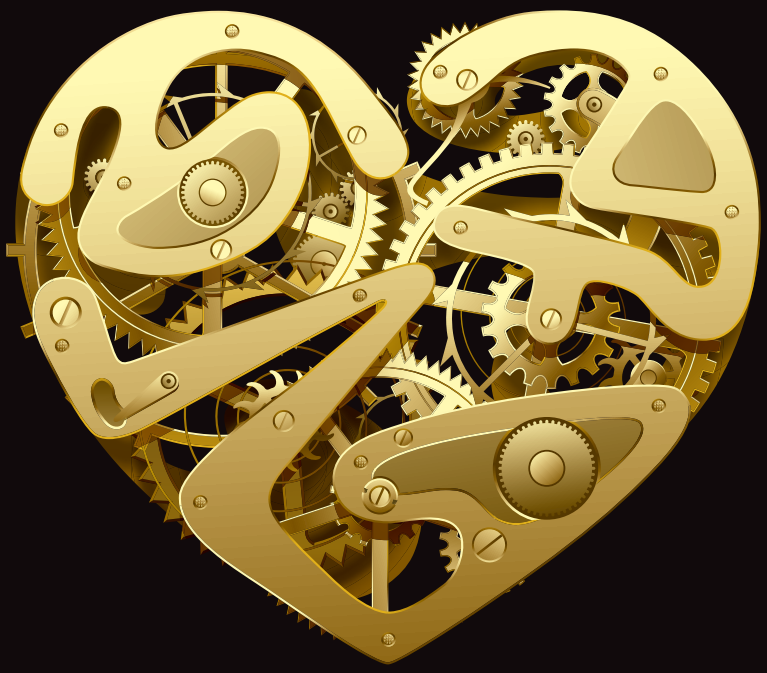
ADD-ON ABLATION SURGERY IN PATIENTS WITH ATRIAL FIBRILLATION

DRIVERS FOR INTERVENTION



Nathalie van Breugel

ADD-ON ABLATION SURGERY IN PATIENTS WITH ATRIAL FIBRILLATION

DRIVERS FOR INTERVENTION

ISBN: 978-90-6464-834-2

Cover design and layout: Ferdinand van Nispen tot Pannerden,
Citroenvlinder DTP & Vormgeving, Bilthoven, The Netherlands
Printing: GVO drukkers en vormgevers, Ede, The Netherlands

ADD-ON ABLATION SURGERY IN PATIENTS WITH ATRIAL FIBRILLATION

DRIVERS FOR INTERVENTION

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Universiteit Maastricht
op gezag van de Rector Magnificus,
Prof. Dr. L.L.G. Soete
volgens het besluit van het college van Decanen,
in het openbaar te verdedigen
op dinsdag 23 december 2014 om 14:00 uur

door

Henrica Nathalia Arnolda Maria van Breugel

PROMOTIECOMMISSIE

Promotor:	Prof. Dr. J.G. Maessen
Co-promotor:	Prof. Dr. S. Gelsomino (Careggi Hospital, Florence, Italy)
Beoordelingscommissie:	Prof. Dr. P.M.H.J. Roekaerts (voorzitter) Prof. Dr. J.C.A. Hoorntje Dr. B.L.J.H. Kietselaer Prof. Dr. M. La Meir

Financial support by Stichting Hartsvrienden RESCAR and the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.
Additional financial support for this dissertation was kindly provided by CompuGroup Medical, Boehringer-Ingelheim and Mortara.

