Outcomes and safety of new techniques for pulmonary vein isolation in patients with paroxysmal and persistent atrial fibrillation

A study based on randomised trials and registries

DAVID MÖRTSELL
Abstract

Atrial fibrillation (AF) is a common disease with a high prevalence in the adult population. Treatment of AF encompasses antiarrhythmic drugs and catheter ablation to reduce symptoms. The aim of this thesis was to study how to best alleviate symptoms of AF in a safe and efficient way comparing pharmacological treatment and the two dominating catheter ablation techniques, cryoballoon (CRYO) ablation and point-by-point radiofrequency (RF) ablation.

Quality of life improved more for those AF patients randomised to treatment with catheter ablation compared to those treated with antiarrhythmic medication after 12 months of follow up (n=155).

We evaluated a proposed optimised CRYO ablation protocol and randomised 140 patients to a single cryoballoon application per vein guided by a mapping catheter (Single cryo) or two cryoballoon applications (Routine). Acute pulmonary vein isolation rate did not differ. Procedure time decreased by 19 minutes with a lower complication rate in the Single cryo-arm. Freedom from AF after one procedure at 12 months did not differ; 73.9.0% (Single cryo) versus 71.4% (Routine).

CRYO ablation was also assessed in persistent AF and paroxysmal AF. Freedom from arrhythmia recurrence was lower after a single ablation in persistent AF (64.9%) compared with paroxysmal AF (82.2%) after 12 months. However, the reduction of AF symptoms and quality of life was excellent in both groups and did not differ after 12 months.

Patients undergoing their first AF ablation with CRYO or RF were included in a registry study. After 12 months, freedom from AF was equal irrespective of AF type, but there was a lower re-ablation rate and need for continued antiarrhythmic drug treatment after CRYO ablation. Procedure duration was reduced by 40 minutes with CRYO and complication rates did not differ.

In conclusion, catheter ablation reduces AF symptoms more than antiarrhythmic drugs and cryoballoon ablation can be further optimised with reduced procedure times and improved safety. Cryoballoon ablation is as efficacious as RF ablation as a first-line therapy in both paroxysmal and persistent AF and the lower re-ablation rates and shorter procedure times may have important clinical implications when choosing AF ablation technique.

Keywords: atrial fibrillation, antiarrhythmic drugs, ablation, cryoballoon, radiofrequency, pulmonary vein isolation, quality of life, arrhythmia monitoring, implantable cardiac monitor, atrial fibrillation burden, health economics

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

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urn:nbn:se:uu:diva-363259 (http://urn.kb.se/resolve?urn=nbn:se:uu:diva-363259)
“Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly wherever and to whatever abysses nature leads, or you shall learn nothing. I have only begun to learn content and peace of mind since I have resolved at all risks to do this.”

Thomas Huxley, Life and Letters of Thomas Henry Huxley - Volume 1

“The most beautiful thing we can experience is the mysterious. It is the source of all true art and all science. He to whom this emotion is a stranger, who can no longer pause to wonder and stand rapt in awe, is as good as dead: his eyes are closed.”

Albert Einstein

To my beloved wife Emelie, who taught me humility and to enjoy the mysteries in life.
List of Papers

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

I. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation - a randomized clinical trial with general health as primary outcome and atrial fibrillation burden assessed by an implantable cardiac monitor

Carina Blomström-Lundqvist, Sigfus Gizurarson, Jonas Schwieler, Steen M. Jensen, Lennart Bergfeldt, Göran Kennebäck, Aigars Rubulis, Helena Malmborg, S. Pekka Raatikainen, Stefan Lönnerholm, Niklas Höglund, David Mörtsell

Submitted

II. Cryoballoon versus radiofrequency ablation for atrial fibrillation – a study of outcome and safety based on the ESC-EHRA atrial fibrillation ablation long-term registry and the Swedish Catheter ablation registry

David Mörtsell, Elena Arbelo, Nikolaos Dagres, Josep Brugada, Cecile Laroche, Serge A Trines, Helena Malmborg, Niklas Höglund, Luigi Tavazzi, Evgeny Pokushalov, Giuseppe Stabile, Carina Blomström-Lundqvist

Published November 2018 in Europace

III. Acute and long-term efficacy and safety with a single cryoballoon application as compared with the standard dual application strategy: a prospective randomized study using the second-generation cryoballoon for pulmonary vein isolation in patients with symptomatic atrial fibrillation

David Mörtsell, Helena Malmborg, Stefan Lönnerholm, Victoria Jansson, Carina Blomström-Lundqvist

Published February 2018 in Europace
IV. Clinical outcome of the 2nd generation cryoballoon for pulmonary vein isolation in patients with persistent atrial fibrillation – a sub-study of the randomized trial evaluating single versus dual cryoballoon applications

David Mörtsell, Victoria Jansson, Helena Malmborg, Stefan Lönnerholm, Carina Blomström-Lundqvist

Accepted for publication in International Journal of Cardiology

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## Contents

Introduction...............................................................................................11  
  History of atrial fibrillation.................................................................11  
  Mechanisms..........................................................................................12  
Prevalence, symptoms and comorbidity.................................................12  
Rate control therapy..............................................................................14  
Rhythm control therapy.........................................................................15  
  Pharmacological therapy.....................................................................15  
  Catheter ablation - pulmonary vein isolation.................................15  
  Catheter ablation beyond pulmonary vein isolation......................19  
Conclusion of introduction....................................................................20

Aims .........................................................................................................21  
  Study I..................................................................................................21  
  Study II.................................................................................................21  
  Study III................................................................................................22  
  Study IV...............................................................................................22

Material and methods ................................................................................23  
  Patient selection....................................................................................23  
  Study design .........................................................................................24  
  Antiarrhythmic drug treatment..............................................................25  
  Ablation procedure................................................................................26  
  Blood samples and biomarkers..............................................................28  
  Follow up..............................................................................................29  
  Quality of life and symptom questionnaires...........................................32  
  Complications........................................................................................33  
  Statistics...............................................................................................33

Main results...............................................................................................37  
  Study I..................................................................................................37  
  Study II..................................................................................................40  
  Study III..................................................................................................43  
  Study IV...............................................................................................46
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD</td>
<td>Antiarrhythmic drug</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>bpm</td>
<td>beats per minute</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>CT</td>
<td>Computer Tomography</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>LA</td>
<td>Left atrium</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>ms</td>
<td>milliseconds</td>
</tr>
<tr>
<td>PV</td>
<td>Pulmonary vein</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
</tbody>
</table>
Introduction

History of atrial fibrillation

Atrial fibrillation (AF) was first reported in 1909 by the renowned British cardiologist, Sir Thomas Lewis, in the British Medical Journal. It was then characterized as a common medical problem with irregular heartbeats often in conjunction a diseased stenotic mitral valve(1).

Electrocardiographic (ECG) recording of the cardiac activity was at this time recently invented and AF defined as an irregular electric pattern arising from the “auricles” of the heart(1). The pathophysiology of AF is a complex and in large parts unknown process. The normal heart rhythm consists of an atrial “pacemaker”, in fact a group of cells in the upper part of the right atrium with spontaneous electrical activity. This phenomenon is called automaticity and this group of atrial myocytes is called the sinus node. Electrical activation in the heart thus starts in the sinus node and is then spread over both right and left atria. A structure called the atrioventricular node connects the atria and the ventricles. The His-Purkinje system are myocytes functioning as electrical conductors. Via dedicated fascicles of the Purkinje-fibres, activation is then spread to the right and left ventricle.

In AF, the organized atrial electrical pattern called sinus rhythm, is substituted by a chaotic multifocal activation of the atria. This pattern is chaotic on surface ECG and the rapid firing typically exceeds 350 beats per minute. The atrioventricular node however does not conduct electric activation at this rate, thus most AF waves are blocked and typically an irregular ventricular response with a moderately elevated resting heart rate is seen.

The multiple-wavelet hypothesis presented already in the 60’s proposes that AF consists of electrical wave fronts that fractionate when they are divided by islets of refractory tissue generating new multiple wavelets acting as the mechanism for perpetuation(2). Multiple interacting wavelets will sustain the arrhythmia as long as the number of wavelets does not fall beneath a critical level(3). The mass and size of the atrium seems important, as more refractory tissue and atrial volume promotes a larger number of wavelets. Indeed, atrial size is predictive of the risk of developing AF and progression to longer and persistent bouts of AF(4).

The wavelet theory gained large support and was the theoretical basis for AF surgery first introduced in the late 80’s. The Cox maze procedure(5) can schematically be described as a surgical way of dividing the fibrillating atria
into smaller islets of atrial tissue electrically isolated from each other, thus stopping wavelet conduction and enforcing a regular atrial pattern directed from the right atrium to the atrioventricular node. Further modifications and details of the Cox maze procedure (6,7), the current Cox IV procedure (8) and thoracoscopic epicardial AF ablation (9,10) are beyond the scope of this thesis, but remain therapeutic options for highly selected symptomatic AF patients, often when other therapies have failed.

Mechanisms

Invasive electrophysiological investigation of the heart had already in the 80’s developed to be a minimally invasive percutaneous technique with catheters advanced to the heart via the central veins (typically femoral, subclavian or jugular veins). Ablation treatment with radiofrequency energy causing heating and local scarring was already established in the 90’s for treatment of arrhythmias such as accessory pathways (11). In 1998, Dr Michel Haissaguerre, showed that initiation of AF is dependent on a triggering electrical activity, most commonly arising from myocytes in the pulmonary veins (PV) (12). Both triggering activity, automaticity and local re-entry in one or several PVs can both initiate and play a part in perpetuation of AF (13,14). These veins transport saturated blood back to the heart from the lungs and typically four separate veins connect to the left atrium. Isolation of PVs showing electrical activity during catheterisation was initially tried as an ablation endpoint for AF but led to a high recurrence rate of AF with multiple catheterisation sessions identifying other triggering sites predominantly in PVs that were silent in the previous sessions (12). Complete pulmonary vein isolation (PVI) and a rather wide area circumferential ablation of the atrial tissue, thus encircling the PV’s (15) was subsequently established as a primary endpoint for catheter-based treatment of atrial fibrillation. In the absolute majority of patients, relapse of AF after ablation is associated with reconnection of one or more PV’s (16) and today PVI remains the cornerstone of a catheter based AF ablation (17).

Prevalence, symptoms and comorbidity

AF is a common disease with a reported prevalence of 0.4-1% in earlier studies (18,19), but the prevalence was higher at 2.9% of the entire adult population when accounting for all types of AF in a Swedish study (20). AF is one of the main causes of visits to the emergency departments, the number of emergency room visits are increasing and thus also health costs (21). Symptoms of AF include palpitations, shortness of breath, fatigue, light-headedness or dizziness, lack of energy during exertion of exercise and sometimes anxiety. The
degree of symptoms vary considerably and AF can be totally asymptomatic in more than a third of all patients; women are more often symptomatic than men(22). Symptoms of AF can be quantified in various ways which is covered more in detail in the Method section below. The most common AF symptom variable reported in trials however, is the European Heart Rhythm Association scale which was initially a four grade scale introduced in 2010(23) (table 1) but later modified with a subdivision of score 2 (24).

Table 1. **EHRA score of AF-related symptoms**

<table>
<thead>
<tr>
<th>EHRA class</th>
<th>Symptoms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>AF without any symptoms</td>
</tr>
<tr>
<td>II</td>
<td>Mild</td>
<td>Normal daily activity not affected</td>
</tr>
<tr>
<td>III</td>
<td>Severe</td>
<td>Normal daily activity affected</td>
</tr>
<tr>
<td>IV</td>
<td>Disabling</td>
<td>Normal daily activity discontinued</td>
</tr>
</tbody>
</table>

EHRA= European Heart Rhythm Association; AF=atrial fibrillation

Furthermore, AF is recognized as a common finding in patients with other characteristics/conditions (table 2) and symptoms can be accentuated i.e. in the presence of comorbidities such as structural heart disease.

Table 2. **Conditions independently associated with atrial fibrillation**

<table>
<thead>
<tr>
<th>Characteristic/condition</th>
<th>AF association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old age(25)</td>
<td>HR:</td>
</tr>
<tr>
<td>60-69 years</td>
<td>4.98 (95% CI 3.49-7.10)</td>
</tr>
<tr>
<td>70-79 years</td>
<td>7.35 (95% CI 5.28-10.2)</td>
</tr>
<tr>
<td>80-89 years</td>
<td>9.33 (95% CI 6.68-13.0)</td>
</tr>
<tr>
<td>Hypertension(25)</td>
<td>HR 1.32 (95% CI 1.08-1.60)</td>
</tr>
<tr>
<td>Heart failure(25)</td>
<td>HR 1.43 (95% CI 0.85-2.40)</td>
</tr>
<tr>
<td>Valvular disease(26)</td>
<td>RR 2.42 (95% CI 1.62-3.60)</td>
</tr>
<tr>
<td>Myocardial infarction(25)</td>
<td>HR 1.46 (95% CI 1.07-1.98)</td>
</tr>
<tr>
<td>Thyroid dysfunction(27)</td>
<td>HR:</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.23 (95% CI 0.77-1.97)</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>RR 1.31 (95% CI 1.19-1.44)</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>RR 1.42 (95% CI 1.22-1.63)</td>
</tr>
<tr>
<td>Diabetes mellitus(25)</td>
<td>HR 1.25 (95% CI 0.98-1.60)</td>
</tr>
<tr>
<td>Obesity(25,28)</td>
<td>HR:</td>
</tr>
<tr>
<td>Overweight (BMI 25-30 kg/m²)</td>
<td>1.13 (95% CI 0.87-1.46)</td>
</tr>
<tr>
<td>Obese (BMI ≥ 31 kg/m²)</td>
<td>1.37 (95% CI 1.05-1.78)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea(29)</td>
<td>HR 2.18 (95% CI 1.34-3.54)</td>
</tr>
<tr>
<td>Smoking(30)</td>
<td>HR:</td>
</tr>
<tr>
<td>Former</td>
<td>1.32 (95% CI 1.10-1.57)</td>
</tr>
<tr>
<td>Current</td>
<td>2.05 (95% CI 1.71-2.47)</td>
</tr>
</tbody>
</table>
Chronic obstructive pulmonary disease(31)  
<table>
<thead>
<tr>
<th>Condition</th>
<th>RR:</th>
<th>CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 60-80%</td>
<td>1.28 (95% CI 0.79-2.06)</td>
<td></td>
</tr>
<tr>
<td>FEV1 &lt; 60%</td>
<td>2.53 (95% CI 1.45-4.42)</td>
<td></td>
</tr>
</tbody>
</table>

Chronic kidney disease(32)  
<table>
<thead>
<tr>
<th>Stage</th>
<th>OR:</th>
<th>CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 or 2</td>
<td>2.67 (95% CI 2.04-3.48)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>1.68 (95% CI 1.26-2.24)</td>
<td></td>
</tr>
<tr>
<td>Stage 4 or 5</td>
<td>3.52 (95% CI 1.73-7.15)</td>
<td></td>
</tr>
</tbody>
</table>

