◆ Congestive heart failure; ▲ Hemodialysis; ○ Hepatitis C; □ Major depression; ● TELA-AF baseline. P values for each comparison of subscale are given in brackets for comparison of the TELA-AF cohort versus CHF; hemolysis; hepatitis C; major depression. PF, physical functioning (0.018/0.127/<0.001/<0.001); RP, role limitation owing to physical problems (0.233/0.525/0.003/0.051); BP, bodily pain (0.156/0.173/0.609/0.005); GH, general health (<0.001/0.002/0.867/0.881); VT, vitality (0.104/0.003/0.010/0.354); SF, social functioning (0.205/0.984/0.627/0.161); RE, role limitation owing to emotional problems (0.564/0.917/0.436/0.016); and MH, mental health (0.411/0.863/0.261/<0.001).

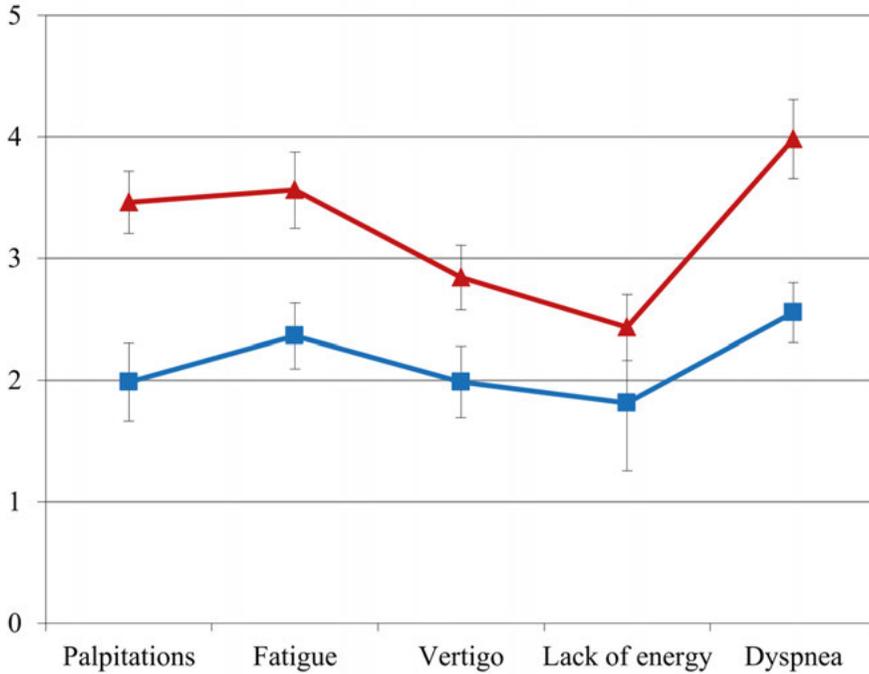


Figure 27. Comparison of symptoms by Symptom Severity questionnaires before surgery versus 12 months after surgery. (▲) Baseline, n=50; (■) 12 months after surgery n=57. Error bars show mean values with 95% CI. P < 0.001 in all symptoms except for Lack of energy (p = 0.002).

Symptoms

The pooled data from the SSQ showed a significant improvement from baseline, 16.3 ± 1.2 to 5.6 ± 1.1 ($p < 0.001$) at 12 months, an improvement that was statistically significant in all five symptoms (Figure 27).

Discussion

Patients with AF have markedly reduced exercise capacity⁴ and degraded QoL⁵ and may develop heart failure, stroke and sudden death⁶. The strategies to prevent complications involve anticoagulation, rate control and treatment of underlying conditions to prevent the progression of AF and reduce morbidity and all-cause mortality. These treatments may relieve the symptoms *per se*, but other strategies might also be required to increase the QoL, such as rhythm control by cardioversion, antiarrhythmic drugs, transvenous CA or SA. The rhythm control strategies, however, have no indication yet to prevent cardiovascular outcomes or withdrawal of anticoagulation or to reduce hospitalization since all studies have resulted in neutral outcomes^{7, 8}. But whether the modern strategy with CA, combination therapy and early therapy leads to a reduction in cardiovascular events remains to be seen in ongoing trials such as EAST AFNET 4 and CABANA.

At present, rhythm control is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy²³. The long-term rhythm control may involve AADs, CA for AF or SA. Unfortunately, a majority of the AADs are only moderately effective in maintaining SR over time and those that are more effective cause significant morbidity and side effects themselves that may negate the inherent advantage of SR⁹. Transvenous CA eliminates AF in a high proportion of cases 70%^{10, 11} and improves QoL^{150-152, 156, 157} although PV reconnection is still a recognized problem^{12, 13} and the result of such intervention is less successful in patients with non-paroxysmal AF^{11, 15}. The Cox-Maze procedure⁹⁷, introduced 30 years ago, is effective^{99, 100}, but has failed to achieve widespread adoption because of its complexity and highly invasive nature. In patients with persistent AF, non-PV triggers for AF are increased as compared to paroxysmal AF¹⁰³. This finding, the poor outcome for patients with persistent AF after PV isolation¹⁰⁴ and also the presence of patients who had failed previous attempts of transvenous CA for PV isolation has led to the development of alternative approaches such as techniques involving SA either as a stand-alone procedure or as a concomitant procedure. There is limited information about the effect of these procedures on rhythm outcome, QoL, left atrial function and safety.

This thesis focuses on the evaluation of QoL using three different techniques, video-assisted epicardial PVI, concomitant left atrial cryo ablation and thoracoscopic left atrial ablation, for SA but also rhythm outcome on long-term, left atrial function and safety for one of the stand-alone procedures, the

video-assisted epicardial PVI. It is indeed important to improve QoL for symptomatic patients with AF but to accomplish this, the AF burden must be reduced and the side-effects tolerable.

Stand-alone epicardial pulmonary vein ablation with or without left atrial ablation (Paper I, II and IV-V)

Rhythm outcome (Paper I, IV)

In **Paper I**, we report the one-year follow-up of the video-assisted epicardial PVI as the first center in the Nordic countries to adopt this technique. At one-year follow-up, 75.8% were clinically free from AF and the results were updated regarding outcome to 71% during long-term follow-up (**Paper IV**), since more patients had completed a 12 months follow. When success rate was related to the type of AF in **Paper I**, the corresponding figures were 79% (19 of 24) for patients with paroxysmal AF, 100% (2 of 2) for those with persistent AF, and 57% (4 of 7) for patients with permanent AF, although the differences did not reach statistical significance. There exists today a range of studies, including both epicardial PVI, GP ablation, division of the ligament of Marshall and LAA excision, with success rates in eliminating AF ranging between 65% and 87% at approximately 12 month follow-up^{158, 163, 182-185}. For patients with paroxysmal AF the success rate is between 73% and 93% at 12 months^{158, 163, 183-185} and for persistent AF 64.7-96%^{158, 163, 183, 184}. There is, however, a divergence in the results explained by various patient selections, different surgeons, definitions for success and various methods for rhythm monitoring.

At 12-month follow-up, Han et al reported¹⁸² a lower success rate of 65% in a mixed AF population, compared to our 71%, which may be explained by their 30-day continuous event monitor potentially able to detect a higher frequency of failures than our 24 h or 48 h Holter recording. Although, the event monitor has the disadvantage of precluding the possibility to spot asymptomatic episodes. Patients-reported symptoms of AF has been found to have poor correlation with actual rhythm, underscoring the importance of continuous home monitoring¹⁸⁶. The patient selection by Han et al., also consisted of a higher proportion of patients with diabetes and hypertension, 6.7% and 75.6%, respectively compared to our **Paper I** where the corresponding figures were 2% and 30% respectively. Both diabetes and hypertension are known predisposing clinical conditions^{66, 67} for AF that may explain the lower success rate among their patients.

A higher proportion of patients clinically free from AF (87%) was reported by Beyer et al in a mixed AF population at 12 months than in our study. However, the patients included had had a much shorter AF duration of 4.9±3.8 years compared to our 8.1±5.5 years and a longer AF duration is predictor for AF recurrences after this procedure^{162, 163}.

Our results in **Paper I** are more in accordance with three other studies^{158, 163, 184} with a success rate of 71.7% to 77%, all with 12 months follow-up and a systematic review including 23 studies of minimally invasive surgery in the treatment of AF resulting in a single procedure success rate of 69% without AADs¹⁸⁷. Unfortunately, because of the revised classification of AF types and the successive application of it, the success rate according to AF type in the previous studies is not reliable. To circumvent this problem, the AF types at baseline were reclassified according to the new 2016 ESC guidelines²³ in the 10 years follow-up in **Paper IV**, to be able to rely on the patient selection related to outcome results.

The 10-year follow-up after the video-assisted epicardial PVI in **Paper IV** is, as a matter of fact, the longest follow-up reported. The observation that there were still 36% freedom from AF/AT on long term demonstrates a clear decline in efficacy as compared with the 71% observed at 12 months, which reminds us that AF is progressive and difficult to treat. Previous studies have reported that the success rate in eliminating AF recurrences is maintained at a high level (69-91%) at least until 18 months following the procedure^{113, 160, 188, 189}.

At 10 years (**Paper IV**), a higher, 45.2%, rate of freedom from AF/AT, was observed in patients with paroxysmal AF than the 0% in those with persistent or longstanding AF which was expected¹⁹⁰, although the number of patients with persistent AF was small. A higher rate of freedom from AF, 92%, 85% and 75% for paroxysmal, persistent and long-standing persistent AF, respectively, was reported after 1-9 years follow-up of 157 patients undergoing epicardial PVI by Wolf et al¹⁹¹. However, the patient's demographics, AAD medications, follow-up duration, and extent of rhythm monitoring were unclear.

There are also reports after 5 years follow-up after similar procedures with a 38% freedom from AF in a mixed AF population¹⁶⁹, 52-69% for paroxysmal AF patients^{162, 163, 170} and 28-41% for persistent AF patients^{162, 163}. Our 10 years follow-up translates to 46.2% AF/AT freedom after 5 years follow-up (58% for paroxysmal and 0% for persistent AF, **Paper IV**). The higher rate of AF freedom, 69%, was reported in a study¹⁷⁰ including patients with a much shorter AF duration, in average 24 months, as compared to our 100 months AF duration. Moreover, the mean left atrial diameter in our study was 45±0.7 mm, which exceeds the reported cut off level for an increased AF recurrence rate.^{162, 163} An AF duration longer than 24 months, as mentioned earlier, and a left atrial diameter ≥40 mm are well known independent predictors of long-term AF recurrences after SA.^{162, 163}

The outcomes after the procedures are also affected by the use of different tools and techniques. Studies reporting outcomes at 5 years follow-up have all included epicardial PV antrum isolation, division of ligament of Marshall and excision of LAA^{162, 163, 169, 170}, but some as in ours, also made GP ablation.^{163, 169} Two studies^{169, 170} switched techniques during the time of their studies and

one¹⁶⁹ used different lesions sets, which makes it difficult to compare outcomes in these different trials.

Role of GP ablation on rhythm outcome

The addition of GP ablation during the procedure was made since GPs have been suggested to play an important role in triggering PV firing^{56, 71-73} for the induction of AF and that vagal denervation have improved the outcome after CA reported previously⁷⁴. In **Paper I**, we found that the vagal GP activity was far more prevalent on the right than on the left side as well as around the ligament of Marshall and Waterston's groove which also has been reported by others^{18, 158, 192}. The patients who previously had transvenous catheter-based AF ablation were found to have significantly fewer active vagal GP sites at baseline than those who had not. Since the GPs are located around the circumference of the LA PV junction, this was expected⁶⁹. Moreover, the number of active GP sites at baseline did not differ between patients who remained free from AF and those with AF recurrence at one-year follow-up in **Paper I**.

At the moment, it is difficult to determine whether the addition of GP ablation improves the result. Zheng et al¹⁹³ found that the number of active GPs is a predictor for AF recurrences after surgery but neither of the studies with at least 5 years follow-up, including **Paper IV**, which made the addition of GP ablation, demonstrated a higher success rate (36-47%)^{163, 169} than the studies without GP ablation (55-69%)^{162, 170}.

A meta-analysis¹⁹⁴ reported inferiority of GP ablation by an endocardial approach as a stand-alone procedure compared to CA of AF. However, a combined ablation procedure (CA of AF plus GP ablation or SA plus GP ablation) produces a better outcome compared to PVI or SA without GP ablation during at least 12-month follow-up period^{194, 195}.

In another meta-analysis¹⁹⁵, patients with paroxysmal AF, GP on top of CA of AF was linked to significantly higher freedom of AT/AT than CA of AF alone. In patients with persistent AF, GP ablation on top of CA of AF compared to CA of AF or GP ablation on top of SA compared to SA of AF was associated with a non-significant trend towards higher rates of AT/AF. One of the included studies randomized patients with persistent AF between SA and GP ablation or SA alone and demonstrated no detectable effect on AF recurrences by adding GP ablation and instead noted more adverse events by GP ablation¹⁹⁶.

There are no results on long-term follow-up and, as a matter of fact, the persistent effect of GP ablation is controversial since reinnervation may exist¹⁹⁷. Furthermore, since the GPs are located around the LA-PV junction, they can also be ablated during PV isolation so therefore it is difficult to compare with absolute PVI alone.