Aan mijn lieve ouders
Voor Frank en de kleine prins

Table of contents

Chapter 1	Introduction	9
Chapter 2	A prospective randomised multicentre comparison on health-related quality of life: the value of add-on arrhythmia surgery in patients with paroxysmal, permanent or persistent atrial fibrillation undergoing valvular and/or coronary bypass surgery	39
Chapter 3	Sinus rhythm conversion after cardiac surgery in patients with pre-operative atrial fibrillation; does it affect post-operative health-related quality of life?	63
Chapter 4	Cost-effectiveness of ablation surgery in patients with atrial fibrillation undergoing cardiac surgery	87
Chapter 5	Maintenance of sinus rhythm after electrical cardioversion for recurrent atrial fibrillation following mitral valve surgery with or without associated radiofrequency ablation	101
Chapter 6	Guideline adherence in antithrombotic treatment after concomitant ablation surgery in atrial fibrillation patients	123
Chapter 7	Ten-year results of surgical radiofrequency ablation for atrial fibrillation in patients undergoing mitral valve surgery: impact of lesion set and surgical techniques on long-term arrhythmia recurrence.	141

Chapter 8 Hybrid thoracoscopic and transvenous catheter ablation of atrial fibrillation 171

Chapter 9 General discussion 189

Addendum 213

Summary 214

Samenvatting 220

Dankwoord 225

Curriculum Vitae 226

Publications 227

Valorisatie addendum 229

Chapter 1

Introduction

Atrial fibrillation

Incidence, prevalence and natural history of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance seen in clinical practice accounting for approximately one-third of hospitalizations[1].

The estimated prevalence of AF is 0.4–1% in the general population, increasing with age[2,3] and it is associated with a higher long-term risk of stroke, heart failure and all cause mortality, especially in women[4,5].

It is commonly associated with a number of cardiac and non-cardiac risk factors including ischaemic heart disease, cardiac failure, valvular heart disease, hypertension, diabetes, alcohol abuse, thyroid disorders and pulmonary disease [6,9].

AF is common in patients who undergo valvular and/or coronary bypass surgery (5-40%) as a result of underlying heart disease and age. It induces aggravating symptoms, impairs cardiac performance due to loss of effective atrial contraction and can lead to heart failure and stroke. Nonetheless, in a non-negligible percentage of people presenting with AF, there is no identifiable aetiology and this subset of patients is often referred to as 'lone AF' (LAF) [10].

ACC/AHA/ESC guidelines[11] applied the term LAF to '… individuals younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension'. A recent international consensus on nomenclature and classification of AF mentions that only AF in the absence of heart disease is termed 'lone' while in the absence of any disease is termed 'idiopathic'[12]. Indeed, LAF does not necessarily mean 'idiopathic'. In addition, in recent years, an increasing body of evidence has indicated several novel epidemiological and pathophysiological associations of AF. It could therefore be hypothesized that many of the recorded lone or idiopathic AF cases are linked to other not well-known factors. However, the diagnosis of LAF is essentially a diagnosis of exclusion, and should be preceded by careful evaluation, including a thorough collection of the patient's medical history, physical examination, blood pressure measurement, laboratory tests, ECG, echocardiography and, according to some experts, chest X-ray and exercise testing[11].

Among that group, LAF occurs in 1.6 to 11.4% of all cases of AF[13-15]. However, the ALFA study (Etude en Activité Libérale de la Fibrillation Auriculaire) reports the proportion of LAF among all cases of AF to be over 30%[16]. In other epidemiological studies LAF was reported to occur in a percentage ranging between 1.9% and 32%[17-19].

Epidemiological data show a male predominance in patients with LAF, since men

constitute 78% of this patient population[20]. In a recent study, this sex difference was further investigated, showing that the proportion of males was greater among sporadic LAF. Sporadic LAF is also more common in men than in women[21].
The natural history of LAF has not been well studied. However, accumulated data suggest that it is associated with a low-risk of progression to permanent AF, mortality, congestive heart failure, and stroke/transient ischaemic attack[20, 22].
The clinical course of LAF also suggests that many of these patients have a paroxysmal form of the arrhythmia, with an estimated risk of progression to permanent AF of 29% over 30 years [20]. Patton and coworkers confirmed the prevalence of a paroxysmal form of LAF (94% of patients) with a lower progression rate (7.8%), but this was evaluated on the basis of a shorter follow-up period[23].
The course of LAF may be influenced by several factors such as left atrial volume. Indeed, Osranek and coworkers[24] demonstrated that patients with LAF and increased left atrial volume at diagnosis or later during the follow-up experienced more adverse events, such as cerebral infarction, myocardial infarction and congestive heart failure. Furthermore, increasing age and the development of hypertension may increase the risk of cerebrovascular events[20]. Finally, approximately 44% of patients with an initial diagnosis of LAF may represent occult cases of arterial hypertension. In these patients, hypertension may affect AF recurrence and treatment outcomes[25].