Alcohol use(33)  
<table>
<thead>
<tr>
<th>Drinks/week</th>
<th>RR:</th>
<th>CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6 drinks/week</td>
<td>1.01 (95% CI 0.94-1.09)</td>
<td></td>
</tr>
<tr>
<td>7-14 drinks/week</td>
<td>1.07 (95% CI 0.98-1.17)</td>
<td></td>
</tr>
<tr>
<td>15-21 drinks/week</td>
<td>1.14 (95% CI 1.01-1.28)</td>
<td></td>
</tr>
<tr>
<td>&gt; 21 drinks/week</td>
<td>1.39 (95% CI 1.22-1.58)</td>
<td></td>
</tr>
</tbody>
</table>

Exercise(34)  
<table>
<thead>
<tr>
<th>Days/week</th>
<th>RR:</th>
<th>CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exercise</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 day/week</td>
<td>0.90 (95% CI 0.68-1.20)</td>
<td></td>
</tr>
<tr>
<td>1-2 days/week</td>
<td>1.09 (95% CI 0.95-1.26)</td>
<td></td>
</tr>
<tr>
<td>3-4 days/week</td>
<td>1.04 (95% CI 0.91-1.19)</td>
<td></td>
</tr>
<tr>
<td>5-7 days/week</td>
<td>1.20 (95% CI 1.02-1.41)</td>
<td></td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; BMI=body mass index; CI=confidence interval; FEV1=forced expiratory volume in 1 second; HR=hazard ratio; OR=odds ratio; RR=risk ratio

AF in a patient with a structurally normal heart and no comorbidities was previously often called “lone atrial fibrillation” or “idiopathic atrial fibrillation” which amounted to approximately 30% of all newly diagnosed patients(35). However, the list of conditions associated with AF in table 2 is by no means exhaustive. New risk factors and associated conditions are emerging, i.e. atrial conduction delay, left ventricular diastolic dysfunction, genetic factors, subclinical atherosclerosis, inflammation, pathological pulse pressure, increased birthweight and excessive caffeine intake. The term “lone atrial fibrillation” should rather be abandoned in this era where further imaging techniques and other diagnostic means increase our knowledge of the pathology in AF at an explosive rate(36). Diagnosing comorbidities and treating them accordingly is paramount when assessing a patient with AF(37).

**Rate control therapy**

AF means loss of atrial contraction and thus diminished atrial contribution to ventricular filling resulting in 20-30% reduction of cardiac output(38). Fast and irregular heart rate can reduce cardiac output further(39). Controlling the ventricular rate is baseline therapy for any AF patient(37). Monotherapy or a combination of digoxin, a betablocker or a calcium channel blocker can control ventricular heart rate and reduce AF symptoms(40). Studies comparing
pharmacological rate control versus medication or ablation aiming to convert and keep the patients in sinus rhythm (rhythm control therapy) has so far been neutral for outcomes such as stroke or mortality, whereas symptoms of AF and quality of life is further improved by rhythm control(41–44). The optimal heart rate is poorly studied but current guidelines that indicate a resting heart rate < 110 bpm constitutes adequate rate control(37). When pharmacological rate control fails, implantation of a pacemaker and performing atrioventricular node ablation is a simple and safe procedure for selected patients(45).

**Rhythm control therapy**

**Pharmacological therapy**

Class I and III drugs according to the Vaughn-Williams classification of anti-arrhythmic drugs(46,47) can convert AF back to sinus rhythm and maintain normal rhythm. Rhythm control drugs for AF are now abundant, but the most common ones for long-term medication aiming to maintain sinus rhythm are flecainide, disopyramide, propaphenone, sotalol, dronedarone and amiodarone(48). Failures of antiarrhythmic drugs, disease progression with more frequent and longer bouts of AF, side effects and especially risk of proarrhythmic effects(49) are the reason why a lot of research has been directed into a more profound understanding of the disease mechanism and possible invasive more curative treatments.

**Catheter ablation - pulmonary vein isolation**

**RF point-by-point**

Creation of overlapping lesions with a focal ablation catheter aiming to achieve PVI is now much easier than in the early work of Haissaguerre et al(12). A procedure is typically guided by preoperative radiology to assess left atrial and PV anatomy, usually a computer tomography of the heart. A mapping system able to record the exact position of a catheter inside the heart and record electrical signals is used. This includes equipment able to interpret small changes of impedance and/or changes in a magnetic field which is created around the thorax of the patient. The physician introduces at least one catheter to the left atrium and creates a three-dimensional map of the atrium and the PV orifices. The preoperative radiological data is used to guide the physician and can also be integrated into the map created with the catheter.

Ablation is subsequently performed by applying radiofrequency (RF) energy with a focal catheter creating heating of the tissue and scar formation. Early experiences of RF ablation in the PVs was reported to be effective but resulted in a high rate of PV stenosis(50). The catheter is today moved around the orifices of the pulmonary veins and a continuous line of ablated tissue
creates a line isolating the PV from the atrium. Typically, this is done by ablating left atrial tissue outside the PVs and creating a long circumferential line isolating the right and left PV’s in pairs, so called wide area circumferential ablation (WACA)(15). Catheters with irrigation are used to optimize thermal injury to the tissue without charring and possible thrombus formation(51).

Continued development of three-dimensional mapping systems have improved accuracy of catheter positions and dramatically reduced need for fluoroscopy (radiation exposure)(52). Catheters giving feedback on the force applied have improved lesion formation, are safe and may improve outcome(53–55). Robotic systems enabling remote navigation of catheters enables the operator to sit outside the operating room further reducing radiation exposure and improving ergonomics(56).

Creating a continuous line with adequate lesions and thus durable PVI remains challenging despite technological advancements. Long-term efficacy measured as freedom from recurrence of atrial arrhythmia with a duration >30 seconds after 12 months in patients with paroxysmal atrial fibrillation is excellent for ablation in a study demonstrating superiority versus antiarrhythmic medication, 86% versus 71%, p=0.001. However, long-term freedom from arrhythmia recurrence in patients with persistent AF after 5 years of follow up is poor, 20.1% after a single ablation and 55.9% after multiple ablations(57). Reconnection of one or more PVs is frequent in patients with relapse of AF(57).

**RF multielectrode circular catheters**

Several circular RF catheters, with or without irrigation, have been developed over the years. The idea is to create a “one-shot” tool to isolate the PVs in a rapid and efficient manner.

The Pulmonary Vein Ablation Catheter (PVAC; Medtronic Ablation Frontiers) was initially introduced 2007. It was a decapolar circular catheter with both mapping and ablation functionality, delivering both bipolar and unipolar RF energy aiming to achieve segmental PVI. An early study reported 100% acute PVI success rate(58), and a later multicentre prospective randomised trial comparing PVAC to WACA by point-by-point RF catheter in paroxysmal AF showed equal freedom from arrhythmia outcome after 12 months, 78 % vs 77% (PVAC vs WACA), p=ns(59). Marked increase of asymptomatic cerebral microembolism in PVAC ablation as compared to irrigated RF-catheter or cryoballoon ablation(60) is a concern. The first generation catheter was later replaced by PVAC Gold with some modifications for improved handling and heat conduction but still without irrigation(61). A circular irrigated catheter with 3D mapping capability (nMARQ, Biosense Webster) was introduced 2013 and also showed comparable long term success measured as freedom from AF after 12 months, 65-80.7%(62,63). Safety is a concern since 2 deaths due to atrio-oesophageal fistulas were reported in a prospective registry including 374 patients who underwent ablation with the nMARQ catheter(64),
an unacceptably high incidence of this very rare and often lethal complication. The product was recalled from the market Feb 2 2015. While circular RF catheter reduces procedure complexity and duration somewhat compared to point-by-point RF ablation, success rates remain comparable when compared to point-by-point RF ablation(65,66). Other multipolar RF catheters exist but are not primarily designed for PVI and are thus beyond the scope of this introduction.

**Laser**

The laser balloon was first tried in humans in 2009 and consists of a catheter with an inflatable balloon with variable diameter and to some extent variable shape which can be positioned in the PV orifice. A good occlusion with the balloon enables the operator to see the endocardium and direct a laser source towards the atrial wall(67). Currently the laser can treat and thus induces thermal injury with scar formation in a sector of 30% of the circumference. To create overlapping scars isolating the PV, the operator must rotate the laser and create overlapping sectors of treated endocardium, but this technique nevertheless has a short learning curve(68). Laser balloon and point-by-point RF ablation for PVI was compared in a randomised prospective multicentre trial including 353 patients with paroxysmal AF. Freedom from arrhythmia recurrence was equal after 12 months, 61.1% versus 61.7% (laser balloon versus RF) and met the non-inferiority criteria, p= 0.003(69).

**Cryo**

Focal cryo catheters for transvenous ablation became available in 1998. The catheter is connected to a cryo console and N₂O flows in the central lumen of the catheter and evaporates at the tip which can reach -80°C. Cryothermal energy is thus induced by pressing a cooled catheter towards the myocardium. When the tissue reaches -20°C a transportation of water from the intracellular to the extracellular space takes place and extracellular ice formation occurs(70). At -30°C lesions are most often reversible, and this temperature can be used for mapping when ablating close to a critical structure in the conduction system, such as an accessory pathway close to the His bundle(71). This is called cryomapping. At -40°C and below intracellular ice formation destroys organelles and the plasma membrane(72). Continued ablation induces damage to adjacent blood vessels resulting in impaired regional blood flow. The rewarming phase contributes to further cell destruction by increased membrane permeability resulting in irreversible damage to mitochondria(73,74). Within the next few days the injury is matured by oedema and inflammation and after one week there is a homogenous and well demarcated lesion(75). Finally, within 4 weeks the lesion is infiltrated by dense collagen and fatty tissue, and the result is dense fibrotic tissue without conductive capabilities(76).

Duration of the optimal cryo application is not known. In preclinical studies, mainly on pigs and dogs, lesions increase and reach a plateau in size after
2-3 minutes(71). The size of the lesion is further influenced by temperature, tissue contact pressure, rate of refrigerant flow and catheter tip size(77). Focal ablation with a cryo catheter is also virtually without pain opposed to RF ablation(78) which demands analgesics and sedation for more extensive ablation in the left atrium.

Focal cryoablation catheters are now available with a 4-, 6- and 8 mm tip. The current Freezor Max\textsuperscript{R} (Medtronic) is a quadripolar 9 Fr catheter with 8 mm tip which can be introduced to the left atrium. It is connected to the same cryoconsole as the cryoballoon for ablation of the connecting sleeves of muscular tissue connecting the PV to the left atrium.

The cryoballoon catheter (Arctic Front\textsuperscript{R}, Medtronic) was first introduced and used in humans in 2006(79) and later replaced by a new cryoballoon catheter (Arctic Front Advance\textsuperscript{R}, Medtronic) in 2012(80). The balloon at the tip of the catheter is inflated by refrigerant N\textsubscript{2}O cooling the inner balloon to approximately -80°C. It is important to recognize that the 2\textsuperscript{nd} generation cryoballoon catheter represents a major improvement in design; the first generation cryoballoon circulated N\textsubscript{2}O via 4 separate channels creating an equatorial band of freezing interface. The 2\textsuperscript{nd} generation cryoballoon was equipped with 8 channels for N\textsubscript{2}O injection, thus creating a more uniform cooling of the entire distal hemisphere of the cryoballoon(80). This translates into easier, more forgiving placement of the cryoballoon and both a higher degree of acute PVI and long-term freedom from AF; in a non-randomised prospective study freedom from arrhythmia recurrence 12 months after a single ablation was 63.9% in the 1\textsuperscript{st} generation versus 83.6% in the 2\textsuperscript{nd} generation cryoballoon group, \( p=0.008 \)(81). The cryoballoon is a 10.5 Fr catheter which is inserted into the left atrium through a dedicated deflectable 12 Fr sheath (Flexcath\textsuperscript{R}, Medtronic), the sheath has also been improved over time to allow for more acute angulation (Flexcath Advance\textsuperscript{R}, Medtronic). The catheter has an inner lumen facilitating insertion of a guidewire or a dedicated multipolar recording catheter (Achieve\textsuperscript{R}, Medtronic) which became available in 2012(82). Contrast can be injected through the catheter to verify adequate PV occlusion. A 4 minute application time has been recommended as a routine, but shorter application times are being explored since animal experimental data indicate a single 2 minute applications with the 2\textsuperscript{nd} generation cryoballoon can create uniform transmural lesions and achieve acute PVI(83). Applications can be blind, simply freezing the antrum of the pulmonary veins while using a guidewire to support the balloon positioning(84). Alternatively, since 2012, an Achieve\textsuperscript{R} catheter can be introduced through the cryoballoon catheter and the recording electrodes positioned in the entrance of the pulmonary vein. PV potentials can then be seen and the effect of cryo applications observed and time to electrical isolation recorded(82).
Figure 1. Cryoballoon with Achieve® catheter occluding the left superior PV

Reproduced with permission of Medtronic, Inc.

A low temperature, a good occlusion, a long thawing time and early disconnection seen on a recording catheter are predictive for both acute PVI and long term disconnection(85–87). Cryoballoon ablation is not without pain unlike focal cryoablation, but patients in general require less sedation and analgesics than in RF ablation and the procedure can be performed under conscious sedation(88).

If PVI fails with a 28 mm diameter balloon, or if a patient with unusually small pulmonary vein diameters is on the table, a smaller 23 mm diameter balloon is available. Finally, if balloon therapy fails a point-by-point cryocatheter such as the Freezor Max® (Medtronic) can be used to add focal cryo lesions to achieve PVI.

RF point-by-point and cryoballoon therapy are now the most common approaches to AF ablation. In the ESC EORP AF ablation long-term registry including 3593 ablations performed April 2012 to April 2015 in 104 EP centres, 72.8% were performed with RF catheter with open irrigation and 19.6% with cryoballoon for paroxysmal AF. The corresponding figures in persistent AF was 83.6% with RF and 8.5% with cryoballoon(89).

Catheter ablation beyond pulmonary vein isolation

Long-term prognosis after ablation of more diseased atria with persistent atrial fibrillation is generally poor with a high degree of arrhythmia recurrence and need for additional ablation procedures(57). There are likely differences in AF initiation and perpetuation between paroxysmal and persistent types of AF; while PV triggers seem important for all AF types, other mechanisms such as fibrosis, rotors and foci outside the PV’s may be important in persistent AF(90).
Ablation of areas of complex fractionated atrial electrograms (CFAE) indicating areas of slow conduction and creating isolating lines in the atria to stop re-entry can organize persistent AF and subsequently attain sinus rhythm during ablation(91). A large randomised RF ablation study on patients with persistent AF however showed no additional benefit or CFAE ablation or creation of additional lines compared to PV isolation only(92).