Role of the ligament of Marshall and excision of left atrial appendage on rhythm outcome

Since the ligament of Marshall, consisting of both a muscle structure and autonomic innervation, has been found to trigger AF⁷⁷ and contribute to the initiation of AF⁷⁸ and the ablation of the ligament has resulted in a reduction of AF episodes⁷⁹, it was believed that the addition of the division of the ligament would improve the success rate after the procedure in **Paper I and IV**. All studies with at least five years follow-up^{162, 163, 169, 170} after the procedure have also made the addition of division of the ligament of Marshall, but to the best of our knowledge, there exists no RCTs appropriately designed, including division of the ligament, to draw any firm conclusion from.

Even the LAA excision may play a role in reducing AF recurrences after the procedure. The LAA seems to play an important role in triggering AF^{80, 81} and CA strategies aiming at electrical LAA isolation demonstrated a reduction of AF recurrences and AF burden⁸¹. However, in an RCT the addition of LAA excision with a stapler compared to epicardial PVI and box lesion alone did not improve the outcome in terms of AF recurrences¹⁹⁸.

Rhythm outcome after surgical ablation in comparison to catheter ablation

The decline in efficacy, 36% freedom from AF/AT at 10 years follow-up in **Paper IV**, may reflect late PV re-conductions but it may also be a sign of disease progression related to aging and emerging comorbidities (diabetes⁶⁶, hypertension, obesity and heart failure⁶⁷) resulting in non-PV triggers such as structural remodelling. Most of the AF recurrences subject to re-ablation in **Paper IV** were, however, related to PV re-conduction and in only a minority of patients were the PVs still isolated. Others reported PV reconnections after surgical isolation in only 62% after the procedure, which however was based on a small population as only 34% of their patients with AF recurrences underwent CA¹⁶⁹.

Pulmonary vein reconnection is by far the most common reason for AF recurrences after transvenous CA^{14, 199}. The importance of complete PVI has been demonstrated in the GAP-AF trial¹⁵⁴. Since the RF clamp applied at the confluence of the veins enables ablation without intervening blood, it is believed that an epicardial PVI results in more durable and transmural lesions as compared to endocardial RF applications. The observation that PV re-conductions appeared later, mean 4 years after SA, and were less frequent (80%) in our patients with AF recurrences in **Paper IV**, than reported after endocardial CA procedures, present in over 90 % of cases²⁰⁰, may indicate that more durable lesions are achieved with SA. The most frequent location of gaps observed in **Paper IV** was left inferior and left superior PV, which is consistent with others mainly reporting re-conductions in left PVs²⁰⁰ after endocardial CA procedures for AF ablation, possibly due to the anatomy of that region²⁰¹.

There are three RCTs¹⁶⁵⁻¹⁶⁷ and two meta-analyses^{22, 168} reporting markedly higher rate of freedom from AF/arrhythmias after SA compared to CA at 12 months follow-up (78% versus 53%) with superior outcomes for both paroxysmal (82% versus 63%) and persistent AF subgroups (74% versus 51%), although major complications were more common after SA, driven by pleural effusions and pneumothorax²². Although, the RCTs were not powered to determine any differences in mortality or stroke rate and the follow-up was only 12 months in most of the studies.

In one of the RCTs, Boersma et al¹⁶⁵ included 124 patients with paroxysmal or persistent AF who had failed at least one AAD and were considered less amenable to CA for AF on the basis of left atrial dilatation and hypertension or failure of prior CA for AF to repeat CA for AF or SA for AF. The SA included epicardial PVI using RF, GP ablation and LAA excision but some additional lines were also made at the discretion of the operator and the ablation of the GP was not made according to a scheme. Additional lines were also added at the discretion of the operator in the CA (RF) group. Overall the freedom from AF was significantly higher 66% for the SA group versus 37% for the CA group at 12 months follow-up. The corresponding figures for patients with paroxysmal AF were 69% in the SA group versus 35% in the CA group, and for patients with persistent AF 56% in the SA group versus 36% in the CA group. However, there were also a significantly higher rate of adverse event in the SA group than for the CA group. The different lesion sets applied makes it difficult to draw any firm conclusions.

The other RCT, Pokushalov et al¹⁶⁶ randomized 64 patients with paroxysmal or persistent AF who had failed prior CA for AF to SA for AF or a redo CA for AF. The SA consisted of video-assisted epicardial PVI (RF), GP ablation, additional lines to create a posterior box lesion and finally exclusion of the LAA. In the CA group (RF), all patients with persistent AF received additional lines connecting the left inferior PV to the mitral annulus and a roofline between the two superior PVs. Overall the freedom from AF was significantly higher, 81% in the SA group versus 47% in the CA group at 12 months follow-up (paroxysmal AF 85% versus 56% and persistent AF 75% versus 36%, respectively). There number of serious adverse events in the SA group was significantly higher in this study too.

Finally, the third RCT by Wang et al¹⁶⁷ randomly assigned 138 patients with paroxysmal AF to either video-assisted thoracoscopic surgery ablation for AF or CA for AF. The SA procedure included epicardial PVI, GP ablation, resection of the ligament of Marshall and LAA excision and was similar to the technique used in **Paper I and IV** and the CA for AF did not include any additional lines. The freedom from AF overall with AADs was higher in the SA group, 89%, than in the CA group 75%. However, the RCT did not include adverse events in the analysis.

The heterogeneity of patients selected in these RCTs and the variation in lesion sets makes all comparisons difficult unless RCTs including patients on

identical indications are conducted in order to select patients suitable for the procedure. The meta-analysis also included observational studies all favoring SA^{202, 203} for freedom from AF except one (Rong et al 2014) but also at the price of a higher complication rate²⁰³. Comparisons after longer follow-ups are also lacking.

Apart from achieving more durable PVI with the SA, the targeting of non-PV triggers potentially attained by dividing the ligament of Marshall⁷⁹, adding the GP ablation¹⁹⁵ and the LAA excision⁸¹, are all believed to contribute to an improved outcome but whether this is true remains to be seen in larger RCTs as mentioned previously.

There are plenty of techniques for SA of AF and the additional value of more lines is still unclear. Patients with persistent AF have poorer outcome after CA for AF and are usually subject to more extensive ablation both regarding SA and CA for AF. After **Paper I**, there was a switch to a totally thorascopic procedure¹⁰⁹ including epicardial PVI, a left atrial box lesion, partial vagal denervation and LAA exclusion and a majority of the patients included had longstanding persistent AF resulting in an overall freedom from AF in 83% (free from AF/AT 76%). In **Paper V**, the QoL after this procedure is evaluated and will be discussed further on. However, the occurrence of iatrogenic LA re-entry tachycardia with procedures involving several ablation lines is a recognized problem and warrants further improvement of the technique²⁰⁴. There are at least two observational studies, one retrospective comparative analysis²⁰² and one prospective observational study²⁰⁵, both including only longstanding persistent AF patients who had not been subject to CA for AF and the patients were treated with either video-assisted minimally invasive ablation or CA. Freedom from AF was obtained in 73-75 % and 32-59.0% during follow-up in the SA group and the CA group respectively. The video-assisted minimally invasive ablation included epicardial PV isolation, division of the ligament of Marshall, GP ablation and LAA excision²⁰² or epicardial PVI, box lesion and LAA excision²⁰⁵ but the CA included some additional lines in the posterior wall^{202, 205} or even ablation of left atrial complex fractionated electrograms²⁰⁵. This further supports the need for larger RCTs including patients with solely persistent or longstanding persistent AF.

Rhythm outcome after surgical ablation compared with hybrid procedures and Cox-Maze IV

There is a non-randomized study with a small sample size comparing the results after hybrid (n=35) versus minimally invasive surgery (n=63) at 12 months follow-up for patients with mainly paroxysmal AF yielding better results in the hybrid group (91.4% versus 82.1)²⁰⁶. In a recent meta-analysis (Pearman et al 2017 Arrhythmia and electrophysiology review 2017;6(4):202-9) also comparing SA for AF and hybrid ablation for AF including only observation studies (n=41), the AF free survival without AADs were similar between the groups at 12 months follow-up (71.5% versus

63.2%) and 24 months (69.5% versus 57.0) and major complications occurred more often with hybrid ablation. This data should be verified in RCTs.

Finally, in a systematic review²⁰⁷ hybrid procedure, Cox-Maze IV and minimally invasive SA, including observational studies, were compared favoring a Cox-Maze procedure but no statistical analyses were done, because of the heterogeneity in methodology and data reporting. Consequently, there is no reliable data yet comparing these techniques to confirm if one of the techniques is superior.

Quality of life and symptoms (Paper I, IV-V)

In the management of AF, symptom relief and improvement of QoL are the primary goal, apart from prevention of thromboembolic complications in patients with risk factors for stroke. Commonly, elimination of AF ameliorates QoL, but the overall AF burden may also influence. Previous adapted rhythm control strategies such as CA²⁰⁸ and Cox-Maze²⁰⁹ have been proven to alleviate the symptoms and improve QoL according to several trials. It is therefore important to demonstrate an improvement in QoL along with freedom from AF when introducing new rhythm control strategies. The generic tool used to measure QoL in **Paper I, III-V**, the SF-36 health survey, is applicable to a broad range of disease states and health conditions and have been most widely employed and has been extensively validated²¹⁰. It has been used in several AF studies^{156, 157} and can therefore be compared between studies and it has been demonstrated that patients with AF have substantially impaired QoL, reflected by SF36⁵. There is also an opportunity to compare with population norms¹⁷² as in **Paper I, III-V** and other disease states⁴² as in **Paper V**. However, the generic scales lack the sensitivity to changes with reductions in AF burden. On the other hand, AF specific scales, such as SSQ, may improve sensitivity and discriminate more effectively between patients with successful and failed rhythm outcome but lack validation. The recommendation is to use both a general and an AF specific measurement scale⁹⁵ as was the case in **Paper I, IV and V**. Both evaluation of QoL and symptoms is limited by treatment expectancy bias but sham procedures would be extremely challenging.

Paper I, IV and V demonstrates that the symptomatic AF patients included, prior to the procedures, have poorer QoL than the general Swedish population in the same age range. The low scores observed in these studies is not a trifling matter, since a difference of 20 or more points was considered a cut off between minor and serious medical conditions in the SF-36 form validity test²¹⁰. In **Paper V**, the QoL at baseline was also comparable to patients suffering from other chronic disease states such as congestive heart failure, hemodialysis, major depression and hepatitis C. The freedom from AF after the video-assisted epicardial PVI at 12 months was 76% (**Paper I**) and in the updated follow-up (**Paper IV**) 71% and both symptoms and QoL improved 12 months

after the procedure and QoL reached the values of the general Swedish population in 4 out of 8 subscales. The epicardial PVI and LA ablation (**Paper V**) also proved to be effective in restoring SR in the majority of AF patients (83%) but also had a number of adverse events as well as a significant number of iatrogenic left atrial flutters after surgery. Still the QoL and symptoms increased from a poor level to a level comparable to that of a standard Swedish population in all subscales except bodily pain. A majority of the patients in **Paper V** had longstanding persistent AF, but similar results were seen within this group with improvements of QoL. In **Paper I**, there was also an improved physical capacity following the procedure further indicating that there was not only a subjective but also an objective improvement after surgery.

There are today some reports of QoL after similar procedures but none of the RCTs comparing SA and CA for AF included QoL as an endpoint. In one retrospective study²⁰³ comparing SA (epicardial PVI and GP ablation) and CA for a second line treatment of AF, 5 of the SF-36 subscales were different between the groups with favour of the SA group. The SA strategy was more effective in preventing AF recurrences than CA for AF in the study as well. At 12 months, SA demonstrated an improvement in 6 out of 8 SF-36 subscales but the CA group did not improve significantly except for SF. There was a lot of missing data in the study, in the SA group and CA group, only 58% and 45%, respectively, replied to the SF-36 questionnaire. It was surprising that the QoL did not improve in the CA group since several other studies have shown an improvement^{156, 157}. SA had significantly more procedural adverse events than CA, but it does not seem to affect the QoL at 12 months follow-up. To the best of our knowledge, all observational studies also supports our findings. Kasirajan et al¹¹³ also reported improved QoL in AF patients, with 80% of patients free of AF, at around 18 months following a procedure including epicardial PVI, GP ablation and linear lesions, by reporting number of unhealthy day summary index. Although, the evaluation of QoL by number of unhealthy days is not recommended according to guidelines and is not a validated instrument for QoL. Two other observational studies^{211, 212} report improvements in QoL by using the same instrument as in **Paper I, IV and IV**, SF-36. Nasso et al²¹¹ performed an epicardial PVI in patients with paroxysmal or persistent AF resulting in an overall freedom from AF in 89% of the patients and improvements in all subscales except vitality. Driessen et al²¹² reported improvements in QoL in 7 of the 8 subscales of the SF-36 after epicardial PVI with or without GP ablation and with Dallas lesion set for patients with persistent AF. The patients with AF recurrences at 12 months had lower scores on 6 of 8 subscales than those without AF recurrences. Moreover, patients with complications of the procedure had no increase in the SF-36 subscales, but in patients in whom procedural complications appeared reversible, the lack of QoL increase was temporary, because these patients had a similar QoL as patients without complications at 12 months.

Paper IV is the first study to report QoL at 10 years after epicardial PVI, GP ablation and LAA excision. At follow-up, the QoL and symptoms remained improved compared to baseline when adjusting for age in **Paper IV** and the QoL reached the values of the Swedish general population in the same age-range even though only a minority (36%) of the patients were free from AF/AT recurrences. Moreover, there were no differences in QoL or symptoms by SSQ between patients with or without AT/AF recurrences at 10 years follow-up which may be related to a higher rate of asymptomatic AF episodes after SA but also to a reduction in AF burden as a majority of patients with AF/AT recurrences underwent CA and/or AAD treatment after failed SA. Asymptomatic episodes of AF are known to be more common after CA for AF than before²¹³. Driessen et al also reported²¹² after a similar SA procedure for SA, that patients with only one AF recurrence improved on the SF-36 subscales similar to the group with no AF recurrences, whereas patients with multiple AF recurrences did not improve after the procedure²¹². The currently used definition of failed intervention, a 30 second AF episode, is thus not rational since many patients with such short episodes may be completely asymptomatic without clinical recurrences requiring treatment. The long-term follow-up is also limited by the influence of comorbidities which might be higher in this subset of AF patients than the general Swedish population and other possible medical interventions during follow-up, emphasizing the need for a comparator group. Furthermore, as mentioned earlier the treatment expectancy bias might also influence. Larger RCTs comparing SA and CA for AF, including both QoL and AF burden as endpoints are warranted.

Left atrial function and size (Paper II)

According to our **Paper II** the epicardial PV isolation and GP ablation does not seem to affect left atrial function or size when assessed 6 months after the procedure. Although, a significant decrease in LA size was seen in patients with the largest LA at baseline. This can be related to the effect of remodeling after maintenance of SR or as a result of the scar tissue shrinkage, the latter of which is contradicted by the lack of effect on contractility. Since enlarged LA is a riskfactor for AF recurrences after the procedure^{162, 163} and AF progression without exception⁶¹, it is important to note that the procedure itself does not counteract its purpose. A reduced atrial function, related to extensive scarring of the LA, may promote thromboembolic events because of insufficient contraction of the atria resulting in the formations of blood clots even if AF is successfully eliminated. Buber et al²¹⁴ concluded that absence of LA contraction resulted in a fivefold increase and a LA volume index ≥ 33 ml/m² in a threefold increase in the risk for thromboembolic stroke after the concomitant RF and cryoablation, even when accounting for CHADS-VASc, in patients in SR at 2 years follow-up.

After the more complex and extensive Cox-Maze III procedure, a sustained reduction of the atrial mechanical function was reported for patients with paroxysmal lone AF^{215, 216}. A meta-analysis recently concluded that successful RF CA in patients with AF significantly decreased LA size and volumes but does not seem to adversely affect LA function²¹⁷.

The left atrial function after minimally invasive surgery for AF have been studied and compared to left atrial function after a hybrid procedure for AF in an observational study although the SA was more extensive including epicardial PVI, GP ablation, box lesion and some additional lines²⁰⁶. The number of patients receiving SA alone was also small (n=28). Left atrial emptying fraction increased significantly at 12 months follow-up in both groups and there were no differences between the groups. At 3 months the LA diameters decreased significantly from baseline with no comparison between the groups and the same pattern was seen at 12 months but without reaching statistical significance.

In a retrospective study, comparing SA with a similar procedure and CA for AF, no differences in LA volumes or left atrial diameter at 12 months follow-up were seen but no measurements were done at baseline to be able to observe any changes²⁰³.

However, the limited time for follow-up, the small number of patient and the missing data may have affected the result in **Paper II** and it warrants confirmation in larger trials. Also, today the guidelines recommend the measurement of LA volume by 3D echocardiography to evaluate LA size. Since the echocardiographic examinations in **Paper II** were done long before LA volume by 3D echocardiography was routine there were no possibilities do repeat the examinations. However, the same method was used at baseline and at 6 months follow-up so a change in area could be detected. Normal values for LA area were recently presented²¹⁸ but comparisons are not recommended since the literature is scarce²¹⁹.

Safety (Paper I, IV)

The most common complication

Major bleeding was the most common complication in **Paper I** perioperatively and during 12 months follow-up. The most vulnerable moment was the dissection around the PVs, accounting for 4 of the 6 bleeding events. In two bleeding events the CPB had to be used, which also have been described by others¹⁶⁹. Only one bleeding event in **Paper I** was related to the exclusion of the LAA, but a significant portion of patients (23.8%) were judged to be at too high risk for such procedure, indicating that this must also be a critical moment. De Maat et al¹⁷⁰ also reported one case where bleeding from the LAA required conversion to median sternotomy and this is further supported by the report of one death due to tearing of the base of the LAA¹⁹². In the learning curve in **Paper I**, most of the bleeding events are depicted in the

last two groups of ten undergoing the procedure, which might be a coincidence because of the small sample size. Although, there is always a learning curve when a new type of surgery is introduced.

Strokes

The LAA exclusion was believed to be an advantage with the SA for an anticipated reduced risk of future thromboembolic events. It has been found to be the dominant location of thrombus in AF and led to the development of LAA occlusion as a therapeutic modality to reduce stroke risk^{107, 220}. However, in **Paper I** there was one stroke within 2 days after surgery, although related to a mistake in the prescription of low-molecular weight heparin, and remarkably 4 strokes at long-term follow-up (**Paper IV**). In two previous studies^{162, 163} reporting their data at 5 years follow-up after the procedure, both used the stapler technique (Endostapler) and recorded 1-5 strokes during follow-up, respectively. Saini et al¹⁶⁹ used a stapler in a majority of their patients and confirmed the absence of flow by intraoperative TEE. In the last 16% of the patients they switched to an Atriclip device. In total they observed 5 strokes or TIAs during follow-up but in one of those patients, the LAA had not been excluded and in three of the patients no residual flow was noted with TEE or MRT and the last patient had a small residual LAA with no leak. Finally, De Maat et al¹⁷⁰ also used two different techniques, stapler or AtriClip device and observed no stroke during follow-up. It has been demonstrated in several studies, both observational and randomized controlled that the stapler excision is not successful in a majority of the patients when assessed by TEE^{221, 222}. Residual LAA flow or incomplete LAA exclusion is associated with an increasing stroke risk²²³. Today, surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery according to guidelines²³. The only technique that is approved by the FDA for closure of the LAA during cardiac surgery is the Atri-clip. There is a large RCT underway to sort out the benefit of LAA exclusion for stroke prevention in the subgroup undergoing concomitant AF surgery²²⁴. In **Paper II**, the LA function and size was found to be preserved 6 months after the procedure, which may have implications on the risk of thromboembolic events. Even though several strokes were noted in **Paper IV** on long-term follow-up of the procedure, it is important to note that the procedure itself does not impair left atrial function, and the strokes are most probably related to the inherent risk for stroke with AF³⁰ and the patients CHADS-VASc profile. Although, it is disappointing that the LAA excision was not enough to prevent strokes. This is an area of development and by using other instruments to excise the LAA and TEE to confirm the result in future studies, it might be possible to prevent strokes. There are already devices using transvenous techniques with LAA occlusion to reduce the stroke risk in patients at high risk and contraindications for anticoagulants.

Other complications and comparison with catheter ablation

The second most common complication in **Paper I** was infection which has not been reported by others. In the two meta-analyses^{22, 168}, comparing SA and CA for AF, major complications in the periprocedural period were more common in the SA than in the CA group, largely driven by pleural effusions and pneumothoraxes. During the follow-up period of 12 months, serious adverse events showed no significant difference between groups¹⁶⁸. Bleeding events, necessitating conversion to sternotomy and CPB are serious and in order to be able to apply this technique, the surgeons must be skilled and it must be shown that it is very unusual. The two of the RCTs comparing SA and CA for AF report 1.7- 3.1% conversion to sternotomy in the SA group and none in the CA group. The risk benefit ratio is important to consider in every patient.

Concomitant AF surgical ablation (Paper III)

Quality of life

The new concomitant SA technologies have proven effective in maintaining SR in patients with AF diagnosed preoperatively, but the number of studies evaluating the effects on QoL is very limited. An improvement in symptoms is, however, the main indication for rhythm control in patients with AF, which is the reason why **Paper III** is important. It is the first prospective, double-blinded randomized, multicentre study and demonstrates no significant improvements in QoL after combined MVS and cryoablation compared with MVS alone at 12 months follow-up in patients with permanent AF. The primary end-point for the main study (SWEDMAF) was freedom from AF at 12 months and significantly more patients who underwent MVS and cryoablation (73.3%) regained SR compared with patients, who underwent MVS alone (42.9%)²⁰. This is supported by a recent meta-analysis which concluded that concomitant AF surgery approximately doubles the risk for freedom from AF¹³³.

It is previously demonstrated that the stand alone 'cut and sew' Maze procedure for AF significantly improved QoL in patients with lone AF evaluated at 12 months²⁰⁹. Moreover, a meta-analysis of RCTs of transvenous CA procedures showed improved QoL compared with AADs at long-term follow-ups²⁰⁸. In **Paper I and IV** the QoL was also improved after stand-alone video-assisted epicardial PVI at both 12-month and 10-years follow-up. Finally, the QoL was improved in Paper V in patients with mainly longstanding-persistent AF subject to thoracoscopic left atrial ablation. Concomitant surgical AF ablation during MVS differs distinctly from both the stand-alone Maze surgery, transvenous AF ablation and stand-alone video-assisted or thoracoscopic epicardial PVI in terms of patient's characteristics, morbidity and AF related symptoms. Patients referred for stand-alone Maze surgery²⁰⁹, CA²⁰⁸ and stand-

alone video-assisted or thoracoscopic epicardial PVI in **Paper I, IV or V**, were younger and most had symptomatic paroxysmal or persistent or longstanding persistent AF without significant cardiovascular comorbidities. In contrast, the patients referred for concomitant MVS and AF ablation are generally older with concomitant cardiovascular diseases and larger LA, and most often have long lasting or permanent AF. Accordingly, it is therefore difficult to evaluate whether the patient's symptoms are related to the AF or the valve disease itself.

There are two non-randomized trials reporting improved QoL by SF-36 in patients undergoing MVS combined with surgical AF ablation as compared with MVS alone^{135, 136}. In the first study of 91 patients with permanent AF, only those patients with SR at follow-up had a better QoL in 5 of 8 subscales according to stepwise logistic regression analysis¹³⁶. In the second study of 147 patients with persistent or longstanding-persistent AF, the QoL improved after combined MVS and RF SA as compared with MVS alone¹³⁵. Since both trials were non-randomized and un-blinded the risk for bias and placebo effects increases.

To the best of our knowledge, there are only two prior RCTs comparing combined MVS and AF ablation with MVS alone, both of which reported no difference in QoL between the patient groups^{21, 132} which further supports our findings. The first trial was single blinded and randomly assigned 49 patients to MVS surgery with or without biatrial modified RF Maze procedure and reported no difference in QoL despite a higher (75%) sinus restoration in the combined MVS group than in the MVS alone group (39%) at 12 months follow-up¹³². In the second trial, 260 patients (non-blinded) with persistent or longstanding persistent AF were randomized to either MVS alone or further to PVI or a biatrial Maze procedure. There were no differences in QoL although freedom from AF was more frequent in the combined MVS group than in the control group at 12 months (63.2% versus. 29.4%).¹³ Furthermore, the permanent pacemaker implantation rate was significantly higher in the ablation group than in the control group.

An important difference in our trial presented in **Paper III** and the two previous RCTs is however that the double-blind design in our trial ensures identical treatment for AF during follow-up and excludes the possibility of a placebo effect. Although the QoL improved at 12 months after surgery compared with baseline, the improvement did not differ between patients in SR and those in AF at follow-up, irrespective of the allocated procedure, indicating that their preoperative symptoms were mainly related to their valve disease. Both patient groups referred for combined MVS with cryoablation and MVS alone reached the QoL for the age-matched Swedish general population at follow-up as shown in **Paper III**. None of these RCTs, including the SWEDMAF trial²⁰, reported any differences in complication rates between the

treatment groups except for an increased risk for permanent pacemaker implantation in the ablation group¹³. However, neither of the studies was statistically powered to demonstrate differences in complication rates.

Apart from reduction in symptoms and improvement in QoL, which at present is the most important indication for rhythm control in patients with AF, reduction in mortality or stroke rate could also be tentative goals for an intervention such as combined MVS and left atrial ablation. Systematic review and meta-analysis, including nine RCTs of concomitant surgical AF ablation during MVS showed, however, no difference between combined MVS and SA vs. MVS alone in terms of 30 day-mortality, all-cause mortality, pacemaker implantation, stroke and thrombo-embolism despite a significantly higher rate of SR in the combined MVS group¹³⁴. A larger systematic review and meta-analysis,¹³³ including 22 RCTs of AF patients scheduled for cardiac surgery and concomitant AF surgery failed to demonstrate with certainty any effects of the concomitant AF surgery on cardiovascular mortality, rate of other adverse events, fatal or non-fatal cardiovascular events, neurological or thrombo-embolic events and health-related QoL, also despite a greater freedom from AF. Again there was an increased risk for permanent pacemaker implantation in the concomitant AF surgical group, although since both SA and Maze cut-and-sew technique were included the result should be interpreted with caution. Apart from these observations, signs of atrial dysfunction have also been reported in patients undergoing combined MVS as compared with MVS alone²²⁵.