Other mechanisms for initiation and maintenance of AF have been proposed and are currently explored. Mapping of persistent AF have identified locally organized electrical patterns, “rotors”, and RF ablation of these have resulted in conversion to sinus rhythm(93). While mapping and ablation of rotors is possible(94) and ablation of local repetitive regular electrical activities added to PVI was superior to PVI alone in a small randomised study(95), these ablation strategies are still under development and need to be further evaluated in larger prospective randomised studies with longer follow-up.

Conclusion of introduction

AF is a common rhythm disorder where rhythm control strategy to maintain sinus rhythm has been shown to improve symptoms and quality of life. Catheter ablation for rhythm control may be superior to antiarrhythmic drugs (AAD) with lower arrhythmia recurrence rates (short burst of AF > 30 seconds), but evidence showing actual reduction of AF burden and improved QoL is lacking. The cornerstone for AF ablation is complete and durable PVI in both paroxysmal and persistent AF, whereas ablation beyond PVI is a matter of debate and further research. Cryoballoon ablation is a new ablation modality for PVI which has evolved and gained widespread use rapidly, but no set ablation protocol has been defined and studies have primarily been performed in patients with paroxysmal AF. There is also a lack of comparative studies between the 2nd generation cryoballoon and the most commonly used technique, open-irrigated RF ablation.
Aims

Randomised studies have established PVI as the endpoint for a successful AF ablation. The last 5 years multiple studies have demonstrated further technical advances and efficacy of catheter ablation, both cryoballoon and RF technology, in atrial fibrillation. Catheter ablation is superior to antiarrhythmic drugs in studies using recurrence of AF with a duration > 30 seconds after 12 months of follow up as the clinical endpoint. Since the main indication for AF ablation and AAD therapy is symptom relief we aimed both to establish clinical efficacy of ablation measured as quality of life and need for further therapy rather than only arrhythmia recurrence. We aimed to answer the following questions:

- Can catheter ablation improve QoL and AF burden more than AADs?
- Is 2nd generation cryoballoon ablation superior to RF ablation?
- How can cryoballoon ablation be optimised and standardised?
- Is cryoballoon ablation applicable also in persistent AF?

Study I

The aim of the “Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation - a randomized clinical trial with general health as primary outcome and atrial fibrillation burden assessed by an implantable cardiac monitor” –trial was to assess if catheter ablation of atrial fibrillation gives higher QoL compared to optimized AAD therapy in patients with symptomatic AF after 12 months follow-up. Main secondary outcomes were to compare symptom severity and AF profile, AF burden and number of cardioversions, hospitalisation, morbidity and safety at 12 months.

Study II

The aim of the “Cryoballoon versus radiofrequency ablation for atrial fibrillation – a study of outcome and safety based on the ESC-EHRA atrial fibrillation ablation long-term registry and the Swedish Catheter ablation registry” -trial was to compare the second generation cryoballoon and irrigated point-
by-point RF ablation regarding clinical outcomes and safety. The primary endpoint was repeat AF ablation and major secondary endpoints included procedure duration, freedom from arrhythmia recurrence, symptoms of AF and safety.

Study III
The aim of the “Acute and long-term efficacy and safety with a single cryoballoon application as compared with the standard dual application strategy: a prospective randomized study using the second-generation cryoballoon for pulmonary vein isolation in patients with symptomatic atrial fibrillation” – trial was to evaluate an optimised cryoballoon ablation algorithm for a single efficacious application per PV using an intraluminal catheter for mapping during freezing. The primary endpoint was to show the same efficacy in acute PVI as in routine double freeze therapy, secondary endpoints included procedure duration, safety and long-term outcome measured as freedom from arrhythmia recurrence, symptoms and QoL.

Study IV
The aim of the “Clinical outcome of the 2nd generation cryoballoon for pulmonary vein isolation in patients with persistent atrial fibrillation – a substudy of the randomized trial evaluating single versus dual cryoballoon applications” – trial was to determine efficacy of cryoballoon ablation in persistent AF. Most important other endpoints were freedom from arrhythmia recurrence, predisposing clinical features for freedom from arrhythmia recurrence, symptoms and QoL.
Material and methods

Patient selection

The trials were conducted on three different AF patient populations. See details on further inclusion and exclusion criteria below for each study:

In study I, 155 patients were included during 2008-2013 at 5 centres.

Table 3. Inclusion/exclusion criteria in study I.

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. age of 30-70 years</td>
<td>7. AF triggered by another supraventricular tachycardia</td>
</tr>
<tr>
<td>2. history of symptomatic AF ≥6 months verified on electrocardiogram in the previous 12 months</td>
<td>8. uncontrolled hypertension</td>
</tr>
<tr>
<td>3. at least one paroxysmal atrial fibrillation episode in the previous 2 months or 2 persistent atrial fibrillation episodes converted to sinus rhythm in the previous 12 months</td>
<td>9. valve disease requiring chronic anticoagulation</td>
</tr>
<tr>
<td>4. failure or intolerance to maximum one antiarrhythmic drug (including beta-blockers).</td>
<td>10. planned valve surgery within 2 years</td>
</tr>
<tr>
<td></td>
<td>11. contraindication to transseptal catheterization</td>
</tr>
<tr>
<td></td>
<td>12. contraindication to vascular access/contraindication to treatment with anticoagulants</td>
</tr>
<tr>
<td></td>
<td>13. acute coronary syndrome within last 3 months</td>
</tr>
<tr>
<td></td>
<td>14. cardiac revascularization procedure within last 6 months</td>
</tr>
<tr>
<td></td>
<td>15. prior cardiac surgery</td>
</tr>
<tr>
<td></td>
<td>16. planned cardiac corrective surgery within 1 year</td>
</tr>
<tr>
<td></td>
<td>17. renal failure requiring dialysis</td>
</tr>
<tr>
<td></td>
<td>18. abnormal liver function tests</td>
</tr>
<tr>
<td></td>
<td>19. lack of informed consent</td>
</tr>
<tr>
<td></td>
<td>20. psychological problem limiting compliance</td>
</tr>
<tr>
<td></td>
<td>21. active abuse of alcohol or other substance</td>
</tr>
</tbody>
</table>

In study II, we pooled two large registries, the EUR Observational Research Programme Atrial Fibrillation Ablation Long-Term registry (EORP AFA) and
data extracted from the Swedish catheter ablation registry. In total, 4657 patients undergoing their first AF ablation during 2012-2015 were included in the dataset.

Table 4. Inclusion/exclusion criteria in study II

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>3. ablation procedures without PVI as part of the ablation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ablation for persistent or paroxysmal AF</td>
<td>4. use of other techniques than the second-generation cryoballoon or a non-circular open irrigation RF ablation catheter as the primary tool</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria:</th>
<th>5. cardiac resynchronization therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. previous catheter ablation or surgery for AF</td>
<td>6. implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>2. long-standing persistent AF defined as persistent AF with a duration &gt; 12 months at the time of ablation</td>
<td>7. patients dependent on ventricular pacing</td>
</tr>
</tbody>
</table>

In study III-IV, 140 patients referred and accepted for their first AF ablation at Uppsala University Hospital were included during 2014-2016.

Table 5. Inclusion/exclusion criteria in study III and IV

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>5. longstanding persistent AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients with paroxysmal or persistent symptomatic AF corresponding to an EHRA score of at least 2</td>
<td>6. hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>2. Aged &lt; 76 years</td>
<td>7. significant valvular disease needing intervention</td>
</tr>
<tr>
<td>3. Referred for their first AF ablation</td>
<td>8. previous open heart surgery or percutaneous valve procedure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria:</th>
<th>9. recent acute coronary syndrome or revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. inability to retain sinus rhythm for at least 1 hour after cardioversion</td>
<td>10. implantable cardioverter-defibrillator or cardiac resynchronization therapy</td>
</tr>
<tr>
<td>2. heart failure with New York Heart Association class 3 or more</td>
<td>11. ventricular pacing dependency</td>
</tr>
<tr>
<td>3. left ventricular ejection fraction of 35% or lower</td>
<td>12. abuse of alcohol or other substances</td>
</tr>
<tr>
<td>4. left atrial diameter of 55 mm or larger (parasternal long-axis)</td>
<td>13. pregnancy or planned pregnancy within a year</td>
</tr>
</tbody>
</table>

Study design

Study I, III and IV were randomised prospective trials. Study II was an analysis of registry data.

Study protocols with prespecified analyses were created and ethical approval obtained from the regional ethics board at Uppsala University, Sweden.
In study I, which was a multicentre trial including 4 Swedish centres and 1 centre from Finland, patients were included and received an implantable loop recorder to quantify AF burden during a run-in period of 2 months. Randomisation in a 1:1 fashion to optimal antiarrhythmic drug treatment or catheter ablation followed.

In study II, we submitted a study protocol to the EurObservational Reseach Programme (EORP) board and Swedish Catheter Ablation registry board. The rationale for pooling the two registries was to power the study enough to show differences in acute procedural outcome and complications comparing RF and cryoballoon ablation. This entailed careful revision/labelling of all parameters in the Swedish database and many hours of cooperation between the statistician at EORP and me. However, the Swedish registry does not include long-term follow-up data except the occurrence of reablation, all other follow up data rely on the EORP AFA registry.

In studies III and IV, which were performed on the same study population, patients were randomised in a 1:1 fashion to either routine cryoballoon ablation or single cryoballoon application guided by a mapping catheter (AchieveR, Medtronic). All work-up including radiology, echocardiography, blood samples, anticoagulation etc was the same up to ablation. Study III compared the outcome between single cryoballoon application guided by the AchieveR catheter and routine ablation. Study IV was a predefined substudy in patients with persistent AF, where patients with paroxysmal AF constituted the control group.

Antiarrhythmic drug treatment

In study I, patients could be randomised to optimal AAD treatment or catheter ablation. Patients who were randomised to the AAD arm were allocated to the most suitable antiarrhythmic drug depending on physician’s choice. Drugs used in the study were flecainide, sotalol, disopyramide, propaphenone, dronedarone and amiodarone (optional).

The change of drug regime was guided by AF symptoms and side effects and undertaken earliest at one month after the initiation of a new antiarrhythmic drug except for amiodarone which required an evaluation of at least three months. Adequate heart rate in AF episodes was defined as 60-80 bpm at rest and 115 bpm at moderate exercise, which was achieved by adding a beta blocker, calcium channel blocker or digitalis in single therapy or combined when needed. Physicians were advised to keep patients in the same treatment arm. Patients who failed all applicable drugs could do a cross-over to catheter
ablation following a trial of minimum of 12 months of AAD treatment. If ablation was performed as a result of cross-over, all end points were evaluated prior to ablation.

Ablation procedure

In study I, ablation was performed with centre’s standard technique (5 different centres). Oral anticoagulation was given at least 4 weeks and left atrial thrombi were excluded by transoesophageal echocardiography 1-2 days before ablation. Heparin or low-molecular weight heparin was used in case of bridging. Heparin was given during the procedure as recommended(17). The procedure included vascular access in the groin, standard transseptal puncture and catheterization and ablation in the left atrium. After isolation of the pulmonary veins, an extra ablation line in the left atrial roof connecting the superior pulmonary veins was optional for persistent AF. PVI had to be demonstrated as entrance block using a circular mapping catheter and block in the roof line by evaluation of double potentials and pacing manoeuvres.

In study II, only ablations aiming for PVI as part of the ablation using focal irrigated RF-catheters with or without contact force technology were permitted in the RF arm, no circular RF “one-shot” devices. In the cryoballoon group, a second generation cryoballoon catheter (Arctic Front Advance®, Medtronic) was used. Standard percutaneous transseptal technique was used and patients were anticoagulated during the procedure. Beyond that small variations in technique and preoperative anticoagulation management exist all over Europe and describing all possible variations is beyond the scope of this thesis.

In studies III and IV, which both were single centre studies performed at Uppsala University Hospital, a rigorous ablation protocol was devised. All patients had a CT scan performed before the procedure and a three-dimensional model of the LA and PVs was prepared in advance using an electroanatomic navigation system (Carto®, Biosense Webster) and available for the operator during the procedure. No patient was excluded from participation in the study for PV anatomy reasons. A TEE was performed in all patients less than 24 hours before ablation to rule out any thrombi. Warfarin treatment was not interrupted. NOAC was interrupted 24 hours before ablation and substituted with a heparin infusion which was stopped 4 hours prior to ablation. Heparin was given after transseptal puncture during catheterization with the goal to maintain an activated clotting time (ACT) > 250.

All catheters were placed percutaneously via the femoral vein. A bipolar catheter was placed in the right ventricle for backup pacing when necessary. A deflectable decapolar catheter was placed in the coronary sinus. After single
transseptal puncture, the left atrial pressure was measured directly using a standard pressure transducer connected to the transseptal sheath(96) at steady state while the patient was breathing spontaneously. A 20–polar circular mapping catheter was positioned in the right superior PV orifice. Atrial pacing was then performed for measurement of conduction times at a cycle length of 400 milliseconds from the upper poles of the circular mapping catheter in the right superior pulmonary vein (RSPV) and then from the proximal and distal coronary sinus electrodes, respectively, for 10 seconds each. Conduction times were measured after steady state at the end of the pacing sequence. The measured time intervals were i) from the proximal coronary sinus to RSPV, ii) from the distal coronary sinus to RSPV, and iii) from the proximal to the distal coronary sinus. Inverting pacing vector, i.e. pacing in the other direction was also done for measurement of bidirectional conduction times. The mapping catheter was then exchanged to a stiff guidewire and the transseptal sheath exchanged to a 12 Fr steerable sheath (Flexcath Advance®, Medtronic) through which a 28 mm CB (Arctic Front Advance®, Medtronic) was placed in the left atrium.

AF ablation was performed with the cryoballoon catheter and patients randomised to either a conventional ablation with two 4-minute “blind” applications with the cryoballoon positioned over a guidewire for each vein or a single 4 minute application for each vein guided by an Achieve® mapping catheter. A good occlusion verified with a contrast injection was pursued. Since pulmonary vein isolation cannot be monitored live in every application with the Achieve catheter, we devised a simple single application criterion:

1. PV isolation within 120 seconds (application aborted otherwise) and entrance block persistent

   OR

2. If mapping was not possible during an application, temperature \(< -40°C\) reached within 120 seconds and entrance block confirmed after application

Applications not fulfilling one criterion above were aborted and the balloon repositioned. If more than four applications had to be aborted, the operator had the opportunity to change strategy (change of balloon size, exchange Achieve® to a stiff guidewire for increased support and as a last resort change to an 8 mm tip focal cryo catheter (Freezor Max®, Medtronic).