There is one registry trial²²⁶ analyzing the risk of concomitant SA by propensity matching 28 739 patients with or without SA, by AF type, primary operation and comorbid risk variables using greedy 1:1 matching algorithms. They found a reduction in relative risk of 30-day mortality and stroke but an increase in renal failure and pacemaker implantation. There is a possibility of bias because the apparent difference in outcome between these two groups of patients may depend on characteristics not observed that affected whether or not the patient received SA instead of due to the effect of the SA per se. RCTs and especially, meta-analyses including several RCTs, are the most accurate study designs.

Moreover, since a combined MVS procedure most likely increases the health care expenditures by the procedure itself and the increased pacemaker dependency post-operatively, a clear clinical benefit must be demonstrated such as reduced morbidity or mortality before it can be recommended for widespread use. Howbeit, the current recommendation according to guidelines^{23,95} is that AF surgery should be considered in patients with symptomatic AF to improve AF related symptoms, considering patients choice informed by an AF Heart Team.

Limitations

Paper I, II and IV-V

These are observational studies (**Paper I, II, IV and V**), with a limited number of patients and with no comparator group. Since the procedures were new at the time, this study design was used to report the initial experience of these techniques. Before larger RCTs can be performed, the procedures must be considered safe and efficient regarding rhythm outcome to be able to include more patients.

Considering this, it is also impossible to draw any conclusions if the GP ablations or division of the ligament of Marshall or exclusion/isolation of the LAA improve the outcome. There was no continuous rhythm monitoring so we cannot exclude the possibility of patients categorized as being in SR having paroxysmal AF. Although, we believe that clinical relevant AF episodes would be documented during the 10-year follow-up (**Paper IV**). Continuous rhythm monitoring is also expensive and associated with a low patient compliance (depending on the method). Nevertheless, Holter recording is considered a standard method for rhythm monitoring. Moreover, there was no documentation on obesity during follow-up, which might account for a progression of AF.

Since **Paper I, IV and V** are non-randomized trials, including patients who were highly motivated by their severe AF-derived symptoms, the evaluation of QoL and symptoms is limited by treatment expectancy bias but sham procedures would be extremely challenging as mentioned before.

There was no TEE used during surgery to confirm that the LAA was completely excised before end of surgery in **Paper I and IV**. In **Paper II**, the left atrial area was measured, and today the recommended measurement of the LA is the LA volume as already mentioned in the discussion. The results in the trials must be confirmed in larger RCTs.

Paper III

The lack of continuous rhythm monitoring means that we cannot exclude that patients categorized as being in SR at follow-up might have had asymptomatic paroxysmal AF. Since we only included patients with permanent AF, one cannot exclude that patients with paroxysmal episodes of AF may have benefit from a combined procedure. Moreover, if we were able to differentiate between AF related symptoms and symptoms related to the valvular disease,

Conclusions

Video-assisted epicardial PV isolation combined with GP ablation for the treatment of AF

- The procedure was found to be a relatively safe and efficacious treatment, improving the QoL, symptoms and exercise capacity at one-year follow-up for patients with symptomatic AF. (**Paper I**).
- At 6 months follow-up, the procedure resulted in no significant alteration of the atrial contractility, mechanical function or size of the LA. Although, this procedure with elimination of AF recurrences and preserved atrial function may decrease the risk for thromboembolic events and may have implications for the risk evaluation of thromboembolic complications after this surgery further studies are warranted to confirm these results. (**Paper II**).
- On long-term, symptoms and QoL were still improved 10 years after the procedure, and were comparable to the levels of the Swedish general population, despite a significant decline in AF freedom. The procedure may therefore be an alternative for highly symptomatic AF patients failing other interventions, although larger RCTs are warranted to assess its risks and benefits and the optimal target population. Stroke seems not to be prevented by LAA excision using this stapler. (**Paper IV**).

Concomitant AF surgical ablation during mitral valve surgery for the treatment of AF

- The addition of surgical AF ablation to MVS did not improve QoL compared to MVS alone in patients with permanent AF. Improved QoL remains the main indication for rhythm control, also including AF patients scheduled for MVS, since no treatment strategy for rhythm control has up to date been associated with any other improved clinical outcomes, such as a reduction in all-cause mortality, morbidity or thrombo-embolism. The strategy of adding surgical AF ablation during MVS can therefore, based on the present and previous data, not yet be justified until scientific evidence demonstrates more benefits than side effects in both a short- and long-term perspective. Further research with larger randomized double-

blinded studies are warranted to evaluate the benefit risk ratio at long-term follow-up (**Paper III**).

Thoracoscopic left atrial ablation for the treatment of AF

- Patients with severely symptomatic AF display poor QoL, similar to other chronic diseases. With an active rhythm control strategy, QoL can be normalized to the level of a standard population. Large RCTs are needed to express certainty in this regard (**Paper V**).

Clinical implications and future perspective

The prevalence of AF is increasing in the population and causing degraded QoL⁵ among a lot of these patients. AF related symptoms, despite rate control, is an indication to adopt a rhythm control strategy²³. New SA techniques such as stand-alone procedures or concomitant during cardiac surgery have been developed to eliminate AF or reduce AF burden but information about the effect on QoL is lacking. Moreover, there is limited information about the rhythm outcome, atrial function and safety after the stand-alone procedures.

There is a large difference between concomitant SA and stand-alone SA. Patients referred for concomitant AF ablation have an indication for cardiac surgery such as MVS, which makes it very hard to distinguish if their symptoms are related to AF or the significant valve disease per se. On the other hand, in patients referred for stand-alone procedures the main indication is AF related symptoms. A large meta-analysis, including 22 RCTs comparing concomitant AF surgery with heart surgery alone, which specifically evaluated the risk for bias, concluded that concomitant AF surgery approximately doubles the risk of freedom from AF while increasing the risk of permanent pacemaker implantation¹⁰¹. The effects on mortality were uncertain and likewise the effect on QoL.

In our study Paper **III**, which is the first double-blinded RCT, thus reducing the risk for the expectancy bias, comparing MVS with cryoablation and MVS alone there was no difference between the groups in QoL using a generic validated instrument, SF-36²¹⁰. This is supported by the finding in the meta-analysis¹⁰¹, although QoL could not be meta-analyzed because sample size at baseline and follow-up was not presented and therefore it was uncertainty about the effect on QoL. Since a combined MVS procedure most likely increases the health care expenditures by the procedure itself and the increased pacemaker dependency post-operatively and no difference in QoL can be observed, which is the main indication for rhythm control, a clear clinical benefit must be demonstrated such as reduced morbidity or mortality before it can be recommended for widespread use. The strategy of adding surgical AF ablation during MVS can therefore, based on the present and previous data, not yet be justified until scientific evidence demonstrates more benefits than side effects in both a short- and long-term perspective. Further research with larger RCTs are warranted to evaluate the benefit risk ratio at long-term follow-up.

There are multiple techniques for stand-alone SA for AF and in this thesis we have evaluated the rhythm outcome, atrial function and safety after video-

assisted epicardial PVI combined with GP ablation, division of the ligament of Marshall and LAA excision (**Paper I, II, IV**). It is the first study to evaluate this procedure at 10 years follow-up. At 12 months 71% of the patients were free from AF recurrences but it was a steady decline to 36% at 10 years follow-up. However, both symptoms and QoL improved at one and 10 years follow-up and reached the level of the general Swedish population on several of the SF-36 subscales. The physical capacity also improved at one year. Nevertheless, there was a high rate of adverse events, although it did not seem to affect QoL in long-term, the frequency of potentially fatal bleeding events cannot be ignored. The left atrial function and size was preserved but the LAA excision was not able to completely prevent strokes. Moreover, in **Paper IV**, the QoL was improved in patients with mainly longstanding-persistent AF subject to epicardial PVI, partial vagal denervation, left atrial ablation and LAA excision.

To be able to predict the benefit risk ratio, patient selection, lesion set for ablation, RCTs comparing CA and SA for AF, including patients on identical indications and longer follow-up are warranted. In the RCTs¹⁶⁵⁻¹⁶⁷ and meta-analyses^{22, 168} available there is a heterogeneity of patients selected and variations of lesion sets used. The SA for AF resulted in a significantly higher portion of patients free of AF at 12 months compared to CA for AF but had a higher rate of immediate post-procedural complications. The SA has also been associated with left atrial tachycardias in the TELA-AF trial¹⁰⁹ and in **Paper IV** but extensive ablation during CA for left atrial substrate modification seems to have the same result.

It seems reasonable that SA for AF could be of benefit in patients with persistent, longstanding persistent or patients with paroxysmal/persistent AF with prior failed CA for AF since this patient selection has poorer outcomes after CA for AF but further trials are needed. Since there is a progressive research and development of more extensive ablation during CA for AF it is hard to tell if it will improve the outcome but probably at a higher cost of radiation. Although, it seems that the hybrid procedure combining SA and CA for AF might be limited by both adverse events from the CA procedure and the SA procedure (Pearman et al 2017 Arrhythmia and electrophysiology review 2017;6(4):202-9).

For patients with AF it is of major importance to increase their QoL and in the future also be able to reduce the morbidity and mortality associated with AF.

This thesis is a significant contribution to our understanding of surgical ablation for the treatment of atrial fibrillation but further research will tell which technique should be used in which AF population.

Summary in Swedish (Sammanfattning på svenska)

Förmaksflimmer är den vanligast förekommande arytm i befolkningen och patienter med denna rytmrubbning kan känna av hjärtklappning, andfåddhet, bröstsmärta, oro eller vara helt asymptomatiska. Förutom symptom pga den snabba och oregelbundna rytmen med minskad fysisk arbetsförmåga och livskvalitet kan förmaksflimmer också bli fatalt pga utveckling av hjärtsvikt, stroke eller plötslig död.

Behandlingen av förmaksflimmer består av ställningstagande till eventuell antikoagulantia, frekvensreglering och behandling av underliggande predisponerande sjukdomar och riskfaktorer för att förhindra komplikationer pga förmaksflimmer. Dessa behandlingar kan i sig minska symptomen och därmed öka livskvalitén som är ett av de primära målen men det kan också behövas rytmreglerande behandling för detta. Hittills har rytmreglerande behandling inte kunnat visa sig minska dödligheten eller sjukligheten vid förmaksflimmer utan den huvudsakliga indikationen är symptomlindring. Rytmregleringen kan bestå i antiarytmika, transvenös kateterablation eller kirurgisk ablation. Det har dock visat sig att antiarytmika bara har måttlig effekt och biverkningarna väger upp nyttan av att patienten går i sinus rytm. Transvenös kateterablation där man isolerar lungvenerna, som har visat sig kunna inducera förmaksflimmer, kan eliminera flimret hos en hög andel patienterna (70%) men rekonduktion i lungvenerna är vanligt och ingreppet är inte lika framgångsrikt för patienter med flimmer som är ihållande (persisterande) jämfört för patienter som har det intermittent (paroxysmalt).

Således har det utvecklats alternativa metoder så som video-assisterad epikardiell lungvensisolering där man isolerar lungvenerna från utsidan på hjärtat genom små incisioner i bröstkorgen och använder videokamera och thorakoskopiska instrument för att uppnå isolering. Behandlingen kan också kombineras med denervation av nervplexus (som har visat sig också kunna initiera förmaksflimmer) och exklusion av förmaksörat (där proppar kan bildas som leder till stroke). Primärt görs detta för patienter där vanlig transvenös kateterablation ej lyckats eller där flimret är ihållande mer än 7 dagar och måste brytas med konvertering. En vidareutveckling av tekniken har skett till en total thorakoskopisk procedur med tillägg av ytterligare linjer som isolerar delar av vänsterförmak för att ytterligare förhindra induktion av förmaksflimmer. I vissa fall kan man också göra kirurgisk ablation av förmaksflimmer

samtidigt som man opererar en mitralisklaff. Det finns dock begränsad med information om livskvalitén efter dessa kirurgiska ablationer mot förmaksflimmer, både som enskilda ingrepp eller kombinerat med mitralisklaffkirurgi. Hos patienter remitterade för mitralisklaffkirurgi är det ju också svårare att veta om de har symptom från förmaksflimret eller om det är symptom från den läckande klaffen. En rytmreglerande behandling ska ju styras av symptom relaterade till förmaksflimret och i sådant fall är det viktigt att visa att patienterna som genomgår kirurgisk ablation förbättras mer än de som bara genomgår klaffkirurgi. Vidare är det också okänt hur långtidsresultaten ser ut efter epikardiell lungvensisolering mot förmaksflimmer. I denna avhandling undersöks livskvalitén vid olika typer av kirurgisk ablation men även graden av flimmerfrihet, vänsterförmaks funktion och risken för komplikationer efter epikardiell isolering av lungvenerna som ett enskilt ingrepp utan övrig indikation för hjärtkirurgi. Det är viktigt att minska symptomen vid förmaksflimmer men detta måste uppnås genom att man kan påvisa flimmerfrihet eller reduktion av flimmerbördan men komplikationerna måste också vara tolerabla.

Studie I

Då vi var ett av de första centrumen i Norden att tillämpa denna nya teknik för kirurgisk isolering av lungvenerna för behandling av förmaksflimmer, ville vi beskriva de initiala resultaten med avseende på flimmerfrihet, påverkan på vänsterförmaks funktion och storlek, fysisk arbetsförmåga, livskvalitet samt grad av komplikationer. 43 patienter med paroxysmalt, persisterande eller permanent förmaksflimmer som alla faller antiarytmika av klass I eller III samt i vissa fall även transvenös kateterablation inkluderades och fick genomgå ingreppet och följdes upp i ett år.

Studien visade att 76% av patienterna var flimmerfria vid uppföljningen, den fysiska arbetsförmågan, symptom och livskvalitet hade alla förbättrats utvärderat med cykelprov och enkäter före och efter operation. Livskvaliteten nådde nu upp till samma nivå som en genomsnittlig svensk befolkning i samma åldersspann. Slutligen kunde vi konstatera att operationstiden mellan de första tio operationerna och de sista tio minskade signifikant men det förekom en del procedurrelaterade komplikationer så som pneumothorax, pleurala utgjutningar men även 14% blödningar som i två fall krävde hjärtlungmaskin.

Studie II

I denna studie ville vi gå vidare och titta på om denna ovanstående operationsteknik där man isolerar lungvenen epikardiellt och denerverar nervplexa påverkar vänster förmaksfunktion och storlek. Detta är viktigt eftersom en försämrad förmaksfunktion kan leda till att proppar bildas även i frånvaro av förmaksflimmer och en förstoring av vänster förmak kan också gynna progress av förmaksflimmer. 27 av de 43 ovanstående patienter som ingick i studie I och hade sinus rytm före operation och vid 6 månaders uppföljning och hade

genomgått rätt typ av ultraljudundersökning av tillräcklig kvalitet för att kunna värdera vänster förmaks area och funktion inkluderades. Vid uppföljningen vid 6 månader var både förmaksfunktionen och storleken på förmaket oförändrat, vilket tyder på att operationen i sig vad gäller förmaksfunktion och storlek inte påverkar vänster förmaks storlek eller funktion för de som blir flimmerfria. Studien är dock liten och resultatet behöver bekräftas i större studier.

Studie III

Kombinerad kirurgisk ablation av förmaksflimmer hos patienter som genomgår mitralisklaffkirurgi har nästan blivit rutin trots bristande information om förbättrad livskvalitet eller andra vinster i form minskad mortalitet. Syftet med denna studie var att utvärdera livskvaliteten efter mitralisklaffkirurgi med eller utan epikardiell vänster förmaks ablation. 65 patienter med permanent förmaksflimmer som randomiserats till mitralisklaffkirurgi med eller utan vänsterförmaksablation i den dubbel-blindade multicenter studien SWEDMAF och svarade på en livskvalitetenkät före och 6 samt 12 månader efter operationen inkluderades i denna substudie. Vid uppföljningen kunde man inte se någon skillnad i livskvalitet hos de patienter som genomgått mitralisklaffkirurgi kombinerat med kryoablation jämfört med de som genomgått enbart mitralisklaffkirurgi och alla uppnådde samma livskvalitet som en genomsnittlig svensk befolkning i samma åldersspann. Det var heller ingen skillnad i livskvalitet för patienter med normal hjärtrytm efteråt eller de mot fortsatt flimmer. Detta väcker frågor kring nuvarande guidelines där detta rekommenderas trots att inga kliniska vinster kan visas.

Studie IV

Detta är en långtidsuppföljning av studie I där de 43 patienterna som genomgått video-assisterad epikardiell lungvensisolering, vagal denervering och excision av förmaksörat samt ytterligare 2 patienter som tillkommit följdes upp i 10 år med avseende på flimmerfrihet, livskvalitet, symptom, komorbiditet och komplikationer. 2 patienter föll bort pga att de ej ville vara med i långtidsuppföljningen och 2 dog (3 resp 9 år efter op). Det har tidigare inte gjorts en så lång uppföljning av denna operationsteknik tidigare. Flimmerfriheten minskade gradvis till 36% av patienterna efter 10 år men trots detta sågs ändå en fortsatt förbättring av livskvaliteten och symptomen jämfört före proceduren. Livskvaliteten nådde också upp på en majoritet av skalorna i enkäten till samma nivå som en genomsnittlig svensk befolkning i samma åldersspann. Under långtidsuppföljningen drabbades 4 personer av stroke talade för att excisionen av vänsterförmaksöra inte varit komplett och att det inte räcker för att helt förebygga stroke.

Studie V

Denna studie är en substudie av en utvärdering av den totalt thorakoskopiska epikardiella lungvensisoleringen och vagala denerveringen med tillägg av ytterligare linjer som isolerar delar av vänsterförmak med fokus på livskvaliteten efter operationen utvärderat med enkäter före och vid 12 månaders uppföljning. Även efter denna operation hos patienter med mer ihållande förmaksflimmer förbättrades livskvaliteten och symptomen. Patienterna hade före operationen betydligt sämre livskvalitet än en genomsnittlig svensk befolkning i samma åldersspann och låg i paritet med den livskvalitet som ses hos patienter med hemodialys, hepatit, hjärtsvikt och depression. Efter operationen nådde de upp till samma nivå som en genomsnittlig svensk befolkning i samma åldersspann.

Acknowledgements

I would like to express my sincere gratitude and appreciation to all those who contributed to this thesis, with special attention to:

All patients who have participated in these studies and their willingness to contribute to advances in medical science.

Carina Blomström-Lundqvist for your endless support, inspiration and being an exceptional supervisor. Thanks to you, this research was initiated from the very beginning. I would also like to thank you for the generosity to let me travel far and wide to present our scientific findings and learn from others and I also enjoyed and appreciated our talks on these trips. Thank you for believing in me, listening to my ideas, encouraging the best performance and accepting me and my shortcomings. Even though we do not agree sometimes we always have good discussions. I could not have had a better supervisor!

Lena Jidéus, my co-supervisor, for your support and inspiration and also having the courage as a surgeon to try a new technique for the treatment of AF.

Per Blomström, Stefan Lönnerholm, Leif Nilsson, Johan Probst, Stefan Thelin, Anders Holmgren, Helena Malmberg, Steen M Jensen, Gunnar Myrdal Einarsson and Victoria Jansson; my co-authors for providing excellent ideas, support and critical review during the process of the papers. A special thanks to **Per Blomström** who made all the electrophysiologic measurements during the procedures and **Leif Nilsson**, the primary surgeon, for having the courage to try a new technique for the treatment of AF.

Göran Granath, Lars Lindhagen, Katja Gabrysch, statisticians, for providing me statistical support and teaching me about statistics.

Eva-Maria Hedin for providing practical support as well as graphical support with figures.

Members of the research group **Panagiottis Arvanitis, Varvara Kommata, David Mörtsell, Bozena Ostrowska, Elena Sciaraffia, Priit Teder** for providing an inspiring environment, productive discussions, collaborations, and support.

The research nurses **Anna Lindberg**, **Yvonne Björkman**, **Pernilla Hallberg**, **Anna Eriksson** and **Rosie Thaning** for helping me contacting patients, but most of all for being cheerful roommates!

Medical student **Sophie Löfström** for helping me with some of the patient interviews and collecting some of the data in Paper IV.

My colleagues at the Department of Cardiology, Uppsala University Hospital, for your support. **Johan Lugnegård**, head of Department, and **Nina Johnston**, head of section, for providing me an environment in which clinical medicine and research can be combined. **Gunnar Frostfelt** for joining me with **Carina Blomström-Lundqvist** from the very beginning.

The **Swedish Heart and Lung Foundation** for research grants.

Kai Eggers and **Nina Johnston**, colleagues and clinical supervisors, for providing me support and sharing your enthusiasm.

Uppsala University Hospital for providing me with a wonderful environment to develop my clinical and research skills.

My friends and neighbours for supporting me, being such good friends, offering me time for relax, pleasures, crayfish parties, ski holidays, barbeques and backpacking in the Swedish mountains. I have missed you during the final preparation of this thesis.

My relatives Gunnar Hjulström, Stina-Clara Hjulström, Lennart Hjulström, Gunilla Nyroos, Helena Fenger-Krog, Johan Andersson, Louise Fenger-Krog, Folke Lundin, Victoria Modin, Krister Modin, Katarina Lundin, Veronica Willners, Cecilia Christersson, Jan Christersson for supporting me.

My extended family **Iwona** and **Claes Kihlberg**, **Niklas**, **Kristina**, **Oscar** and **Hanna** for your love and support.

My late grand-parents **Astrid Hjulström**, **Jonas Bagge** and **Elsa Bagge** for your love. Also **Filip Hjulström**, whom I never met but has been an inspiration. I miss you all.

My brother **Fredrik Bagge** for your love and support and care of my children.

My father **Lars Bagge** and my mother **Harriet Bagge** for your love, unconditional support and giving me all the opportunities. I love and miss you from the moon and back and feel so sorry that you cannot share this with me.

My family, **Carl Bagge** and our children **Emilia**, **Amanda** and **Felicia**, for your support and love. Carl, a special thanks for the IT-support during the years, proof-reading of this thesis and help with figures. Also thanks for making me dinner, taking care of our home, children and me during the final part of this thesis. I will never stop loving you all.

References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* May 9 2001;285:2370-2375.
2. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart* Nov 2001;86:516-521.
3. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* Jul 11 2015;386:154-162.
4. Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy. *J Am Coll Cardiol* Aug 15 2006;48:721-730.
5. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med* May 2006;119:448 e441-419.
6. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* Oct 1 2002;113:359-364.
7. Kotecha D, Kirchhof P. Rate and rhythm control have comparable effects on mortality and stroke in atrial fibrillation but better data are needed. *Evid Based Med* Dec 2014;19:222-223.
8. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. *Pacing Clin Electrophysiol* Jan 2013;36:122-133.
9. Camm AJ. Safety considerations in the pharmacological management of atrial fibrillation. *Int J Cardiol* Jul 21 2008;127:299-306.
10. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* Aug 2009;2:349-361.
11. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* Apr 2013;2:e004549.
12. Balt JC, Karadavut S, Mulder AA, Luermans JG, Wijffels MC, Boersma LV. Conduction recovery in patients with recurrent atrial fibrillation after pulmonary vein isolation using multi-electrode duty cycled radiofrequency ablation. *J Interv Card Electrophysiol* Aug 2013;37:197-204.

13. Callans DJ, Gerstenfeld EP, Dixit S, Zado E, Vanderhoff M, Ren JF, Marchlinski FE. Efficacy of repeat pulmonary vein isolation procedures in patients with recurrent atrial fibrillation. *J Cardiovasc Electrophysiol* Sep 2004;15:1050-1055.
14. Ouyang F, Antz M, Ernst S, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. *Circulation* Jan 18 2005;111:127-135.
15. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. *Heart Rhythm* Jun 2010;7:835-846.
16. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* May 7 2015;372:1812-1822.
17. Wolf RK, Schneeberger EW, Osterday R, Miller D, Merrill W, Flege JB, Jr., Gillinov AM. Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation. *J Thorac Cardiovasc Surg* Sep 2005;130:797-802.
18. Mehall JR, Kohut RM, Jr., Schneeberger EW, Taketani T, Merrill WH, Wolf RK. Intraoperative epicardial electrophysiologic mapping and isolation of autonomic ganglionic plexi. *Ann Thorac Surg* Feb 2007;83:538-541.
19. Pruitt JC, Lazzara RR, Dworkin GH, Badhwar V, Kuma C, Ebra G. Totally endoscopic ablation of lone atrial fibrillation: initial clinical experience. *Ann Thorac Surg* Apr 2006;81:1325-1330; discussion 1330-1321.
20. Blomström-Lundqvist C, Johansson B, Berglin E, Nilsson L, Jensen SM, Thelin S, Holmgren A, Edvardsson N, Källner G, Blomström P. A randomised double-blind study of epicardial left atrial cryoablation for permanent atrial fibrillation in patients undergoing mitral valve surgery - the SWEDish Multi-centre Atrial Fibrillation study (SWEDMAF)
21. Gillinov AM, Gelijns AC, Parides MK, et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med* Apr 9 2015;372:1399-1409.
22. Phan K, Phan S, Thiagalingam A, Medi C, Yan TD. Thoracoscopic surgical ablation versus catheter ablation for atrial fibrillation. *Eur J Cardiothorac Surg* May 23 2015.
23. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* Oct 07 2016;37:2893-2962.
24. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Wittteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* Sep 2013;34:2746-2751.
25. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* Feb 25 2014;129:837-847.
26. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation* Jun 23 2015;131:2176-2184.
27. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, Smith CJ. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke* Feb 2014;45:520-526.