In the routine group, adequate occlusion was judged by the operator from the density of the occlusive venogram. Applications were aborted mainly due to
poor temperature drop (operator’s preference), but two full 4 minute applications were used for each vein irrespective of degree of occlusion or temperature. In both groups, when ablating the right superior PV and also at operator’s preference on the right inferior PV, screening for damage on the phrenic nerve was performed. In the vast majority of patients who received conscious sedation and analgesics for the procedure, the patient was asked to take a deep breath every 20:th second while the operator checked movement of the right diaphragm with fluoroscopy. In a small number of patients who were under general anaesthesia, the coronary sinus catheter was positioned to capture the right phrenic nerve with high output pacing and continued phrenic nerve pacing performed during the application as described elsewhere(97). PVI was finally verified with a separate circular mapping catheter (Lasso) in both groups before retracting all catheters.

In patients treated with NOAC a heparin-infusion was started 3 hours after ablation and continued until the next original dose of a NOAC (usually at 8 pm in the evening of the procedure). However, in the last few months of the study, our anticoagulation regiment changed, and NOAC patients then received their original dose 4 hours after ablation.

Blood samples and biomarkers

In study I, laboratory tests including routine tests for AF ablation, anticoagulation and treatment with AADs. NT-proBNP, serum-creatinine, CRP, sodium, potassium, calcium, albumin, bilirubin, ALP, ASAT, ALAT, LD, γGT, glucose, TSH, T3, free T4, haemoglobin, leucocytes, thrombocytes, APTT, and INR were taken and a sample was also saved for future research use (biobank).

In study II, no blood samples were mandatory in either of the registries used for this dataset. Routine blood samples such as haemoglobin and serum-creatinine were entered in the database of the EORP AFA study and subsequently available for analyses.

In studies III and IV, routine blood samples were taken for all AF ablation procedures as a clinical routine (haemoglobin, serum-creatinine, INR).

N-terminal pro-brain natriuretic peptide (NT pro-BNP), which is correlated with AF burden(98) and a predictor of recurrent arrhythmia after ablation(99), was collected before the ablation procedure and at 12 months follow up. Blood samples (gel vacutainer) was centrifuged at the core lab at Uppsala University hospital within 4 hours of sample taken. Sample was then stored at 2-8°C up to 48 hours and analysed during office hours at the core lab.
Follow up

**In study I**, clinical follow-up was scheduled at 3, 6, 9, 12, 18, 24, 30, 36 and 48 months. The implantable cardiac monitor (Reveal XT®, Medtronic) was implanted after inclusion before the run-in period and interrogated at each visit by a study nurse, the physician seeing the patient was blinded for implantable cardiac monitor data and the device was explanted at the time of battery depletion. A 24-hour Holter recording was performed at 6, 12, 24 and 36 months follow-up. Symptom and quality of life questionnaires were collected (for details, see description of the study). An exercise test and a transthoracic echocardiogram was performed at baseline and then at 12, 24 and 36 months follow-up. The results of 12 months follow-up are analysed and the results included in this thesis, long-term follow-up has yet to be analysed but will be the object of future research. Flowchart below (figure 2).

**In study II**, all EORP AFA patients had a clinical follow-up after 12 months when symptom and quality of life questionnaires and medical history was collected. Monitoring for recurrence of arrhythmia with for example a Holter ECG was recommended but not mandatory. Initially three years of follow up was planned but this was abandoned. However, 24 months of follow up is available on a large number of patients. No clinical follow up was available on the cohort recruited from the Swedish catheter ablation registry.

**In studies III and IV**, clinical follow-up was scheduled at 3, 6 and 12 months. A 7 day Holter ECG was performed at 6 and 12 months. Symptom and quality of life questionnaires described elsewhere, were collected at 6 and 12 months. Flowchart below (figure 3).

Rhythm monitoring strategies are summarized in table 6 below.

**Table 6. Rhythm monitoring in study I-IV**

<table>
<thead>
<tr>
<th>Study</th>
<th>ECG</th>
<th>24 hour Holter</th>
<th>7 day Holter</th>
<th>ICM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3, 6, 12, 18, 24, 30, 36, 48 months</td>
<td>6, 12, 24, 36 months</td>
<td></td>
<td>Yes*</td>
</tr>
<tr>
<td>II</td>
<td>12 months</td>
<td>12m#</td>
<td></td>
<td>Optional</td>
</tr>
<tr>
<td>III-IV</td>
<td>3, 6, 12 months</td>
<td>6, 12 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*interrogated at each visit by study nurse, #recommended

Abbreviation: ICM = implantable cardiac monitor
Figure 2. Flowchart for study I – thesis includes results up to 12 months follow up

- Baseline – referral visit (day 0)
  - Inclusion and exclusion criteria met – plan for Rx
  - Risk factors for thromboembolic complications?

- Yes: Initiate warfarin or anti-platelets
  - Plan for allocated therapy
  - Implant ICM

- No: Plan for allocated therapy, including preablation warfarin

- Run-in (2 months)
  - Assess Atrial Fibrillation Profile
  - Randomization

- PVI (Group A)

  - Allocated treatment initiated within maximal 2 mo from randomization.

  - AF ablationa, b
    - If SR without AF recurrence: AC discontinued in low risk pts.
      - AA drugs discontinued.
      - If symptoms persist and AF recurs – rehabilitation is possible.b
    - If SR without AF recurrence: AC discontinued in moderate risk pts.
      - If symptoms persist and AF recurs – rehabilitation is possible.b
    - If symptoms persist and AF recurs – rehabilitation is possible.b
      - AC discontinued in high risk pts at discretion of investigator.

  - 3 months FU
    - 6 months FU
      - 9 months Nurse visit
        - 12 months FU
          - Baseline evaluations repeated
            - Primary endpoint evaluated
              - 24 and 36 months FU
                - Baseline evaluations repeated
                  - 48 months FU

Drug strategy (Group D)

  - Antiarrhythmic Drugs2
    - If symptoms persist and AF recurs – drug may be changed.2
  - If symptoms persist and AF recurs – drug may be changed.2
    - If symptoms persist and AF recurs – drug may be changed.2

Abbreviations: AC – Anticoagulants

a Start allocated therapy within maximal 2 months after randomization.
b Re-ablation within 4 weeks after decision for rehabilitation, but earliest 3 months after latest procedure.

If symptoms persists and worsens due to AF recurrence – antiarrhythmic drug may be changed at earliest 1 month after drug initiation, and for amiodarone at earliest 3 months after initiation.

2 Anticoagulants may be discontinued in risk pts if maintenance of sinus rhythm is documented.

Log book

No
Figure 3. Flowchart for studies III and IV

Log book

Baseline – (day 0)
LA size and LV function, thrombus formation

TTE/TEE, CT

Inclusion criteria met?

Yes

Exclusion criteria met?

No

Randomization 1:1

Ablation

Standard ablation

Single application ablation

Clinical evaluation
withdraw AA medication if pat is free from symptoms

If SR without AF recurrence:
- AC discontinued in low risk pats.
If symptoms and AF recurs:
- reablation offered

Second ablation

Ablation according to treatment protocol of initial randomization

12 months FU

Clinical evaluation repeated and symptoms questionnaire.
Primary endpoint evaluated

Reablation within 4 weeks after decision for reablation, but earliest 6 months after latest procedure. Anticoagulants may be discontinued in risk pats if maintenance of sinus rhythm is documented. *= can be off-site, records and ECG acquired. Abbreviations: AC=Anticoagulants
Quality of life and symptom questionnaires

Several different instruments were used to measure and quantify symptoms in AF:

**SSQ.** Symptom severity questionnaire, is a simple AF symptom questionnaire often used in studies. This questionnaire includes 5 subscales (palpitations, fatigue, shortness of breath, light-headedness or dizziness, lack of energy during exertion or exercise) with scores ranging 1-5 with lower scores signifying less symptoms.

**EHRA.** European Heart Rhythm Association symptom scale, was introduced in practice guidelines from the EHRA/ESC in 2010(23) where the treating physician can quantify AF symptoms from grade I (no symptoms) to grade IV (symptoms at rest), see table 1 in the introduction.

**DRSQ.** Diagnosis-related symptom questionnaire, is an inventory of the specific symptoms a patient experiences due to AF. This was collected at baseline and the degree (better, no change, worse) of the same symptoms was evaluated at 6, 12, 24, 36 and 48 months follow up in study I. A variation of this was a simple inventory of specific AF symptoms at baseline and the presence or absence of these symptoms at follow up, this was used in study II.

**Afib QoL.** Atrial fibrillation Quality of Life, is a questionnaire specifically developed for AF. Three categories (domains) of activity are defined and points awarded to the response to questions in each domain; psychological (7 questions), physical (8 questions) and sexual (3 questions). Response to each question is 1-5 points (low points indicating inability/impairment). Maximum total points are 90 (no impairment) and lowest possible is 18 (maximum impairment).

**SF-36.** Short form -36, measures general health and quality of life. It is a comprehensive questionnaire containing 8 subscales with scores ranging from 0-100 with the lower scores representing a poor quality of life(100).

**EQ5D-5L.** EuroQoL 5 Dimensions 5 Levels, can be used to measure impact of a treatment on health economics. The EQ5D questionnaire is one of the most generalized and reproducible scores used in evaluation of many treatments both in cardiovascular medicine and elsewhere(101,102). Description of health includes five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems.
A general score of health, scale 0-100, is also indicated. The EQ5D score is also adjusted for different populations (happiness or suffering are not perceived in same way in Sweden as in the US for example).

An overview of how these different instruments were used is in table 7. A more comprehensive description of how and when these questionnaires were used is available in the individual studies.

### Table 7. Questionnaires used in study I-IV

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSQ</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>EHRA score</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DRSQ</td>
<td>X</td>
<td>X*</td>
<td>X</td>
</tr>
<tr>
<td>Afib QoL</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D-5L</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*simple inventory of specific symptoms and their presence/absence at follow up

### Complications

All complications during AF ablation or associated hospital stay were recorded (study I-IV). Adverse events were also side effects due to medication with antiarrhythmic drugs such as bradycardia, ventricular tachycardia, other specific side effects or extended hospital stay. Patients were asked for new symptoms or diseases, hospitalization, medication for any cause at every follow-up. Hospital records were retrieved and scrutinized for any serious adverse event. Complications/adverse events were classified according to relationship to the study protocol and logged.

### Statistics

Two-sided tests and a p-value of <0.05 was considered significant in all statistical tests and confidence intervals. Histograms were used to visualise continuous variables to assess and verify normal distribution. Continuous variables were reported as mean ± standard deviation (SD). Nominal variables were expressed as frequencies or proportions.

**In study I**, based on a slower than projected accrual of study subjects despite attempts to improve recruitments and indications from two studies that the expected difference in primary end point (General Health) was larger than originally anticipated(103,104), the Steering Committee decided, after careful consideration of potential alternatives including a further prolongation of the
study period, to recalculate the original sample size (270 patients). The new sample size calculation, based on these two publications, assumed that the expected difference in the primary end point (General Health) between the treatment groups was at least 10.5 units (corresponding to 15% improvement, assuming a mean General Health of 70 units in the medication group). The originally anticipated difference was 7 units (corresponding to an improvement of 10%). A sample size of approximately 116 patients in total was required for a power of 80% and a type I error of 5% (two-sided alternative). Forty patients were added to ensure the calculated number of patients for analysis at 12 months allowing drop-outs during the 4 years follow-up. Based on historical data, it was assumed that the variable was normally distributed and that the standard deviation for the change in General Health was approximately 20 units.

Baseline data were given as the mean with SD for continuous variables and percentages for categorical variables. The mean difference between treatment groups was presented with 95% confidence intervals (CIs). The primary end point General Health at 12 months was analyzed using a t-test with the Last Observation Carried Forward-method for observations with (partially) missing data, in accordance with the pre-specified primary analysis approach. As a post-hoc sensitivity analysis the primary end point and SF-36 quality of life scores were evaluated using multiple imputation for missing values in a mixed-effect model repeated measure-model with fixed effects for treatment group, visit (including baseline, 6 months and 12 months) and visit*treatment group, random patient (within site) effect and site as repeated effect. All randomized patients were included in the Intention-To-Treat analysis. Secondary continuous variables, including the predefined analysis of atrial fibrillation burden, which was redefined as a post hoc analysis, were also analyzed using Analysis of Covariance (ANCOVA) with the corresponding baseline values as covariates. Time to event data was analyzed using Kaplan-Meier graphs and log-rank tests. A post-hoc explorative ANCOVA was used to assess the relationship between the improvement in General Health score and the reduction in atrial fibrillation burden, including the effect of randomized treatment and number of antiarrhythmic drugs tested during follow-up. A two-sided P value of less than 0.05 was considered statistically significant. No adjustments for multiple comparisons were undertaken and p-values should not be used to infer definitive treatment effects for secondary outcomes. Data were managed by Viedoc database software. Analyses were conducted with SAS software, version 9.4.

In study II, which was a registry study, group comparisons were made using non-parametric Kruskal–Wallis test. Categorical variables were reported as percentages. Group comparisons were made using a chi-square test or Fisher’s exact test (if any expected cell count was <5). For qualitative variables with
more than two possibilities, the Monte Carlo estimates of the exact p-values are used. Plots of the Kaplan-Meier curves for arrhythmia-free survival, repeat ablation and cardioversion according to cryoballoon and RF ablation were performed. The survival distributions were compared using the log-rank test. A separate adjusted (age, gender, type of AF before ablation and registry) Kaplan-Meier curve was plotted for repeat ablation. A subgroup analysis was performed for the relationship between reablation and ablation modality (cryoballoon versus RF) using Cox regression in order to build a Forest plot. Interactions between subgroup and ablation modality were added to the model. Values for RF ablation were taken as the reference. Hazard ratios for each subgroup modality, p-value of interaction and observation used were presented in the Forest plot. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

In study III, sample size calculation was based on the hypothesis that a single application strategy would be less than 10% as efficacious in obtaining PVI, the primary outcome, compared to two applications (90% versus 80% efficacy rates). Based on a 90% power calculation with a significance level set to 0.05, 520 PVs were needed, corresponding to a study population of 140 patients. For a non-inferiority analysis, an acceptable clinical difference in obtaining acute PVI was defined as a difference less than 3%.

Student’s t-test was used for continuous variables, nominal variables expressed as frequencies or proportions were analysed with Fisher’s exact test or Pearson’s chi squared test where applicable. A Kaplan-Meier curve was constructed to describe arrhythmia-free survival. Non-inferiority testing of difference in proportions was used as an alternative way of interpreting the standard confidence interval for the difference in proportions, where the interpretation depends on the location of the appropriate confidence limit in comparison to the pre-defined delta limit. Analyses were performed using SAS statistical software version 9.4 and JMP statistical software version 13.2.0 (both from SAS Institute, Inc., Cary, NC, USA).

In study IV, Student’s t-test was used for continuous variables, nominal variables expressed as frequencies or proportions were analysed with Fisher’s exact test or Pearson’s chi squared test where applicable. Kaplan-Meier curves were constructed to describe freedom from AF recurrence in persistent AF patients as compared to those with paroxysmal AF. Univariate analysis (nominal logistic regression) was performed for baseline and pre-ablation predictors for freedom from arrhythmia recurrence. Multivariate analysis was performed for baseline and pre-ablation predictors with a univariate significant correlation to freedom from arrhythmia recurrence but limited to max three variables due to the limited number of events in the study. A separate Kaplan-Meier curve combining the type of AF and the strongest predictor for the same outcome was created to illustrate the effect of the predictor between the AF
types. All analyses were performed using JMP statistical software version 13.2.0 (SAS Institute, Inc., Cary, NC, USA).
Main results

Study I

*Patients:
In total 155 patients were included during 2008-2013, 79 patients randomised to PVI and 76 to AAD. In the ablation group, 4 patients did not receive the allocated intervention (3 consents withdrawn and 1 inferior vena cava anomaly) and in the AAD group 2 patients did not receive the allocated intervention (1 consent withdrawn and 1 declined AAD treatment after inclusion but completed follow-up). After 12 months 75 patients in each group were analysed. Baseline study population demographics were well-matched and is presented in Table 1 (limited data presented, see full manuscript study I for complete demography). A majority of patients in both study groups had never tried a class I or III AAD before inclusion.

Table 8. *Baseline characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ablation N=79</th>
<th>Drug N=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - year</td>
<td>55.8 (10.6)</td>
<td>56.3 (8.9)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>58 (73.4)</td>
<td>62 (81.6)</td>
</tr>
<tr>
<td>Type of atrial fibrillation;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal, no. (%)</td>
<td>55 (70.5)</td>
<td>57 (75.0)</td>
</tr>
<tr>
<td>Persistent, no. (%)</td>
<td>23 (29.5)</td>
<td>19 (25.0)</td>
</tr>
<tr>
<td>Atrial fibrillation duration by history – years, median</td>
<td>4.9 (4.7)</td>
<td>5.6 (5.6)</td>
</tr>
<tr>
<td>Left atrial diameter - mm</td>
<td>41.7 (6.4)</td>
<td>41.7 (4.9)</td>
</tr>
</tbody>
</table>

Plus–minus values are means (1SD); all other figures are numbers with percentages in brackets unless otherwise stated.

*Primary endpoint and overall quality of life:
General health improved significantly more so by ablation than by antiarrhythmic medication from baseline to 12 months with a mean treatment difference of 8.9 points (95% CI 3.1 to 14.7), p=0.003, Figure 4.
Secondary outcomes:

*EHRA symptom score* improved significantly more by ablation; mean treatment difference -0.5 (95% CI -0.9 to -0.2, p=0.003).

*Atrial fibrillation burden* recorded by the implantable cardiac monitor decreased significantly in both the ablation and the medication group (Figure 5). The mean reduction in atrial fibrillation burden from run-in to 12 months was statistically significantly greater by ablation than by antiarrhythmic medication in the post-hoc covariance analysis (Figure 5).

*The rate of freedom from atrial fibrillation* episodes on the implantable cardiac monitor during the 12 months follow-up did not differ significantly between the ablation and the medication group. The cumulative 24-hour Holter showed no significant difference in freedom from episodes between the ablation and medication group.

*Serious adverse events*, procedural or drug related and cardiovascular in the two treatment groups are shown in Table 9.
Table 9. Serious adverse events by randomised treatment

<table>
<thead>
<tr>
<th>Events</th>
<th>Ablation N=79</th>
<th>Drug N=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural or drug initiation related complicationsa</td>
<td>10 (12.7)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Cardiovascular complications during follow up</td>
<td>4 (5.1)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Sum of total complications</td>
<td>14 (17.7)</td>
<td>18 (23.7)</td>
</tr>
</tbody>
</table>

There were no atrio-oesophageal fistulae, pulmonary vein stenosis, or procedure-related deaths. Figures are numbers and percentages in brackets. aAll antiarrhythmic drug related events led to withdrawal of the drug.

Figure 5. Atrial fibrillation burden from the implantable cardiac monitor

Atrial fibrillation burden during run-in and at four time points during follow-up in patients allocated to catheter ablation versus antiarrhythmic medication. The difference for the change of atrial fibrillation burden from run-in to the first time point (0-3 months) and second time point (3-6 months), respectively, after start of therapy was not statistically significant between treatment groups. The reduction in burden was significantly greater in the ablation than in the medication group from run-in to the third (6-9 months) and last time point (9-12 months) respectively, according to the ancillary covariance analysis. AF denotes atrial fibrillation.
Study II

Patients:
A total of 4657 patients having their first AF ablation during 2012-2015 were included, 982 patients constituted the CRYO group (481 from the EORP AFA registry and 501 from the Swedish catheter ablation registry) and 3675 patients from the RF group (1878 from the EORP AFA registry and 1797 from Swedish catheter ablation registry). Baseline demographics are presented in Table 10. The CRYO patients were older and had more strokes, sleep apnoea, and antiarrhythmic drug failures prior to ablation while the RF patients had more congestive heart failures and persistent AF.

Table 10. Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>RF</th>
<th>CRYO</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>59.2±10.3</td>
<td>59.9±10.5</td>
<td>0.015</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>2539 (69.1)</td>
<td>649 (66.1)</td>
<td>0.071</td>
</tr>
<tr>
<td>Type of AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>2267 (63.7)</td>
<td>740 (75.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Persistent</td>
<td>1291 (36.3)</td>
<td>241 (24.6)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m2), mean±SD</td>
<td>28.5±4.6</td>
<td>28.1±4.1</td>
<td>0.251</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1060 (56.6)</td>
<td>247 (51.7)</td>
<td>0.052</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>314 (24.2)</td>
<td>38 (12.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>252 (19.7)</td>
<td>62 (20.7)</td>
<td>0.702</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>184 (14.1)</td>
<td>49 (16.2)</td>
<td>0.367</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>193 (10.3)</td>
<td>49 (10.2)</td>
<td>0.951</td>
</tr>
<tr>
<td>Thromboembolic events **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>65 (3.5)</td>
<td>26 (5.4)</td>
<td>0.049</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>53 (2.8)</td>
<td>15 (3.1)</td>
<td>0.733</td>
</tr>
<tr>
<td>Peripheral embolism</td>
<td>14 (0.7)</td>
<td>1 (0.2)</td>
<td>0.331</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>56 (3.2)</td>
<td>26 (6.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>COPD</td>
<td>46 (2.5)</td>
<td>14 (3.0)</td>
<td>0.512</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>42 (2.3)</td>
<td>8 (1.7)</td>
<td>0.431</td>
</tr>
<tr>
<td>CHA2DS2-VASc Score, mean±SD</td>
<td>1.6±1.4</td>
<td>1.6±1.3</td>
<td>0.538</td>
</tr>
<tr>
<td>EHRA score, mean±SD</td>
<td>2.4±0.6</td>
<td>2.4±0.6</td>
<td>0.959</td>
</tr>
<tr>
<td>Antiarrhythmic drugs tested***</td>
<td>1657 (89.1)</td>
<td>444 (92.7)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

*= SWEAFA and AFA EORP registry; # AFA EORP registry alone; **=including haemorrhagic stroke; ***=any Class I or III antiarrhythmic drug before ablation. Figures are N patients followed by percentage within parenthesis unless otherwise stated, for legibility the total number of observations is not given but may differ for each variable.

Primary endpoint:
The rate of reablation within a minimum of 12 months follow-up was significantly lower in the CRYO group than in the RF group, 7.8 % versus 11 %, p
=0.005, as shown in a Kaplan-Meier curve for repeat ablation within one year, adjusted for differences in the study populations (Figure 6).

*Figure 6.* Kaplan-Meier survival curve for reablation at 1 year follow-up, adjusted

Survival from reablation for atrial fibrillation, atypical atrial flutter or atrial tachycardia. Adjusted for differences between the study populations.

**Other endpoints:**

*Procedure duration* was significantly shorter in the CRYO than in the RF group, (mean±SD) 133.6±45.2 minutes versus 174.6±58.2 minutes, p<0.001. If the comparison was limited to only patients who underwent PVI alone, the procedure time was still significantly shorter in the CRYO versus the RF group, (mean±SD) 131.2±43.6 minutes versus 167.3±65.2 minutes, p<0.001.

*Fluoroscopy time* was also shorter for CRYO in the PVI alone subset, (mean±SD) 24.35±15.57 versus 25.05±23.64 (CRYO versus RF), p<0.001.

*Symptoms of AF;* patients in the CRYO group were less symptomatic than those in the RF group, with a significantly lower average EHRA score after 12 months, (mean±SD) 1.4±0.6 versus 1.5±0.7, p=0.045 with a difference in degree of score improvement from baseline to 12 months that almost reached statistical significance, -1.1±0.8 versus -1.0±0.9 (mean±SD), p=0.059.

*Freedom from arrhythmia recurrence* did not differ between the CRYO versus the RF group, 70.2% versus 68.2%, p=0.438. Patients with paroxysmal AF undergoing CRYO versus RF ablation showed no difference in freedom
from arrhythmia recurrence, 73.4 % versus 73.0%, p=0.898. Nor was there a difference in freedom from arrhythmia recurrence among persistent AF patients undergoing either PVI alone with CRYO (56.1%), PVI alone with RF (61.4%) or PVI with RF combined with additional lines/CFAE ablation (62.0%), p=0.5444 for differences between groups (Figure 7). Continued medication with class I or III AAD after 12 months was significantly less prevalent in the CRYO than in the RF group, 26.9% versus 38.7%, p<0.001.

Complications
Type of complications differed between groups; there were more phrenic nerve palsies in the CRYO group, 1.5% versus 0%, p<0.001, but more cardiovascular adverse events in the RF group, 2.8% versus 1.6%, p=0.035.

Total complication rates did not differ; 53/982 (5.4%) versus 191/3675 (5.2%), in the CRYO versus the RF group, p=0.81.

Figure 7. Kaplan-Meier for outcome arrhythmia recurrence in persistent AF

Arrhythmia recurrence includes atrial fibrillation, atypical atrial flutter or atrial tachycardia with a duration of at least 30 seconds on any type of recording/monitoring device
Abbreviations: PVI=Pulmonary vein isolation, CFAE=complex fractionated atrial electrograms
Study III

Patients:
Baseline demographics for the 140 included patients during 2014-2016 are presented in table 11.

Table 11. Baseline demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single cryo N=69</th>
<th>Routine N=70</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.9±9.08</td>
<td>68.3±10.0</td>
<td>0.673</td>
</tr>
<tr>
<td>Sex, males, N (%)</td>
<td>48 (69.6)</td>
<td>54 (77.1)</td>
<td>0.312</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.9±4.4</td>
<td>27.7±4.3</td>
<td>0.868</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>29 (42.0)</td>
<td>35 (50.0)</td>
<td>0.346</td>
</tr>
<tr>
<td>Ischemic heart disease, N (%)</td>
<td>3 (4.3)</td>
<td>6 (8.6)</td>
<td>0.312</td>
</tr>
<tr>
<td>Congestive heart failure, N (%)</td>
<td>6 (8.7)</td>
<td>6 (8.6)</td>
<td>0.980</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>8 (11.6)</td>
<td>5 (7.1)</td>
<td>0.368</td>
</tr>
<tr>
<td>Px/Pers AF, N (%)</td>
<td>34/35 (49.3/50.7)</td>
<td>28/42 (40.0/60.0)</td>
<td>0.271</td>
</tr>
<tr>
<td>EHRA score (1-4)</td>
<td>2.7±0.6</td>
<td>2.7±0.7</td>
<td>0.759</td>
</tr>
<tr>
<td>CHA2DS2-VASc (1-9)</td>
<td>1.4±1.1</td>
<td>1.4±1.2</td>
<td>0.964</td>
</tr>
<tr>
<td>AF history (months)</td>
<td>78.3±77.1</td>
<td>91.8±90.6</td>
<td>0.351</td>
</tr>
<tr>
<td>LA volume index (ml/m2)</td>
<td>40.9±15.0</td>
<td>40.7±12.5</td>
<td>0.930</td>
</tr>
</tbody>
</table>

Figures are mean ± 1 standard deviation unless otherwise stated. Figures in brackets are %.
Hypertension defined as diagnosis and pharmacological treatment before inclusion. Diabetes defined as diagnosis and pharmacological treatment before inclusion.
Abbreviations: AF = atrial fibrillation; N = number of patients; BMI = body mass index; EHRA = European Heart Rhythm Association; px = paroxysmal; pers = persistent; LA = left atrium;

Primary endpoint:
Pulmonary vein isolation was achieved in 267/269 (99.3%) of the PV’s in the Routine group as compared to 271/271 (100%) of the PVs in the Single cryo group, p=0.2477. Assuming a delta limit of 0.03, non-inferiority testing based on all veins supports the conclusion of non-inferiority between the study groups, p=0.015.

Secondary endpoints:
The procedure time was significantly reduced by a mean 16% (19 minutes) using the Single cryo CB technique versus the Routine technique; 99.4±33.3 minutes versus 118.4±34.3 minutes, p=0.0015 (figure 8).

The fluoroscopy exposure did not differ between the Single cryo versus Routine group, 17.9±11.3 minutes versus 16.3±10.3 minutes, p=0.3448 (figure 8).

Mapping with Achieve catheter; pulmonary vein potentials were used as a criterion during a freeze in 64% of all applications in the Single cryo-group. The time to isolation (TTI), meaning loss of PV potentials was 41.4 ± 27.6 (mean ± SD) seconds. No PV fulfilling the 120 second TTI criterion showed early
reconnection. The final mapping with a separate 20 pole circular mapping catheter confirmed PVI in all 271 mapped PVs in the Single cryo group.

*Freedom from arrhythmia recurrence* was 73.9% in the Single cryo group versus 71.4% in the Routine group, respectively, p=0.742, after 12 months according to surface ECG or Holter/telemetry monitoring after a single ablation (figure 9).

*Figure 8. Procedure duration and fluoroscopy time*

Boxplot shows mean and distribution 25% to 75% in central box; lines show minimum and maximum value dots outliers. Exclusion of outliers did not change p-value significantly.
Figure 9. Kaplan-Meier estimate of freedom from arrhythmia recurrence

Freedom from arrhythmia recurrence is defined as the absence of any AF or atypical flutter episode longer than 30 seconds on 7 day Holter or ECG recording. Figures below the curve denote numbers at risk.

Symptoms and QoL assessed by EHRA score, SSQ and EQ5D-5L all improved but the magnitude of improvement after 12 months did not differ between the groups (table 12). The EHRA score improvement (mean ± standard deviation) at 12 months was -1.38±0.83 vs -1.44±0.90, in the Single cryo versus the Routine arm, p=0.69.