28. Mairesse GH, Moran P, Van Gelder IC, et al. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electro-fisiología (SOLAECE). *Europace* Oct 1 2017;19:1589-1623.
29. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* Oct 1978;28:973-977.
30. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* Aug 1991;22:983-988.
31. Onalan O, Crystal E. Left atrial appendage exclusion for stroke prevention in patients with nonrheumatic atrial fibrillation. *Stroke* Feb 2007;38:624-630.
32. Lim HS, Willoughby SR, Schultz C, et al. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *J Am Coll Cardiol* Feb 26 2013;61:852-860.
33. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J* May 2013;34:1475-1480.
34. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* Sep 8 1998;98:946-952.
35. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *Eur Heart J* Apr 2013;34:1061-1067.
36. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med* May 1995;98:476-484.
37. Kotecha D, Holmes J, Krum H, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* Dec 20 2014;384:2235-2243.
38. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Am Heart J* Sep 2013;166:442-448.
39. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med* Jun 3 2014;160:760-773.
40. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* Jan 2014;174:107-114.
41. Steinberg BA, Kim S, Fonarow GC, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* May 2014;167:735-742 e732.
42. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* Oct 2000;36:1303-1309.
43. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Interv Card Electrophysiol* Jun 2000;4:369-382.

44. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol* Apr 2008;1:62-73.
45. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* Sep 3 1998;339:659-666.
46. Haissaguerre M, Jais P, Shah DC, Garrigue S, Takahashi A, Lavergne T, Hocini M, Peng JT, Roudaut R, Clementy J. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. *Circulation* Mar 28 2000;101:1409-1417.
47. Patterson E, Jackman WM, Beckman KJ, Lazzara R, Lockwood D, Scherlag BJ, Wu R, Po S. Spontaneous pulmonary vein firing in man: relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *J Cardiovasc Electrophysiol* Sep 2007;18:1067-1075.
48. Atenza F, Almendral J, Moreno J, et al. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: evidence for a reentrant mechanism. *Circulation* Dec 5 2006;114:2434-2442.
49. Kumagai K, Yasuda T, Tojo H, Noguchi H, Matsumoto N, Nakashima H, Gondo N, Saku K. Role of rapid focal activation in the maintenance of atrial fibrillation originating from the pulmonary veins. *Pacing Clin Electrophysiol* Nov 2000;23:1823-1827.
50. Brundel BJ, Henning RH, Kampinga HH, Van Gelder IC, Crijns HJ. Molecular mechanisms of remodeling in human atrial fibrillation. *Cardiovasc Res* May 2002;54:315-324.
51. Wijffels MC, Kirchhof CJ, Dorland R, Allesie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* Oct 1 1995;92:1954-1968.
52. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J* Jul 1959;58:59-70.
53. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol* Aug 14 2012;60:628-636.
54. Shivkumar K, Ellenbogen KA, Hummel JD, Miller JM, Steinberg JS. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: first multicenter experience of focal impulse and rotor modulation (FIRM) ablation. *J Cardiovasc Electrophysiol* Dec 2012;23:1277-1285.
55. Po SS, Scherlag BJ, Yamanashi WS, Edwards J, Zhou J, Wu R, Geng N, Lazzara R, Jackman WM. Experimental model for paroxysmal atrial fibrillation arising at the pulmonary vein-atrial junctions. *Heart Rhythm* Feb 2006;3:201-208.
56. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. *Heart Rhythm* Jun 2005;2:624-631.
57. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *J Am Coll Cardiol* Jun 18 2003;41:2197-2204.

58. Kistler PM, Sanders P, Dodic M, Spence SJ, Samuel CS, Zhao C, Charles JA, Edwards GA, Kalman JM. Atrial electrical and structural abnormalities in an ovine model of chronic blood pressure elevation after prenatal corticosteroid exposure: implications for development of atrial fibrillation. *Eur Heart J* Dec 2006;27:3045-3056.
59. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol* Feb 26 2008;51:802-809.
60. Hoit BD, Shao Y, Gabel M, Walsh RA. Left atrial mechanical and biochemical adaptation to pacing induced heart failure. *Cardiovasc Res* Apr 1995;29:469-474.
61. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE. Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation* Feb 1976;53:273-279.
62. Shi Y, Ducharme A, Li D, Gaspo R, Nattel S, Tardif JC. Remodeling of atrial dimensions and emptying function in canine models of atrial fibrillation. *Cardiovasc Res* Nov 2001;52:217-225.
63. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* Jul 6 1999;100:87-95.
64. Shinagawa K, Shi YF, Tardif JC, Leung TK, Nattel S. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. *Circulation* Jun 4 2002;105:2672-2678.
65. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, Packer DL, Hammill SC, Shen WK, Gersh BJ. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* Jun 19 2007;115:3050-3056.
66. Aksnes TA, Schmieder RE, Kjeldsen SE, Ghani S, Hua TA, Julius S. Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial). *Am J Cardiol* Mar 1 2008;101:634-638.
67. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* Nov 2005;26:2422-2434.
68. Kapa S, Venkatachalam KL, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: an elegant interaction and emerging concepts. *Cardiol Rev* Nov-Dec 2010;18:275-284.
69. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec* Feb 1997;247:289-298.
70. Hou Y, Scherlag BJ, Lin J, Zhang Y, Lu Z, Truong K, Patterson E, Lazzara R, Jackman WM, Po SS. Ganglionated plexi modulate extrinsic cardiac autonomic nerve input: effects on sinus rate, atrioventricular conduction, refractoriness, and inducibility of atrial fibrillation. *J Am Coll Cardiol* Jul 3 2007;50:61-68.
71. Scherlag BJ, Yamanashi W, Patel U, Lazzara R, Jackman WM. Autonomically induced conversion of pulmonary vein focal firing into atrial fibrillation. *J Am Coll Cardiol* Jun 7 2005;45:1878-1886.
72. Zhou J, Scherlag BJ, Edwards J, Jackman WM, Lazzara R, Po SS. Gradients of atrial refractoriness and inducibility of atrial fibrillation due to stimulation of ganglionated plexi. *J Cardiovasc Electrophysiol* Jan 2007;18:83-90.

73. Schauerte P, Scherlag BJ, Patterson E, Scherlag MA, Matsudaria K, Nakagawa H, Lazzara R, Jackman WM. Focal atrial fibrillation: experimental evidence for a pathophysiologic role of the autonomic nervous system. *J Cardiovasc Electrophysiol* May 2001;12:592-599.
74. Pappone C, Santinelli V, Manguso F, et al. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. *Circulation* Jan 27 2004;109:327-334.
75. Scherlag BJ, Po S. The intrinsic cardiac nervous system and atrial fibrillation. *Curr Opin Cardiol* Jan 2006;21:51-54.
76. Scanavacca M, Pisani CF, Hachul D, Lara S, Hardy C, Darrieux F, Trombetta I, Negrao CE, Sosa E. Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal atrial fibrillation. *Circulation* Aug 29 2006;114:876-885.
77. Hwang C, Wu TJ, Doshi RN, Peter CT, Chen PS. Vein of marshall cannulation for the analysis of electrical activity in patients with focal atrial fibrillation. *Circulation* Apr 4 2000;101:1503-1505.
78. Lin J, Scherlag BJ, Lu Z, Zhang Y, Liu S, Patterson E, Jackman WM, Lazzara R, Po SS. Inducibility of atrial and ventricular arrhythmias along the ligament of marshall: role of autonomic factors. *J Cardiovasc Electrophysiol* Sep 2008;19:955-962.
79. Katritsis D, Ioannidis JP, Anagnostopoulos CE, Sarris GE, Giazitzoglou E, Korovesis S, Camm AJ. Identification and catheter ablation of extracardiac and intracardiac components of ligament of Marshall tissue for treatment of paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* Jul 2001;12:750-758.
80. Hocini M, Shah AJ, Nault I, et al. Localized reentry within the left atrial appendage: arrhythmogenic role in patients undergoing ablation of persistent atrial fibrillation. *Heart Rhythm* Dec 2011;8:1853-1861.
81. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an under-recognized trigger site of atrial fibrillation. *Circulation* Jul 13 2010;122:109-118.
82. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* Feb 2010;137:263-272.
83. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* Nov 2010;138:1093-1100.
84. Fujino T, Yamashita T, Suzuki S, Sugiyama H, Sagara K, Sawada H, Aizawa T, Igarashi M, Yamazaki J. Characteristics of congestive heart failure accompanied by atrial fibrillation with special reference to tachycardia-induced cardiomyopathy. *Circ J* Jun 2007;71:936-940.
85. Calo L, De Ruvo E, Sette A, Sciarra L, Scioli R, Sebastiani F, Topai M, Iulianella R, Navone G, Liroy E, Gaita F. Tachycardia-induced cardiomyopathy: mechanisms of heart failure and clinical implications. *J Cardiovasc Med (Hagerstown)* Mar 2007;8:138-143.
86. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* Jun 7 2005;45:1832-1839.

87. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* Oct 7 1997;96:2455-2461.
88. Goldstone AB, Patrick WL, Cohen JE, Aribeana CN, Popat R, Woo YJ. Early surgical intervention or watchful waiting for the management of asymptomatic mitral regurgitation: a systematic review and meta-analysis. *Ann Cardiothorac Surg* May 2015;4:220-229.
89. Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, Wen MS, Chen WJ, Yeh YH, See LC. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. *Cardiovasc Diabetol* Aug 10 2014;13:123.
90. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* Nov 20 2013;310:2050-2060.
91. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* Feb 6 2007;49:565-571.
92. Holmqvist F, Guan N, Zhu Z, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* May 2015;169:647-654 e642.
93. Anselmino M, Matta M, D'Ascenzo F, et al. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* Dec 2014;7:1011-1018.
94. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* May 16 2012CD005049.
95. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* Sep 15 2017.
96. Slama R, Blondeau P, Aigueperse J, Cachera J, Degeorges M, Albou E. [Surgical creation of an auriculoventricular block and implantation of a stimulator in 2 cases of irreducible rhythm disorders]. *Arch Mal Coeur Vaiss* Mar 1967;60:406-422.
97. Cox JL, Schuessler RB, D'Agostino HJ, Jr., Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* Apr 1991;101:569-583.
98. Cox JL, Boineau JP, Schuessler RB, Jaquiss RD, Lappas DG. Modification of the maze procedure for atrial flutter and atrial fibrillation. I. Rationale and surgical results. *J Thorac Cardiovasc Surg* Aug 1995;110:473-484.
99. Ballaux PK, Geuzebroek GS, van Hemel NM, Kelder JC, Dossche KM, Ernst JM, Boersma LV, Wever EF, Brutel de la Riviere A, Defauw JJ. Freedom from atrial arrhythmias after classic maze III surgery: a 10-year experience. *J Thorac Cardiovasc Surg* Dec 2006;132:1433-1440.
100. Albage A, Johansson B, Kenneback G, Kallner G, Schersten H, Jideus L, Swedish Arrhythmia Surgery G. Long-Term Follow-Up of Cardiac Rhythm in 320 Patients After the Cox-Maze III Procedure for Atrial Fibrillation. *Ann Thorac Surg* Apr 2016;101:1443-1449.

101. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM, Malaisrie SC. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev* Aug 22 2016;CD011814.
102. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. *Circulation* Nov 21 2000;102:2619-2628.
103. Kurotobi T, Iwakura K, Inoue K, Kimura R, Okamura A, Koyama Y, Totsyoshima Y, Ito N, Fujii K. Multiple arrhythmogenic foci associated with the development of perpetuation of atrial fibrillation. *Circ Arrhythm Electrophysiol* Feb 2010;3:39-45.
104. Parkash R, Verma A, Tang AS. Persistent atrial fibrillation: current approach and controversies. *Curr Opin Cardiol* Jan 2010;25:1-7.
105. Saltman AE, Rosenthal LS, Francalancia NA, Lahey SJ. A completely endoscopic approach to microwave ablation for atrial fibrillation. *Heart Surg Forum* 2003;6:E38-41.
106. Bisleri G, Manzato A, Argenziano M, Vigilance DW, Muneretto C. Thoracoscopic epicardial pulmonary vein ablation for lone paroxysmal atrial fibrillation. *Europace* Mar 2005;7:145-148.
107. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* Feb 1996;61:755-759.
108. Bauer M, Hetzer R. Video-assisted thoracoscopic surgical treatment of lone atrial fibrillation. *Multimed Man Cardiothorac Surg* Jan 01 2009;2009:mmcts 2008 003848.
109. Probst J, Jideus L, Blomstrom P, Zemgulis V, Wassberg E, Lonnerholm S, Malmborg H, Blomstrom Lundqvist C. Thoracoscopic epicardial left atrial ablation in symptomatic patients with atrial fibrillation. *Europace* Oct 2016;18:1538-1544.
110. Krul SP, Driessen AH, van Boven WJ, Linnenbank AC, Geuzebroek GS, Jackman WM, Wilde AA, de Bakker JM, de Groot JR. Thoracoscopic video-assisted pulmonary vein antrum isolation, ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first results of a hybrid surgical-electrophysiological approach for atrial fibrillation. *Circ Arrhythm Electrophysiol* Jun 2011;4:262-270.
111. Wang JG, Xin M, Han J, Li Y, Luo TG, Wang J, Meng F, Meng X. Ablation in selective patients with long-standing persistent atrial fibrillation: medium-term results of the Dallas lesion set. *Eur J Cardiothorac Surg* Aug 2014;46:213-220.
112. Sirak JH, Schwartzman D. Interim results of the 5-box thoracoscopic maze procedure. *Ann Thorac Surg* Dec 2012;94:1880-1884.
113. Kasirajan V, Spradlin EA, Mormando TE, Medina AE, Ovadia P, Schwartzman DS, Gaines TE, Mumtaz MA, Downing SW, Ellenbogen KA. Minimally invasive surgery using bipolar radiofrequency energy is effective treatment for refractory atrial fibrillation. *Ann Thorac Surg* May 2012;93:1456-1461.
114. Weimar T, Vosseler M, Czesla M, Boscheinen M, Hemmer WB, Doll KN. Approaching a paradigm shift: endoscopic ablation of lone atrial fibrillation on the beating heart. *Ann Thorac Surg* Dec 2012;94:1886-1892.
115. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. *J Am Coll Cardiol* Jul 03 2012;60:54-61.