Complications are presented in table 13. There was a lower complication rate in the Single cryo-group, 2.9% versus 12.9%, p=0.03 (table 2). All phrenic nerve paralyses were transient within 12 months during follow-up (at longest 9 months in one patient). There were no deaths and no thromboembolic episodes during the 12 months follow-up.

Table 12. Symptoms and QoL changes after 12 months

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single cryo</th>
<th>Routine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSQ total</td>
<td>-5.6±4.</td>
<td>-5.4±5.2</td>
<td>0.82</td>
</tr>
<tr>
<td>EHRA score</td>
<td>-1.4±0.8</td>
<td>-1.4±0.9</td>
<td>0.86</td>
</tr>
<tr>
<td>EQ5D-5L global</td>
<td>+9.29±17.36</td>
<td>+9.18±20.40</td>
<td>0.97</td>
</tr>
<tr>
<td>EQ5D-5L index</td>
<td>+0.04±0.17</td>
<td>+0.04±0.18</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Figures are mean ± 1 standard deviation unless otherwise stated.
Abbreviations: SSQ = Symptom severity questionnaire; EHRA = European Heart Rhythm Association
Table 13. Complications (procedural and during 12 months follow up)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Routine N=70</th>
<th>Single cryo N=69</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, N (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Transient ischemic attack, N (%)</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Tamponade, N (%)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Pericarditis, N (%)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Phrenic nerve paralysis*, N (%)</td>
<td>4 (5.7)</td>
<td>1 (1.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Ulcus/dyspepsia, N (%)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Gastroparesis&lt;sup&gt;b&lt;/sup&gt;, N (%)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>PV stenosis, N (%)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Any complication, N (%)</td>
<td>9 (12.9)</td>
<td>2 (2.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<sup>a</sup> Impaired field of vision after ablation but computer tomography showed no cerebral pathology and neurological symptoms disappeared after 5 days.

<sup>b</sup> Persistent at discharge and very symptomatic the first month but recovered completely after 3 months.

Figures in brackets are %. Abbreviations: N = number of patients; NA = not applicable

Study IV

Patients:

In total, 77 patients with persistent AF (PersAF) underwent ablation, of whom 75 completed 12 months of follow-up. Sixty-two paroxysmal AF (PAF) patients underwent ablation and 61 completed follow-up. Patients with PersAF had a significantly higher body mass index and a higher left atrial volume index than those with PAF, while the other pre-specified baseline clinical variables did not differ between groups (table 14).
Table 14. *Baseline demographics including left atrial pressure and conduction times*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PersAF ( N=77 )</th>
<th>PAF ( N=62 )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.0±9.1</td>
<td>61.0±10.0</td>
<td>0.522</td>
</tr>
<tr>
<td>Sex, males, N (%)</td>
<td>59 (76.6)</td>
<td>43 (69.4)</td>
<td>0.343</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5±4.3</td>
<td>27.0±4.3</td>
<td>0.041</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>38 (49.4)</td>
<td>26 (41.9)</td>
<td>0.398</td>
</tr>
<tr>
<td>Ischemic heart disease, N (%)</td>
<td>5 (6.5)</td>
<td>4 (6.5)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Congestive heart failure, N (%)</td>
<td>8 (10.4)</td>
<td>4 (6.5)</td>
<td>0.548</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>6 (7.8)</td>
<td>7 (11.3)</td>
<td>0.564</td>
</tr>
<tr>
<td>EHRA score (1-4)</td>
<td>2.6±0.6</td>
<td>2.8±0.7</td>
<td>0.076</td>
</tr>
<tr>
<td>CHA₂DS²VASc (1-9)</td>
<td>1.4±1.2</td>
<td>1.4±1.1</td>
<td>0.706</td>
</tr>
<tr>
<td>AF history (months)</td>
<td>88.2±74.8</td>
<td>81.2±95.0</td>
<td>0.641</td>
</tr>
<tr>
<td>AAD treatment, N (%)</td>
<td>51 (66.2)</td>
<td>34 (54.8)</td>
<td>0.221</td>
</tr>
<tr>
<td>NT pro-NBP (ng/L)</td>
<td>421.4±609.4</td>
<td>324.4±389.2</td>
<td>0.293</td>
</tr>
<tr>
<td>LA volume index (ml/m²)</td>
<td>42.9±16.0</td>
<td>38.1±9.9</td>
<td>0.043</td>
</tr>
<tr>
<td>LA pressure, max (mmHg)</td>
<td>23.8±7.9</td>
<td>22.2±7.1</td>
<td>0.222</td>
</tr>
<tr>
<td>LACT CS prox - RSPV (ms)</td>
<td>102.4±21.6</td>
<td>93.3±19.8</td>
<td>0.024</td>
</tr>
<tr>
<td>LACT CS dist - RSPV (ms)</td>
<td>105±19.1</td>
<td>98.7±28.2</td>
<td>0.117</td>
</tr>
<tr>
<td>LACT CS prox - CS dist (ms)</td>
<td>40.5±10.1</td>
<td>40.1±9.6</td>
<td>0.812</td>
</tr>
</tbody>
</table>

Figures are mean ± 1 standard deviation unless otherwise stated. Figures in brackets are %.
Abbreviations: PersAF = Persistent atrial fibrillation; PAF = Paroxysmal atrial fibrillation; N = number of patients; BMI = body mass index; EHRA = European Heart Rhythm Association; AF = atrial fibrillation; AAD = Antiarrhythmic drug; NT pro-BNP = N-terminal pro-brain natriuretic peptide; LA = left atrium; LACT = left atrial conduction time; ms = milliseconds; CS prox = coronary

*Arrhythmia recurrence:*
The rate of freedom from atrial arrhythmias was 64.9% after a single cryoballoon ablation procedure and 68.8% after one or more procedures in the PersAF group, which was significantly lower compared to PAF patients; 82.2% (p=0.029) and 83.9% (p=0.048) respectively, at 12 months (figure 10A).
Figure 10. Kaplan-Meier curves of freedom from arrhythmia after a single AF ablation procedure after 12 months follow up in patients with persistent AF (PersAF) and paroxysmal AF (PAF) in A, and in subgroups delineated by normal or pathological LAVI size in B.

The numbers below the figures denote the number of patients ‘at risk’ in each group.
Abbreviations: PAF = paroxysmal AF; PersAF = persistent AF; PAFnLAVI = paroxysmal AF and normal left atrial volume index; PersAFnLAVI = persistent AF and normal left atrial volume index; PAFpLAVI = paroxysmal AF and pathological left atrial volume index; PersAFpLAVI = persistent AF and pathological left atrial volume index.

Symptoms, quality of life and continued treatment:
The EHRA score, SSQ score and the EQ5D-5L global score improved in the PersAF group. The PAF group improved as well. Even though the magnitude of EHRA score improvement during follow-up was significantly lower in the
PersAF than in the PAF group (table 15), the 12 months scores were not significantly different between PersAF and PAF groups; 1.3±0.6 versus 1.2±0.5, p=0.313.

The frequency of continued AAD treatment after 12 months was 5/75 (6.7%), which did not differ from that in patients with PAF, 1/61 (1.6%), p=0.22.

Table 15. Treatment differences regarding symptoms and quality of life in patients with persistent AF as compared to those with paroxysmal AF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAF</th>
<th>PersAF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSQ total</td>
<td>-6.0±5.2</td>
<td>-5.0±4.2</td>
<td>0.27</td>
</tr>
<tr>
<td>EHRA score</td>
<td>-1.6±0.9</td>
<td>-1.3±0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>EQ5D-5L global</td>
<td>+7.7±17.3</td>
<td>+10.4±20.3</td>
<td>0.47</td>
</tr>
<tr>
<td>EQ5D-5L index</td>
<td>+0.05±0.21</td>
<td>+0.03±0.14</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Figures are mean ± 1 standard deviation unless otherwise stated.
Abbreviations: PersAF = Persistent atrial fibrillation; PAF = Paroxysmal atrial fibrillation; SSQ = Symptom severity questionnaire; EHRA = European Heart Rhythm Association; EQ5D-5L = EuroQol Group 5 level EQ5D

Left atrial pressure and conduction times:
The left atrial pressure at baseline is also shown in table 14 and did not differ from those in PAF patients. Patients with PersAF had a longer left atrial conduction time on the vector between proximal electrodes on the coronary sinus catheter and the right superior PV (CS prox-RSPV) than in patients with PAF, while the other 2 vectors did not differ between the groups. Pacing in the other direction for each vector showed no differences between AF types (not displayed in table 14).

Predictors of AF recurrences:
Univariate analysis identified left atrial volume index (LAVI) (p=0.0046) and type of AF (p=0.0345) as predictors of freedom from arrhythmia recurrence. Left atrial conduction time also entered analysis but added nothing significant to the model and only LAVI remained significant in the multivariate regression analysis (p=0.0239). The baseline LAVI in PersAF patients was 42.9±16.0 ml/m², which was significantly higher than that in the PAF group (table 14). The AF recurrence rate differed significantly between the patient groups related to AF type and LAVI (figure 1B) with the poorest outcome in PersAF patients with pathological LAVI while those with normal LAVI did not differ from PAF patients with pathological LAVI. Intergroup differences were not significant except for the group with PersAF and pathological LAVI, which had significantly worse outcome (freedom from AF) compared to all other groups, i.e. to PAF and high LAVI, 54.6% vs 72.7%, p=0.036, and compared to PAF and normal LAVI, 54.6% vs 85.7%, p<0.0001 (figure 10B).

Safety:
Adverse events including hospitalization for any cardiac cause occurred in 8/77 (10.4%) PersAF patients which did not differ from the rate seen in PAF patients, 5/62 (8.1%), p=0.77. The number of phrenic nerve paresis at discharge was 2/77 (2.6%), which was comparable to that in PAF patients, 2/62 (3.2%). There were no strokes, oesophageal fistulas or deaths and no patient had an unresolved adverse event at the 12 months follow-up.
Discussion

Ablation vs antiarrhythmic drugs

We aimed to answer the common and important question many physicians and patients are confronted with; should symptomatic AF be treated with catheter ablation or with AADs? Antiarrhythmic drugs are either moderately effective or carry a risk of side effects and that limit the net gain of treatment(107). Study I demonstrated significantly greater improvement of QoL measured as general health after catheter ablation in comparison to optimized ADD treatment. In our study patients could have tried maximum one AAD including a beta-blocker prior to inclusion and only a minority actually had tried and failed a class I or III ADD (table 8). Our study is thus comparable to other trials evaluating catheter ablation as a first line strategy(103,108,109).

Previous AF ablation trials have so far had short burst of AF (typically defined as duration > 30 seconds) as the primary endpoint for success in studies. However, the correlation between AF symptoms and detection of AF recurrence is very inaccurate and intermittent monitoring with Holter recordings vastly underestimates both AF recurrence and AF burden(110,111). In a prospective study evaluating continuous rhythm monitoring after catheter ablation in 143 patients, where 45 patients had no AF recurrence and 98 patients had at least 1 episode of AF, 13 patients who had no AF recurrence still reported symptoms, and 45 patients with 1 or more AF episodes had no symptoms at all.

Comparison of AF treatments should thus optimally include continuous rhythm monitoring for adequate AF detection and correlation to arrhythmia symptoms and careful evaluation of symptoms and QoL. A recent study including 419 catheter ablation patients indicates that AF episodes > 6 minutes as detected on an implantable cardiac monitor may be a reasonable arrhythmia recurrence endpoint, in this study episodes <2 minutes were rare and clinically irrelevant for lack of symptoms. Freedom from arrhythmia recurrences with a duration > 6 minutes after 12 months was 56% in patients with paroxysmal AF and 40% in the persistent AF group(112). In study I our patients received an implantable cardiac monitor for continuous rhythm monitoring and were randomised after a baseline evaluation of arrhythmia burden and symptoms.

In our study, catheter ablation reduced both AF symptoms and AF burden to a higher degree compared to AAD treatment after 12 months of follow up. Our findings thus support the conclusion of earlier studies. In a randomised
study including 112 patients who had failed at least one AAD, catheter ablation (PVI + additional lesions at the discretion of the physician) was compared to AAD treatment and both arrhythmia recurrence (more than 30 seconds of AF) and QoL (measured by SF-36 questionnaire) was superior with catheter ablation\(^{(108)}\). A larger randomised study comparing first-line ablation to AAD treatment in paroxysmal AF reported long-term outcome after 5 years of follow up with sustained higher freedom from arrhythmia recurrence, 86% versus 71%, and superior QoL in the ablation group, both comparisons with a \(p<0.001\)\(^{(113)}\).

The finding that AF burden reduction is correlated to improvement of symptoms also supports the conclusion that the superior AF burden reduction after catheter ablation is indeed the main mechanism of AF symptom reduction, not the placebo effect of an invasive procedure as has been suggested\(^{(114)}\).

The results after catheter ablation in study I, which was performed before the introduction of the second generation cryoballoon, could have been even more in favour of ablation given the improved results both for freedom of arrhythmia recurrence and improvement of AF symptoms in study III\(^{(115)}\). Outcome measured as freedom from AF has been improved when comparing the original and second generation cryoballoon in paroxysmal AF by 63.9% versus 83.6%, \(p=0.008\) (first vs second generation cryoballoon)\(^{(81)}\). Also, in persistent AF which constituted almost 30% of the catheter ablation patients in study I, results after ablation has improved with the second generation cryoballoon. While no randomised study comparing outcome between first and second generation cryoballoon in persistent AF exists, a study with first generation cryoballoon ablation in persistent AF\(^{(116)}\) reported 48% freedom from AF after 12 months compared to the results in study IV, 64.9%.

Current guidelines still recommend a trial with AAD treatment before ablation but suggest a direct ablation strategy as a treatment option in selected patients\(^{(37)}\). Study I supports early ablation and adds scientific support to advocate that patients suitable for AF ablation should be offered this treatment rather than AADs.

**Cryoballoon ablation**

Although cryoballoon ablation has evolved following introduction of the second generation cryoballoon, no strict ablation protocol exists. Study III is to our knowledge the first randomised study comparing the efficacy and safety of a single second-generation cryoballoon application to two standard consecutive applications for PVI. Our demonstration of a high acute efficacy and safety after a single cryoballoon application per vein while retaining a long-term clinical efficacy, even in an AF population with mainly persistent AF, acknowledges a new standardized technique for PVI and verifies previous
non-randomised studies using single cryoballoon applications\(117,118\). Another randomised trial comparing single applications guided by a spiral catheter and a preset time to isolation versus a standard non-guided single application, found no difference regarding freedom from AF/atrial tachycardia (AT) at 12 months\(119\) although the trial was not powered to demonstrate any statistical difference on outcome. As the number of patients with atrial fibrillation is increasingly growing posing a significant health economic challenge, it has become even more important to identify effective and safe treatment strategies. One of the most important selection criteria for an ablation tool is apart from efficacy, a short procedure time and a high safety, which was one of our drive forces in designing study III. The procedure time in study III was a mean of 19 minutes shorter in the Single versus the Routine cryo group and could potentially have been even shorter if it was not for the use of an additional circular mapping catheter intended to unmask PV potentials not detected by the Achieve\(^R\) catheter. A shorter procedure time may enable more procedures to be performed in a single theatre within office hours, which potentially has health economic implications.

Adequate sedation and pain management during AF ablation can be challenging and only 22.5% of all AF ablations were performed under general anesthesia in a large European AF ablation registry including 3593 patients\(89\). A majority of all AF ablations are thus performed under sedation with preserved spontaneous breathing. A possible advantage with single versus double cryoballoon applications is that it could reduce the number of painful applications which facilitates the use of light sedation, although this was not evaluated in our trial.

Fewer cryoballoon applications would potentially be associated with lower complication rates, as would fewer or no reintroductions of cryoballoons or separate circular mapping catheters for recording of entrance block even though the risk or air embolism is small. In study III, the procedure-related complications were significantly lower in the single as compared with the double cryoballoon application arm, indicating as expected that single cryoballoon applications is a safer strategy. The use of oesophageal temperature monitoring during cryoballoon ablation is controversial and was not used in studies III and IV. It was recently reported that the use of oesophageal probes for temperature monitoring increases the risk of oesophageal lesions\(120\), which contradicts earlier reports on its preventive effects\(121\). One cannot exclude though that oesophageal temperature monitoring may have prevented the oesophageal ulcer seen in study III.

Our study showed a higher degree of real time visualisation of PV potentials with the Achieve\(^R\) catheter; 64% during a freeze as compared to 47-55% in previous studies.
A small prospective single-centre study(125), including 20 patients showed a discrepancy between PVI verification with the AchieveR and a 20 polar circular mapping catheter, reporting that the Achieve mapping catheter on a per-PV basis correctly detected isolation in 74/80 (93%) PVs. Apart from being non-randomised, small and not blinded, it was unclear whether entrance block post-ablation was evaluated in those PVs in which real-time recordings could not be detected prior to ablation. The new AchieveR catheter (Achieve AdvanceR, Medtronic) with improved rotational response and 10 poles rather than 8 and available in a larger size may overcome this limitation. In our study, the demonstration of PV entrance block with the AchieveR catheter after ablation seemed reliable as it was confirmed by a traditional 20-pole circular mapping catheter in all PVs. Utilising the AchieveR alone to verify PVI is, based on our study, thus judged to be justified in a clinical setting, reducing procedure time further, fluoroscopy exposure and the risk of air embolism.

Although long-term results in study III after a first AF ablation procedure in terms of freedom from arrhythmia recurrence on Holter or surface ECG was lower (74% and 71 % in the Single Cryo and Routine arm, respectively) as compared to other studies reporting effects of a single application with the second-generation cryoballoon(117,126), their arrhythmia surveillance was less extensive and limited to 24-hour Holter monitoring. Another important difference is the one-month blanking period in study III and IV as opposed to a 3-month blanking period in most other trials. Moreover, none of the studies were randomised, results were based on retrospective data(126) or small patient populations(117) and a majority were paroxysmal AF patients. In study IV which focused on the type of AF and predictors of arrhythmia recurrence, paroxysmal AF patients had excellent outcome with freedom from AF in 82.2% after 12 months, comparable to other studies (124,126,127).

The observed rate of 64.9% freedom from arrhythmia in persistent AF in study IV was comparable to the results in other prospective non-randomised studies using the second generation cryoballoon for PVI and repeated Holter-ECGs for arrhythmia monitoring(128–130), 60-67% freedom from AF. An earlier non-randomised study using the first generation cryoballoon reported a lower success rate with freedom from AF 48% after 12 months in patients with persistent AF(116). When compared to trials using RF energy in patients with persistent AF, the freedom from atrial arrhythmia after a single procedure has varied between 35 and 67% in both controlled (131,132) and observational studies(57,133). Despite the use of additional ablation strategies including a “step-wise approach”(91), ablation of complex fractionated atrial electrograms (CFAEs) and extra linear lesions on top of PVI in persistent AF patients(92), the freedom from recurrences have not exceeded those achieved with PVI using the second generation cryoballoon, as seen in the present and other trials(128,129). This is discussed in-depth in the next section, “Choice of technique in AF ablation”.

54
The clinical outcome in study III in terms of AF symptoms reported by the patient or investigators was excellent with close to 80% of all patients being asymptomatic and classified in EHRA class I at 12 months after ablation, and with no differences between the treatment groups. We could not find any differences in symptom scores or QoL between the single cryoballoon applications and routine cryoballoon application groups in study III, which was not surprising given the similar long-term clinical outcome regarding AF recurrences and AF symptoms. In study IV, improvement of EHRA score was significantly larger in the paroxysmal AF group, which may in part be related to their lower quality of life (numerically higher EHRA score) at baseline compared to the persistent AF group, which was an expected finding as paroxysmal AF patients are more symptomatic than persistent AF patients (134). Equal rate of continued AAD treatment and no difference in quality of life at 12 months cast further doubt on the clinical usefulness of “short episodes of atrial arrhythmia” as the primary outcome when comparing clinical efficacy in AF ablation trials.

Among the clinical variables analysed for predicting AF recurrence after cryoballoon ablation in study IV, left atrial volume index (LAVI) was as important as the type of AF (figure 10B). The left atrial volume has been identified as a predictor for AF recurrence after both RF (135) and second generation cryoballoon procedures (136). In the latter observational study (136), an left atrial area > 21 cm² and a history of AF > 2 years were the two most important risk factors for AF relapses in patients with persistent AF. The observation that LAVI > 42 ml/m² in study IV predicted relapse of arrhythmia and that persistent AF patients with normal LAVI had comparable outcomes as paroxysmal AF patients with increased LAVI is consistent with a previous trial using RF energy (137), which also showed that depending on the left atrial volume the relapse rate in paroxysmal AF patients could even be higher than that observed in patients with non-paroxysmal AF (20.0% vs. 10.9% per person/year, respectively, p = 0.041). The higher AF recurrence rate in persistent AF patients versus in those with paroxysmal AF in the present study, may in part be explained by their higher BMI (138–140), and higher LAVI (137), both shown to be powerful predictors of AF recurrence.

The longer left atrial conduction times in one of the explored pacing vectors at baseline in the persistent AF versus the paroxysmal AF group in study IV may reflect their larger left atrial volume or the presence of fibrosis. Large areas of low voltage (> 30% of the left atrial area) has been reported as a powerful predictor of AF recurrence after AF ablation (141). The acquisition of high-density voltage maps is time-consuming and hard to incorporate in clinical practice whereas a conduction time is easily acquired, the value of which needs to be further explored for prediction of outcome in persistent AF patients.
Choice of technique in AF ablation

Study II was a large multi-national European prospective registry study comparing the cryoballoon versus the conventional irrigated tip RF techniques for AF ablation regarding outcome and safety. This study answers important clinical questions since conventional irrigated RF and cryoballoon ablation are the two main energy sources in Europe(89). AF ablation is primarily performed to reduce symptoms and improve quality of life(37). Our choice of primary endpoint, the rate of reablation, is not the most common one which is rather freedom of arrhythmia recurrence usually measured as the first occurrence of an arrhythmia episode longer than 30 seconds. However, we believe that re-ablation is a very clinically relevant endpoint as it is prompted by an inadequate clinical response to the first procedure, while the time to a first single AF recurrence with a short duration does not reflect the goal of AF ablation and is highly dependent on the type and frequency of monitoring(142).

The rate of reablation was thus significantly lower in study II after cryoballoon than after RF ablation in a real-world mixed population of both paroxysmal and persistent AF. This supports earlier reports from a sub-analysis of the randomised study, FIRE AND ICE, in which patients treated with the second generation cryoballoon had significantly fewer redo ablations, direct-current cardioversions, all-cause hospitalisations and cardiovascular hospitalisations during follow-up than those treated with RF ablation(143).

In study II, EHRA score which is a measure for AF-related symptoms, was lower (less severe symptoms) in the cryoballoon than in the RF group after 12 months, which is in line with their markedly lower rate of continued anti-arrhythmic drug use, supporting their lower reablation rate, all of which may have a positive health economic impact on long-term favouring the cryoballoon technology. Withdrawal of antiarrhythmic drugs may not only improve quality of life and health costs but also increase safety, as many of these drugs are potentially pro-arrhythmic.

The comparable arrhythmia-free survival rates in the cryoballoon and RF group in study II, 70.2% and 68.2%, respectively, is consistent with two recent studies comparing cryoballoon and RF ablation in paroxysmal AF. In the German AF ablation registry (144) including only paroxysmal AF patients, the use of a first-generation cryoballoon may have influenced the finding of similar arrhythmia recurrence rates after one year for cryoballoon (45.8%) and RF ablations (45.4%), p=0.87. In a meta-analysis, including 6473 AF patients, the similar atrial arrhythmia recurrence rates in the cryoballoon and RF ablation group after 16 months (risk ratio, RR 95% confidence interval [95% CI] = 1.01 [0.90-1.14], P = 0.83), may also be influenced by their predominant use of the first-generation cryoballoon catheter(145). Prospective, randomised AF ablation trials comparing the cryoballoon and RF energy in patients with par-
oxysmal AF have shown comparable rates of freedom from arrhythmia recurrences at six months (64.1% versus 63.1%) (146) and at mean of 18 months (78.6 % versus 76.9 %) (147), although in the later study, the first-generation cryoballoon was also used in a significant portion of patients (147).

Cryoballoon ablation, with its contiguous lesions for circumferential antrum PVI, creates a wider non-excitable lesion area than contact force RF energy catheters(148) and laser balloon ablation(149). A small prospective study comparing PV reconnection at repeat ablation after second-generation cryoballoon versus contact force RF ablation also showed a higher degree of PV reconnection in the RF group versus the cryoballoon group (36.1% versus 20.4% of all PVs, p=0.01(150). Despite improved properties developed in the 2nd generation balloon with a wider cooling area encompassing the entire frontal hemisphere rather than an equatorial band(151) which improves the rate of perioperative acute PVI(152), the AF recurrence rate has still remained higher in persistent AF patients than in paroxysmal AF patients, as was shown in study IV. The higher recurrence rates in patients with persistent as compared with paroxysmal AF has been well known for both RF energy(153) and the first generation cryoballoon technique(116). In a retrospective study with the second generation cryoballoon, the freedom from arrhythmia recurrence after a single procedure was 61.3% for persistent AF and 85.8% for paroxysmal AF patients, p<0.001(154). The improved outcomes observed with the second generation cryoballoon is likely to be related to more durable PVI although one cannot rule out that the extensive antral lesion also eliminates other potential perpetuators/triggers. In a small study including 43 patients with careful left atrial voltage mapping before and after second generation cryoballoon ablation only 27% of the posterior wall remained unablated after routine PVI ablation(155).

Study II included a sizeable number of patients with persistent atrial fibrillation, 1291 patients in the RF group and 241 patients in the cryoballoon group. The higher rate ablation of CFAEs or lines used in the persistent AF patients in the RF group did not improve outcome measured as long-term freedom from arrhythmia recurrence or fewer reablations, as compared to the cryoballoon group. Thus, there was no difference in arrhythmia recurrence or rate of reablation between PVI with cryoballoon vs PVI with RF vs PVI combined with additional ablation lines/CFAE with RF as illustrated in figure 6. This finding is in line with a randomised study which failed to demonstrate any benefit of adding CFAE ablation or linear lesions to PVI in persistent AF patients(92). Two recent studies have reported similar findings showing no benefit of additional ablation beyond PVI; in the first randomising 113 patients between PVI and PVI+lines (anterior+posterior lines creating a box lesion)(156) and in the second study randomising 124 patients between PVI and PVI+substrate modification (CFAE ablation for a maximum of two hours until sinus rhythm and additional lines if AF organised to atrial tachycardia or atrial flutter)(157). These findings are in line with the present perception that CFAE
Ablation and linear lesions on top of PVI are of limited value (17). Randomised studies comparing the second generation cryoballoon and the open-irrigated contact force RF ablation catheter for PVI are lacking, although in a small non-randomised study, the freedom from arrhythmia after a single procedure off AADs at 12 months was 28/50 (60%) for the cryoballoon and 27/50 (56%) for RF, p = 0.71 (158), which was comparable to the findings in study II and IV. Our findings in study II thus support the results in smaller randomised studies showing no clinical benefit of CFAE ablation and adding lines beyond PVI in patients with persistent AF, again supporting durable PVI as both the primary endpoint in persistent AF ablation and explaining the improved success with the second generation cryoballoon.

Safety is also paramount when defining standards for new invasive treatments such as second generation cryoballoon ablation in AF. In the previously mentioned meta-analysis (145), procedure-related complications were comparable in cryoballoon and RF energy procedures (risk ratio [95% CI] = 0.92 [0.66-1.28], P = 0.61). Cryoballoon ablation led to higher rates of phrenic nerve palsy (RR [95% CI] = 13.60 [3.87-47.81], P < 0.01) but lower rates of cardiac tamponade (RR [95% CI] = 0.48 [0.25-0.89], P = 0.02) than RF ablation (145). Study II showed a similar complication rate with more frequent phrenic nerve palsy but less frequent cardiovascular complications in the CRYO group than in the RF group. However, the overall complication rate did not differ, 53/982 (5.4%) versus 191/3675 (5.2%), in the cryoballoon versus the RF group, p = 0.81 and was even lower at 2.9% in the single application group in study III.

The shorter procedure time for cryoballoon compared to RF ablation as shown in study II has been reported by others previously (147, 159). While a reduction of procedure time by approximately 40 minutes may not seem much, it can certainly make the difference if an electrophysiology lab aims to perform more than 2 or 3 procedures per day within office hours. As demonstrated in study III, where the procedure time was another 35 minutes shorter compared to study II (99.4 ± 33.3 minutes), optimised cryoballoon ablation with an efficient single application per PV may shorten the procedure time even further. The possibility to perform more AF ablations/lab due to reduced procedure time in conjunction with the reduction of repeat ablations observed in study II may be beneficial both for health economy and waiting lists. In the FIRE AND ICE trial (147), the average cost saving per patient in the CRYO group after 18 months of follow-up was €640, in total €245 000 in that study with 374 patients in the CRYO group (160). In another study emphasising the health economic impact of need for reablation within a year after index ablation; patients with reablation had higher rates of emergency department visits (43.4% vs. 32.2%; < 0.001) and subsequent hospitalisation (35.6% vs. 21.5%; p < 0.001), after excluding hospitalisations for the repeat procedure. Total medical
cost was higher for patients with repeat ablation ($52,821 vs. $13,412; p < 0.001), and it remained 46% higher even after excluding the cost associated with additional ablations ($19,621 vs. $13,412; p < 0.001)(161). The large and increasing number of AF patients(20) result in a larger demand on emergency departments and hospitalisation for AF meaning that the main cost of the disease for society is also growing(162). Effective treatments that reduce hospitalisation for AF are thus important not just for the individual patient but also for health economy.