116. Providencia R, Lambiase PD, Srinivasan N, Ganesh Babu G, Bronis K, Ahsan S, Khan FZ, Chow AW, Rowland E, Lowe M, Segal OR. Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. *Circ Arrhythm Electrophysiol* Oct 2015;8:1017-1029.
117. Mohanty S, Gianni C, Mohanty P, et al. Impact of Rotor Ablation in Nonparoxysmal Atrial Fibrillation Patients: Results From the Randomized OASIS Trial. *J Am Coll Cardiol* Jul 19 2016;68:274-282.
118. Cox JL, Boineau JP, Schuessler RB, Ferguson TB, Jr., Cain ME, Lindsay BD, Corr PB, Kater KM, Lappas DG. Successful surgical treatment of atrial fibrillation. Review and clinical update. *JAMA* Oct 9 1991;266:1976-1980.
119. Henn MC, Lancaster TS, Miller JR, Sinn LA, Schuessler RB, Moon MR, Melby SJ, Maniar HS, Damiano RJ, Jr. Late outcomes after the Cox maze IV procedure for atrial fibrillation. *J Thorac Cardiovasc Surg* Nov 2015;150:1168-1176, 1178 e1161-1162.
120. Lall SC, Melby SJ, Voeller RK, Zierer A, Bailey MS, Guthrie TJ, Moon MR, Moazami N, Lawton JS, Damiano RJ, Jr. The effect of ablation technology on surgical outcomes after the Cox-maze procedure: a propensity analysis. *J Thorac Cardiovasc Surg* Feb 2007;133:389-396.
121. Obadia JF, el Farra M, Bastien OH, Lievre M, Martelloni Y, Chassignolle JF. Outcome of atrial fibrillation after mitral valve repair. *J Thorac Cardiovasc Surg* Aug 1997;114:179-185.
122. Saxena A, Kapoor J, Dinh DT, Smith JA, Shardey GC, Newcomb AE. Preoperative atrial fibrillation is an independent predictor of worse early and late outcomes after isolated coronary artery bypass graft surgery. *J Cardiol* Mar 2015;65:224-229.
123. Saxena A, Dinh DT, Reid CM, Smith JA, Shardey GC, Newcomb AE. Does preoperative atrial fibrillation portend a poorer prognosis in patients undergoing isolated aortic valve replacement? A multicentre Australian study. *Can J Cardiol* Jun 2013;29:697-703.
124. Jessurun ER, van Hemel NM, Defauw JJ, Brutel De La Riviere A, Stofmeel MA, Kelder JC, Kingma JH, Ernst JM. A randomized study of combining maze surgery for atrial fibrillation with mitral valve surgery. *J Cardiovasc Surg (Torino)* Feb 2003;44:9-18.
125. Albrecht A, Kalil RA, Schuch L, Abrahao R, Sant'Anna JR, de Lima G, Nesralla IA. Randomized study of surgical isolation of the pulmonary veins for correction of permanent atrial fibrillation associated with mitral valve disease. *J Thorac Cardiovasc Surg* Aug 2009;138:454-459.
126. Chevalier P, Leizorovicz A, Maureira P, et al. Left atrial radiofrequency ablation during mitral valve surgery: a prospective randomized multicentre study (SAFIR). *Arch Cardiovasc Dis* Nov 2009;102:769-775.
127. de Lima GG, Kalil RAK, Leiria TLL, Hatem DM, Kruse CL, Abrahao R, Sant'anna JRM, Prates PR, Nesralla IA. Randomized study of surgery for patients with permanent atrial fibrillation as a result of mitral valve disease. *The Annals of Thoracic Surgery* 2004;77:2089.
128. Doukas G, Samani NJ, Alexiou C, Oc M, Chin DT, Stafford PG, Ng LL, Spyt TJ. Left atrial radiofrequency ablation during mitral valve surgery for continuous atrial fibrillation: a randomized controlled trial. *JAMA* Nov 9 2005;294:2323-2329.

129. Srivastava V, Kumar S, Javali S, Rajesh TR, Pai V, Khandekar J, Agrawal N, Patwardhan AM. Efficacy of three different ablative procedures to treat atrial fibrillation in patients with valvular heart disease: a randomised trial. *Heart Lung Circ Jun 2008*;17:232-240.
130. Deneke T, Khargi K, Grewe PH, Laczkovics A, von Dryander S, Lawo T, Muller KM, Lemke B. Efficacy of an additional MAZE procedure using cooled-tip radiofrequency ablation in patients with chronic atrial fibrillation and mitral valve disease. A randomized, prospective trial. *Eur Heart J Apr 2002*;23:558-566.
131. Abreu Filho CAC, Lisboa LAF, Dallan LAO, Spina GS, Grinberg M, Scavavacca M, Sosa EA, Ramires JAF, Oliveira SA. Effectiveness of the Maze Procedure Using Cooled-Tip Radiofrequency Ablation in Patients With Permanent Atrial Fibrillation and Rheumatic Mitral Valve Disease. *Circulation August 30 2005*;112:1-20-25.
132. von Oppell UO, Masani N, O'Callaghan P, Wheeler R, Dimitrakakis G, Schiffelers S. Mitral valve surgery plus concomitant atrial fibrillation ablation is superior to mitral valve surgery alone with an intensive rhythm control strategy. *Eur J Cardiothorac Surg Apr 2009*;35:641-650.
133. Huffman MD, Malaisrie SC, Karmali KN. Concomitant Atrial Fibrillation Surgery for People Undergoing Cardiac Surgery. *JAMA Cardiol Mar 01 2017*;2:334-335.
134. Phan K, Xie A, Tian DH, Shaikhrezai K, Yan TD. Systematic review and meta-analysis of surgical ablation for atrial fibrillation during mitral valve surgery. *Ann Cardiothorac Surg Jan 2014*;3:3-14.
135. Joshibayev S, Bolatbekov B. Early and long-term outcomes and quality of life after concomitant mitral valve surgery, left atrial size reduction, and radiofrequency surgical ablation of atrial fibrillation. *Anatol J Cardiol Mar 23 2016*.
136. Forlani S, De Paulis R, Wolf LG, Greco R, Polisca P, Moscarelli M, Chiariello L. Conversion to Sinus Rhythm by Ablation Improves Quality of Life in Patients Submitted to Mitral Valve Surgery. *The Annals of Thoracic Surgery 2006*;81:863-867.
137. Gillinov AM, Bakaeen F, McCarthy PM, et al. Surgery for paroxysmal atrial fibrillation in the setting of mitral valve disease: a role for pulmonary vein isolation? *Ann Thorac Surg Jan 2006*;81:19-26; discussion 27-18.
138. Gillinov AM, Bhavani S, Blackstone EH, et al. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. *Ann Thorac Surg Aug 2006*;82:502-513; discussion 513-504.
139. Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a meta-analysis. *J Thorac Cardiovasc Surg May 2006*;131:1029-1035.
140. Onorati F, Mariscalco G, Rubino AS, Serraino F, Santini F, Musazzi A, Klersy C, Sala A, Renzulli A. Impact of lesion sets on mid-term results of surgical ablation procedure for atrial fibrillation. *J Am Coll Cardiol Feb 22 2011*;57:931-940.
141. Pappone C, Oreto G, Lamberti F, Vicedomini G, Loricchio ML, Shpun S, Rillo M, Calabro MP, Conversano A, Ben-Haim SA, Cappato R, Chierchia S. Catheter ablation of paroxysmal atrial fibrillation using a 3D mapping system. *Circulation Sep 14 1999*;100:1203-1208.
142. Robbins IM, Colvin EV, Doyle TP, Kemp WE, Loyd JE, McMahan WS, Kay GN. Pulmonary vein stenosis after catheter ablation of atrial fibrillation. *Circulation Oct 27 1998*;98:1769-1775.

143. Marrouche NF, Martin DO, Wazni O, et al. Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: impact on outcome and complications. *Circulation* Jun 3 2003;107:2710-2716.
144. Luik A, Radzewitz A, Kieser M, et al. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation* Oct 6 2015;132:1311-1319.
145. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* Jun 9 2016;374:2235-2245.
146. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* Jan 11 2011;57:160-166.
147. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* May 7 2013;61:1894-1903.
148. Scherr D, Khairy P, Miyazaki S, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol* Feb 2015;8:18-24.
149. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* Feb 2014;35:501-507.
150. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* Oct 25 2012;367:1587-1595.
151. Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace* Mar 2015;17:370-378.
152. Walfridsson H, Walfridsson U, Nielsen JC, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation: results on health-related quality of life and symptom burden. The MANTRA-PAF trial. *Europace* Feb 2015;17:215-221.
153. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency Ablation vs Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation: A Randomized Trial. *JAMA* June 1 2005;293:2634-2640.
154. Kuck KH, Hoffmann BA, Ernst S, Wegscheider K, Treszl A, Metzner A, Eckardt L, Lewalter T, Breithardt G, Willems S, Gap AFAC. Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol* Jan 2016;9:e003337.
155. Pappone C, Rosanio S, Augello G, et al. Mortality, Morbidity, and Quality of Life After Circumferential Pulmonary Vein Ablation for Atrial Fibrillation Outcomes From a Controlled Nonrandomized Long-Term Study. *J Am Coll Cardiol* 2003;42:185-197.
156. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* Jan 27 2010;303:333-340.

157. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* Dec 9 2008;118:2498-2505.
158. McClelland JH, Duke D, Reddy R. Preliminary results of a limited thoracotomy: new approach to treat atrial fibrillation. *J Cardiovasc Electrophysiol* Dec 2007;18:1289-1295.
159. Edgerton JR, Jackman WM, Mack MJ. Minimally invasive pulmonary vein isolation and partial autonomic denervation for surgical treatment of atrial fibrillation. *J Interv Card Electrophysiol* Dec 2007;20:89-93.
160. Matsutani N, Takase B, Ozeki Y, Maehara T, Lee R. Minimally invasive cardiothoracic surgery for atrial fibrillation: a combined Japan-US experience. *Circ J* Mar 2008;72:434-436.
161. Wylie JV, Jr., Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. *Heart Rhythm* May 2008;5:656-662.
162. Hu QM, Li Y, Xu CL, Han J, Zhang HB, Han W, Meng X. Analysis of risk factors for recurrence after video-assisted pulmonary vein isolation of lone atrial fibrillation--results of 5 years of follow-up. *J Thorac Cardiovasc Surg* Nov 2014;148:2174-2180.
163. Zheng S, Li Y, Han J, Zhang H, Zeng W, Xu C, Jia Y, Wang J, Guo K, Jiao Y, Meng X. Long-term results of a minimally invasive surgical pulmonary vein isolation and ganglionic plexi ablation for atrial fibrillation. *PLoS One* 2013;8:e79755.
164. Guo QZ, Zhu D, Bai ZX, Shi J, Shi YK, Guo YQ. A novel "box lesion" minimally invasive totally thoracoscopic surgical ablation for atrial fibrillation. *Ann Acad Med Singapore* Jan 2015;44:6-12.
165. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, Sandoval E, Calvo N, Brugada J, Kelder J, Wijffels M, Mont L. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation* Jan 3 2012;125:23-30.
166. Pokushalov E, Romanov A, Elesin D, Bogachev-Prokophiev A, Losik D, Bairamova S, Karaskov A, Steinberg JS. Catheter versus surgical ablation of atrial fibrillation after a failed initial pulmonary vein isolation procedure: a randomized controlled trial. *J Cardiovasc Electrophysiol* Dec 2013;24:1338-1343.
167. Wang S, Liu L, Zou C. Comparative study of video-assisted thoracoscopic surgery ablation and radiofrequency catheter ablation on treating paroxysmal atrial fibrillation: a randomized, controlled short-term trial. *Chin Med J (Engl)* 2014;127:2567-2570.
168. Kim HJ, Kim JS, Kim TS. Epicardial thoracoscopic ablation versus endocardial catheter ablation for management of atrial fibrillation: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* Jun 2016;22:729-737.
169. Saini A, Hu YL, Kasirajan V, Han FT, Khan MZ, Wolfe L, Gunda S, Koneru JN, Ellenbogen KA. Long-term outcomes of minimally invasive surgical ablation for atrial fibrillation: A single-center experience. *Heart Rhythm* Sep 2017;14:1281-1288.
170. De Maat GE, Pozzoli A, Scholten MF, Van Gelder IC, Blaauw Y, Mulder BA, Della Bella P, Alfieri OR, Benussi S, Mariani MA. Long-term results of surgical minimally invasive pulmonary vein isolation for paroxysmal lone atrial fibrillation. *Europace* May 2015;17:747-752.