Catheter ablation with RF reduces hospitalisation and expenditures in patients with AF(163), but cryoballoon ablation even more so when compared to RF in the FIRE AND ICE study, due to a reduction of reablations (33%), all-cause hospitalisation (21%) and cardioversion (50%)(160). Study II supports this finding in a real-life setting with reduced number of reablations after cryoballoon as compared to RF. Cryoballoon ablation procedure times are also significantly shorter than RF as shown in study II and can be further reduced with preserved efficacy as shown in study III. Overall complication rate does not differ between cryoballoon and RF as shown in study II. A first line invasive strategy in symptomatic AF should thus be cryoballoon ablation to a larger extent than the current situation in Europe where cryoballoon was used only in 15.9% of all AF ablations in a large registry study(89).
Limitations

There are several limitations in studies I-IV. The first limitation is the absence of blinding in all studies. As no trial included a sham ablation procedure, differences in symptoms and quality of life could in part be related to a placebo effect. On the other hand, in study I, by continuous rhythm recording two months before randomisation with recordings blinded to both patients and physicians, it was possible to assess true baseline atrial fibrillation burden for the comparison of treatment effects with minimal bias. Moreover, in study I the finding that the improvement in General Health was inversely related to the reduction in atrial fibrillation burden while the effect of randomised treatment disappeared, favours a true treatment effect rather than a placebo effect. Another limitation is the potential for type 1 error related to multiple secondary endpoints and the absence of a prespecified statistical approach to deal with them. All secondary endpoints should therefore be interpreted as exploratory.

In study II, it is important to recognise the inherent limitations of registry data including potentially important differences in baseline data. A propensity score matching was not possible since all clinical data were not available for the SWEAFA population. In order to compensate for this limitation, we adjusted for the differences between the study populations by an adjusted Kaplan Meier-curve for the primary endpoint which showed the same findings as the one unadjusted. Furthermore, a careful subgroup analysis did not support that baseline differences such as the type of AF affected the primary outcome re-ablation. Nevertheless, our findings should be interpreted carefully.

Also, in study II, Holter monitoring and implantable loop recorders were more frequently used in the CRYO as compared to the RF group, which may have underestimated the rate of arrhythmia recurrence in the RF group. In study II, information about the use of a contact-force RF ablation catheter was not available, but hitherto convincing data about a possible superior efficacy for AF ablation on long-term follow-up is lacking. While repeated 7-day Holter’s constitutes a reasonable level of arrhythmia monitoring in studies III-IV, implantable loop recorders (used in study I) would have been more accurate for the assessment of arrhythmia recurrence and burden.

Complications tend to be underreported in registry data (study II) when compared to prospective randomised clinical trials (study I, III and IV).
Conclusion

Based on the results in my thesis, patients with symptomatic atrial fibrillation despite use of antiarrhythmic medication or a beta-blocker, improved their QoL more after catheter ablation when compared to optimised treatment with AADs. Furthermore, the plausible mechanism of the higher degree of QoL improvement was the higher degree of reduction of AF burden after catheter ablation, which makes the improved QoL unlikely to be a placebo effect.

The lower reablation rates, lower AAD medication rates, fewer symptoms at follow-up and shorter procedure times observed with the cryoballoon as compared to RF ablation, favouring the cryoballoon versus radiofrequency energy, may have important clinical implications when choosing AF ablation technique.

Single cryoballoon applications as compared with two applications for each PV using a circular inner lumen mapping catheter to verify early and lasting PVI translates into reduced procedure time and complication rate with preserved clinical efficacy in treatment of symptomatic AF. Left atrial volume is as important as the type of AF as a predictor for clinical outcome after cryoballoon ablation.

The cryoballoon seems to be a feasible and effective technique as a first-line strategy also in patients with persistent AF with outcomes comparable to RF ablation and with paroxysmal AF patients provided left atrial volume is normal. While RF is flexible and can be used to modify other possible triggers and substrates, routine CFAE ablation and adding additional lines failed to show clinical benefit in persistent AF. These observations support the adoption of PVI as the primary treatment in not only paroxysmal but also persistent AF and that the cryoballoon is an excellent ablation method of choice.

In summary, AF patients can now be offered ablation rather than AADs and PVI with a single cryoballoon application per PV is a fast and safe treatment irrespective of AF type.
Clinical implementation

While an individual assessment remains important, catheter ablation should be offered to more patients in the AF population rather than treatment with AADs. A simple subcutaneous “injection” of an arrhythmia monitoring device such as an implantable cardiac monitor should be employed more frequently to evaluate AF recurrence, AF burden and guide further interventions.

While specifics can be further optimised current state-of-the-art cryoballoon ablation should now include mapping during application with the goal of a single efficient application for each PV.

Evidence of efficacy with cryoballoon ablation has been lacking for patients with persistent AF. In our studies we add to the existing evidence showing as expected a lower freedom of arrhythmia outcome as compared to paroxysmal AF but an excellent symptom reduction. Furthermore, the lack of benefit of routine CFAE ablation and adding lines in persistent AF, supports the findings in other randomised studies. Efficient “one-shot” tools such as the cryoballoon facilitate a fast, safe PVI and need to be further developed and show long-term efficacy. In our opinion cryoballoon ablation is now a viable treatment option in all patients with symptomatic AF, irrespective of type and should be the primary treatment to a much higher degree.

Cryo-technology is constantly developing, and new balloons, flexible sheaths and mapping catheters and linear ablation catheters will further improve therapy. While the mechanism of poorer outcome in persistent AF remains uncertain, left atrial volume should be incorporated in the preoperative assessment rather than type of AF. In order to further improve outcome in persistent AF both durable PVI and mapping and ablation of possible other targets to achieve a truly individualised ablation approach needs to be explored in future research.

For optimal clinical efficacy in AF patients a more holistic approach also incorporating adequate assessment of cardiovascular risk factors and therapies improving outcome after ablation and quality of life, such as weight loss in obesity, would be advisable. However, this thesis aims to be an instrument for fellow arrhythmologists and other physicians to advocate ablation and in particular cryoballoon technique as an efficient tool for the huge number of patients suffering from atrial fibrillation, “forever” waiting for an AF ablation.
SUMMARY IN SWEDISH

INTRODUKTION
Förmaksflimmer (atrial fibrillation, AF) är vanlig sjukdom med hög förekomst hos den vuxna populationen. Behandling av AF omfattar farmakologisk och invasiv behandling för att minska symtom och antikoagulation för att minska risken för ischemisk stroke. Syftet med denna avhandling är att studera hur man på bästa sätt kan lindra symptom vid AF på ett säkert och effektivt sätt. Farmakologisk behandling och de två dominerande kateterablationsteknikerna, kryoballong (cryoballoon, CRYO) ablation och punkt-för-punkt radiofrekvens (RF) ablation med sk irrigation kommer att studeras och jämföras.

METODER OCH RESULTAT
I studie I inkluderades patienter i åldern 30–70 år med minst 6 månaders anamnes på AF och maximalt ett misslyckat behandlingsförsök med antiarytmiska läkemedel klass I alternativt III eller en beta-blockerare. Patienterna rekryterades från 5 olika sjukhus. De viktigaste exklusionskriterierna var: vänster kammas ejektionsfraktion <35%, vänster förmaksdiameter > 60 mm och tidigare AF ablation. Av de 155 inkluderade patienterna randomiserades 79 patienter till lungvensisolering och 76 till tidigare oprövade antiarymika. De första tre månaderna var blindade för analys av hjärtrytmen. Livskvaliteten (Quality of life, QoL) mättes med Short Form-36 frågeformulär och implantbar hjärtmonitor användes för kontinuerlig rytmmonitorering. Studien inkluderade patienter från juli 2008 till maj 2013 som följdes i fyra år. Hela studien avslutades september 2017, och 97% av patienterna fullföljde studien. Det viktigaste effektmåttet var livskvalitet (General Health, obblindat), där 0 (väst) - 100 (bäst), 10 poängs skillnad definierades som kliniskt betydande; sekundärt effektmått var förmaksflimmerbelastning vid 12 månader. Sjuttiofem patienter genomgick ablation, två bytte till medicinering med antiarytmika; 74 erhöll medicinering, men åtta bytte till ablation (sk ”cross-over”). Livskvaliteten förbättrades mer av ablation än av medicinering; medelvärde (förändring) 61,8 (11,9) jämfört med 62,7 (3,1); genomsnittlig behandlingsskillnad 8,9, 95% CI 3,1 till 14,7, p = 0,003. Förmaksflimmerbörda (% av tiden) minskade mer genom ablation än med medicinering; medel -19,9% vs -11,6%, minsta medelskillnad -6,8%, CI -12,9 till -0,7, p = 0,03. De vanligaste komplikationerna var urosepsis hos 5,1% av ablationspatienterna och läkemedelsbiverkningar (ej arytmii) hos 6,6% i läkemedelsgruppen.
I studie II inkluderades 4657 patienter som genomgått sin första AF-ablation, 982 med CRYO och 3675 med RF-energi från det Svenska Kateterablations-registret och Atrial Fibrillation Ablation Long Term-registret från Europeiska Kardiologföreningen. Det primära effektmåttet var förekomsten av en ny AF-ablation inom 1 år. De viktigaste sekundära effektmåtten inkluderade procedurtid, andel återfall av förmaksarytmi och komplikationsfrekvens. Frekvensen reablation efter 12 månader var signifikant lägre i CRYO jämfört med RF-gruppen, 7,8% jämfört 11%, p = 0,005, medan frihet från återfall av arytm (med minst 30 sekunders varaktighet) inte skilde sig mellan grupperna, 70,2% mot 68,2%, p = 0,44. Resultatet påverkades inte av AF-typ eller extra ablation utöver lungvensisolering. I sk Cox-regressionsanalys för reablation hade patienter med paroxysmalt AF signifikant lägre risk med CRYO, riskförhållande 0,56 (p = 0,041). Procedurtiden var signifikant kortare med CRYO än RF, (medelvärde ± SD) 133,6 ± 45,2 minuter jämfört med 174,6 ± 58,2 minuter, p <0,001. Komplikationsrisken var likvärdig; 53/982 (5,4%) jämfört med 191/3675 (5,2%), CRYO vs RF, p = 0,806.

I studie III randomiserades patienter med symtomatiskt AF till en enda kryoballong-applikation per lungven som guidades av en cirkulär mapping­kateter, Achieve®-kateter (Single Cryo-arm) eller två kryoballong-applikationer med standardledare (Routine Cryo-arm). Det primära effektmåttet var andelen akuta fullständiga lungvensisoleringar (pulmonary vein isolation, PVI) vid proceduren. Sekundära effektmått var frihet från AF som utvärderades med hjälp EKG vid 3, 6 och 12 månader samt 7 dagars-Holter vid 6 och 12 månader, AF symtom mättes med SSQ (”symptom severity questionnaire”), EHRA-poäng samt livskvalitet mätt med EQ5D-5L vid 12 månader. Hos de 140 patienter som inkluderades uppnåddes PVI hos 271 (100%) lungvener i Single Cryo-gruppen och hos 269/271 (99,3%) lungvener i Routine Cryo-gruppen, p = 0,25. Procedurtiden var kortare i Single Cryo-gruppen, medelvärde ± standardavvikelse 99,4 ± 33,3 minuter jämfört med 118,4 ± 34,3 minuter, p = 0,0015. Grad av frihet från återfall i AF efter en ablation skilde sig ej mellan grupperna efter 12 månaders uppföljning, 73,9% (Single Cryo) jämfört med 71,4% (Routine Cryo), p = 0,74. Symtom och livskvalitet skilde sig inte heller mellan de två grupperna. Det var en lägre komplikationsfrekvens i Single Cryo-gruppen, 2,9% jämfört med 12,9%, p = 0,03.

Studie IV var en i förväg planerad substudie på samma studiepopulation som i studie III där utfallet för patienter med ihållande, sk persisterande AF (PersAF) studerades. Frekvensen för arytmiaåterfall vid 12 månader hos patienter med PersAF, n = 77, jämfördes med återfallsfrekvensen hos patienter med paroxysmalt AF (PAF), n = 62. Andra effektmått var symtom på AF, livskvalitet, procedurtid, applikationstid för ablation, reablation och komplikationer. Variblalar som predisserade för arytmiaåterfall analyserades för hela studiepopulationen.
Andelen patienter med frihet från återfall av arytmii var 64,9% efter en ablation var 68,8% efter en eller flera ablationer i PersAF-gruppen, vilket var signifikant lägre jämfört med PAF-patienter; 82,2% (p = 0,029) respektive 83,9% (p = 0,048) vid 12 månader. Förbättringen av EHRA-poäng (-1,3 ± 0,8, p <0,0001), symtomskattningspoäng (SSQ) (-5,0 ± 4,2, p <0,0001) och EQ5D-5L globalt poäng (+ 10,4 ± 20,3, p = 0,0002) efter ablationen var signifikant jämfört med utgångsnivån i PersAF-gruppen. Reablationsfrekvens var 7/77 (9,1%), vilket ej skilde sig från den hos PAF-patienter, 9/62 (14,5%), p = 0,42. Procedurtiden, 104,8 ± 37,4 jämfört med 113 ± 31,2 minuter (p = 0,129), applikationstiden med kryoballong, 1605 ± 659 mot 1521 ± 557 sekunder (p = 0,103) och komplikationsfrekvensen efter 12 månader, 8/77 (10,4%) mot 5/62 (8,1%) (p = 0,77) skilde sig inte heller mellan PersAF och PAF-patienter.

SLUTSATSER
Livskvaliteten förbättrades betydligt mer för AF-patienter som behandlades med kateterablation jämfört med antiarytmisk medicinering.

De föreligger ett lägre behov av ny ablation och kortare procedurtider när kryoballong jämförs med RF-ablation. Trots de begränsningar som finns med registerstudier, kan våra resultat ha viktiga kliniska konsekvenser vid val av ablationsteknik.

En enda kryoballong-applikation per lungven förkortar procedurtiden utan försämrad klinisk effekt vad gäller återfall av arytmier och symtom jämfört med rutinbehandling med minst 2 applikationer/lungven. Detta kombinerat med den lägre komplikationsfrekvensen visar vägen för för en ny standardmetod för lungvensisolering med kryoballong.

Både symptom och livskvalitet förbättrades hos patienter med ihållande AF efter ablation med kryoballong. Andelen patienter som var fria från återfall av arytmii var god och jämförbar med resulterna i tidigare RF-studier, men som förväntat lägre än hos patienter med paroxysmal AF. Kryoballongen verkar vara en effektiv teknik även hos patienter med ihållande AF.
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