171. Driessen AH, Berger WR, Chan Pin Yin DR, Piersma FR, Neefs J, van den Berg NW, Krul SP, van Boven WP, de Groot JR. Electrophysiologically Guided Thoracoscopic Surgery for Advanced Atrial Fibrillation: 5-Year Follow-up. *J Am Coll Cardiol Apr* 4 2017;69:1753-1754.
172. Sullivan M, Karlsson J. The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population. *J Clin Epidemiol Nov* 1998;51:1105-1113.
173. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care Jun* 1992;30:473-483.
174. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med Mar* 2 2006;354:934-941.
175. Cohen J. A power primer. *Psychol Bull Jul* 1992;112:155-159.
176. Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. *Circulation Nov* 1980;62:1054-1061.
177. Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, Haass M. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart Mar* 2002;87:235-241.
178. Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. The Necosad Study Group. *Am J Kidney Dis Apr* 1997;29:584-592.
179. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology Jan* 1998;27:209-212.
180. Komaroff AL, Fagioli LR, Doolittle TH, Gandek B, Gleit MA, Guerriero RT, Kornish RJ, 2nd, Ware NC, Ware JE, Jr., Bates DW. Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. *Am J Med Sep* 1996;101:281-290.
181. Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD, McGlynn EA, Ware JE, Jr. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *JAMA Aug* 18 1989;262:907-913.
182. Han FT, Kasirajan V, Kowalski M, Kiser R, Wolfe L, Kalahasty G, Shepard RK, Wood MA, Ellenbogen KA. Results of a minimally invasive surgical pulmonary vein isolation and ganglionic plexi ablation for atrial fibrillation: single-center experience with 12-month follow-up. *Circ Arrhythm Electrophysiol Aug* 2009;2:370-377.
183. Beyer E, Lee R, Lam BK. Point: Minimally invasive bipolar radiofrequency ablation of lone atrial fibrillation: early multicenter results. *J Thorac Cardiovasc Surg Mar* 2009;137:521-526.
184. Yilmaz A, Geuzebroek GS, Van Putte BP, Boersma LV, Sonker U, De Bakker JM, Van Boven WJ. Completely thoracoscopic pulmonary vein isolation with ganglionic plexus ablation and left atrial appendage amputation for treatment of atrial fibrillation. *Eur J Cardiothorac Surg Sep* 2010;38:356-360.
185. Edgerton JR, Brinkman WT, Weaver T, Prince SL, Culica D, Herbert MA, Mack MJ. Pulmonary vein isolation and autonomic denervation for the management of paroxysmal atrial fibrillation by a minimally invasive surgical approach. *J Thorac Cardiovasc Surg Oct* 2010;140:823-828.

186. Mehall JR, Kohut RM, Jr., Schneeberger EW, Merrill WH, Wolf RK. Absence of correlation between symptoms and rhythm in "symptomatic" atrial fibrillation. *Ann Thorac Surg Jun 2007*;83:2118-2121.
187. Krul SP, Driessen AH, Zwinderman AH, van Boven WJ, Wilde AA, de Bakker JM, de Groot JR. Navigating the mini-maze: systematic review of the first results and progress of minimally-invasive surgery in the treatment of atrial fibrillation. *Int J Cardiol Jun 5 2013*;166:132-140.
188. Wudel JH, Chaudhuri P, Hiller JJ. Video-assisted epicardial ablation and left atrial appendage exclusion for atrial fibrillation: extended follow-up. *Ann Thorac Surg Jan 2008*;85:34-38.
189. Castella M, Pereda D, Mestres CA, Gomez F, Quintana E, Mulet J. Thoracoscopic pulmonary vein isolation in patients with atrial fibrillation and failed percutaneous ablation. *J Thorac Cardiovasc Surg Sep 2010*;140:633-638.
190. Tzou WS, Marchlinski FE, Zado ES, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol Jun 2010*;3:237-242.
191. Wolf RK. Treatment of lone atrial fibrillation: minimally invasive pulmonary vein isolation, partial cardiac denervation and excision of the left atrial appendage. *Ann Cardiothorac Surg Jan 2014*;3:98-104.
192. Edgerton JR, Edgerton ZJ, Weaver T, Reed K, Prince S, Herbert MA, Mack MJ. Minimally invasive pulmonary vein isolation and partial autonomic denervation for surgical treatment of atrial fibrillation. *Ann Thorac Surg Jul 2008*;86:35-38; discussion 39.
193. Zheng S, Zeng Y, Li Y, Han J, Zhang H, Meng X. Active ganglionated plexi is a predictor of atrial fibrillation recurrence after minimally invasive surgical ablation. *J Card Surg Mar 2014*;29:279-285.
194. Zhou Q, Hou Y, Yang S. A meta-analysis of the comparative efficacy of ablation for atrial fibrillation with and without ablation of the ganglionated plexi. *Pacing Clin Electrophysiol Dec 2011*;34:1687-1694.
195. Kampaktsis PN, Oikonomou EK, D YC, Cheung JW. Efficacy of ganglionated plexi ablation in addition to pulmonary vein isolation for paroxysmal versus persistent atrial fibrillation: a meta-analysis of randomized controlled clinical trials. *J Interv Card Electrophysiol Sep 08 2017*.
196. Driessen AHG, Berger WR, Krul SPJ, van den Berg NWE, Neefs J, Piersma FR, Chan Pin Yin D, de Jong J, van Boven WP, de Groot JR. Ganglion Plexus Ablation in Advanced Atrial Fibrillation: The AFACT Study. *J Am Coll Cardiol Sep 13 2016*;68:1155-1165.
197. Sakamoto S, Schuessler RB, Lee AM, Aziz A, Lall SC, Damiano RJ, Jr. Vagal denervation and reinnervation after ablation of ganglionated plexi. *J Thorac Cardiovasc Surg Feb 2010*;139:444-452.
198. Romanov A, Pokushalov E, Elesin D, et al. Effect of left atrial appendage excision on procedure outcome in patients with persistent atrial fibrillation undergoing surgical ablation. *Heart Rhythm Sep 2016*;13:1803-1809.
199. Verma A, Kilicaslan F, Pisano E, et al. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation Aug 2 2005*;112:627-635.
200. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, Neven K, Kokturk B, Konstantinidou M, Metzner A, Fuernkranz A, Kuck KH. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation Dec 7 2010*;122:2368-2377.

201. Sauer WH, McKernan ML, Lin D, Gerstenfeld EP, Callans DJ, Marchlinski FE. Clinical predictors and outcomes associated with acute return of pulmonary vein conduction during pulmonary vein isolation for treatment of atrial fibrillation. *Heart Rhythm* Sep 2006;3:1024-1028.
202. Wang J, Li Y, Shi J, Han J, Xu C, Ma C, Meng X. Minimally invasive surgical versus catheter ablation for the long-lasting persistent atrial fibrillation. *PLoS One* 2011;6:e22122.
203. De Maat GE, Van Gelder IC, Rienstra M, Quast AF, Tan ES, Wiesfeld AC, Pozzoli A, Mariani MA. Surgical vs. transcatheter pulmonary vein isolation as first invasive treatment in patients with atrial fibrillation: a matched group comparison. *Europace* Jan 2014;16:33-39.
204. Fink T, Schluter M, Heeger CH, et al. Stand-Alone Pulmonary Vein Isolation Versus Pulmonary Vein Isolation With Additional Substrate Modification as Index Ablation Procedures in Patients With Persistent and Long-Standing Persistent Atrial Fibrillation: The Randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation). *Circ Arrhythm Electrophysiol* Jul 2017;10.
205. Haldar SK, Jones DG, Bahrami T, et al. Catheter ablation vs electrophysiologically guided thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: The CASA-AF Study. *Heart Rhythm* Nov 2017;14:1596-1603.
206. La Meir M, Gelsomino S, Luca F, Pison L, Parise O, Colella A, Gensini GF, Crijns H, Wellens F, Maessen JG. Minimally invasive surgical treatment of lone atrial fibrillation: early results of hybrid versus standard minimally invasive approach employing radiofrequency sources. *Int J Cardiol* Aug 20 2013;167:1469-1475.
207. Je HG, Shuman DJ, Ad N. A systematic review of minimally invasive surgical treatment for atrial fibrillation: a comparison of the Cox-Maze procedure, beating-heart epicardial ablation, and the hybrid procedure on safety and efficacy. *Eur J Cardiothorac Surg* Oct 2015;48:531-540; discussion 540-531.
208. Shi LZ, Heng R, Liu SM, Leng FY. Effect of catheter ablation versus anti-arrhythmic drugs on atrial fibrillation: A meta-analysis of randomized controlled trials. *Exp Ther Med* Aug 2015;10:816-822.
209. Lonnerholm S, Blomstrom P, Nilsson L, Oxelbark S, Jideus L, Blomstrom-Lundqvist C. Effects of the maze operation on health-related quality of life in patients with atrial fibrillation. *Circulation* Jun 6 2000;101:2607-2611.
210. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* Mar 1993;31:247-263.
211. Nasso G, Bonifazi R, Del Prete A, Del Prete G, Lopriore V, Bartolomucci F, Calafiore AM, Speziale G. Long-term results of ablation for isolated atrial fibrillation through a right minithoracotomy: toward a rational revision of treatment protocols. *J Thorac Cardiovasc Surg* Aug 2011;142:e41-46.
212. Driessen AHG, Berger WR, Bierhuizen MFA, Piersma FR, van den Berg NWE, Neefs J, Krul SPJ, van Boven WP, de Groot JR. Quality of life improves after thoracoscopic surgical ablation of advanced atrial fibrillation: Results of the Atrial Fibrillation Ablation and Autonomic Modulation via Thoracoscopic Surgery (AFACT) study. *J Thorac Cardiovasc Surg* Sep 27 2017.
213. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, Morillo CA, Khaykin Y, Birnie D. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. *JAMA Intern Med* Jan 28 2013;173:149-156.

214. Buber J, Luria D, Sternik L, Raanani E, Feinberg MS, Goldenberg I, Nof E, Gurevitz O, Eldar M, Glikson M, Kuperstein R. Left atrial contractile function following a successful modified Maze procedure at surgery and the risk for subsequent thromboembolic stroke. *J Am Coll Cardiol* Oct 04 2011;58:1614-1621.
215. Lonnerholm S, Blomstrom P, Nilsson L, Blomstrom-Lundqvist C. Atrial size and transport function after the Maze III procedure for paroxysmal atrial fibrillation. *Ann Thorac Surg* Jan 2002;73:107-111.
216. Lonnerholm S, Blomstrom P, Nilsson L, Blomstrom-Lundqvist C. Long-term effects of the maze procedure on atrial size and mechanical function. *Ann Thorac Surg* Mar 2008;85:916-920.
217. Zhuang Y, Yong YH, Chen ML. Updating the evidence for the effect of radiofrequency catheter ablation on left atrial volume and function in patients with atrial fibrillation: a meta-analysis. *JRSM Open* Mar 2014;5:2054270414521185.
218. Kou S, Caballero L, Dulgheru R, et al. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. *Eur Heart J Cardiovasc Imaging* Jun 2014;15:680-690.
219. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* Mar 2015;16:233-270.
220. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. *Eur J Cardiothorac Surg* May 2015;47:847-854.
221. Lee R, Vassallo P, Kruse J, Malaisrie SC, Rigolin V, Andrei AC, McCarthy P. A randomized, prospective pilot comparison of 3 atrial appendage elimination techniques: Internal ligation, stapled excision, and surgical excision. *J Thorac Cardiovasc Surg* Oct 2016;152:1075-1080.
222. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol* Sep 09 2008;52:924-929.
223. Aryana A, Singh SK, Singh SM, O'Neill PG, Bowers MR, Allen SL, Lewandowski SL, Viera EC, d'Avila A. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm* Jul 2015;12:1431-1437.
224. Whitlock R, Healey J, Vincent J, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann Cardiothorac Surg* Jan 2014;3:45-54.
225. Johansson B, Bech-Hanssen O, Berglin E, Blomstrom P, Holmgren A, Jensen SM, Kallner G, Nilsson L, Thelin S, Karlsson T, Edvardsson N, Blomstrom-Lundqvist C. Atrial function after left atrial epicardial cryoablation for atrial fibrillation in patients undergoing mitral valve surgery. *J Interv Card Electrophysiol* Jan 2012;33:85-91.
226. Badhwar V, Rankin JS, Ad N, Grau-Sepulveda M, Damiano RJ, Gillinov AM, McCarthy PM, Thourani VH, Suri RM, Jacobs JP, Cox JL. Surgical Ablation of Atrial Fibrillation in the United States: Trends and Propensity Matched Outcomes. *Ann Thorac Surg* Aug 2017;104:493-500.

Acta Universitatis Upsaliensis

*Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 1418*

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-338097



ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2018