Pathophysiology

The onset and the maintenance of AF require an event (trigger) that initiates the arrhythmia and the presence of a predisposing substrate and genetic factors that perpetuate it. Additional factors may also cooperate as modulators in facilitating initiation or continuation of AF.
AF behaves as a progressive disease in which the arrhythmia itself may induce further structural changes and a worsening in the underlying diseases, thus creating a vicious cycle ("AF begets AF") that does nothing except it does make the myocardial architecture distortion worse, and very often leads to paroxysmal AF becoming persistent or permanent[26, 27]. Structural remodelling only seems to be reversible during the first phases of the arrhythmic disorder, but its extent is crucial because it may reach a threshold beyond which sinus rhythm can no longer be restored[26]. In addition, AF can be maintained by re-entry and/or rapid focal ectopic firing[28].
The mechanism maintaining AF is often called the driver. The irregular atrial

discharge typical of AF may result from an irregular atrial response to a rapidly discharging regularly firing driver resulting from either local ectopic firing or a single localized re-entry circuit. Alternatively, fibrillatory activity may be caused directly by multiple functional re-entry circuits varying in time and space.
Several recent studies have focused on the underlying substrate in patients with LAF[29]. For instance, patients with LAF have an abnormal atrial substrate and these abnormalities are essential contributors to the "second factor" that promotes progression of AF. Studies employing electrophysiological and electro-anatomic mapping gave new insights into the nature of abnormalities within the atria of patients with LAF: a) Structural abnormalities characterized by atrial dilation and lower mean atrial voltage, suggesting the loss of atrial myocardium; b) Conduction abnormalities, characterized by prolongation of conduction times, longer P-wave duration and slower conduction; c) Impaired sinus node function; d) Increase in effective refractory period consistent with prior studies evaluating clinical substrates for AF but in contrast to the remodeling attributed to AF itself.
Furthermore, it has been demonstrated that left ventricular diastolic dysfunction relates to left atrial dilatation and stretch as well as to the development of AF[30]. In addition, a recent echocardiographic case-control study demonstrated that in patients with paroxysmal LAF, LA area and volume were larger than in healthy volunteers, despite there being similar LV dimensions, ejection fraction, and diastolic function and regardless of the recurrence of the arrhythmia[30]. Thus, 2-dimensional echocardiography in the antero-posterior dimension underestimates the true LA size in patients with paroxysmal LAF[31]. Even in the presence of normal LV systolic and diastolic functions, LA diameter, and LA systolic activity, the LA diastolic performance may be compromised in patients with LAF, as evidenced by abnormalities of the systolic phase of pulmonary vein (PV) flow[32]. It would seem that LV diastolic and LA abnormalities are prevalent in apparently LAF but it is still unclear whether they represent a cause and/or consequence of the arrhythmia.

Genetic factors

Evidence of a genetic contribution in the development of AF was first provided in 1943 by Wolff[33] who documented transmission of LAF in a family with an autosomal dominant pattern of inheritance. Since that time, large epidemiological studies have documented evidence of heritability in AF, in particular in the context of LAF[34-36].
It is now evident that LAF may be caused by mutations of different genes

controlling cardiac excitability such as the potassium channel genes KCNQ1, KCNE2, KCNJ2 KCNE5, KCNA5 and KCNH2 or the SCN5A sodium channel gene[37-42]. The final effect of ion channel mutations is reduced action potential duration. Consequently, carriers of genetic channelopathies have a short atrial refractory period that creates a vulnerable substrate for the development of AF. The mechanism-translating cellular hyper- excitability secondary to SCN5A gain-of-function mutations into the phenotype of AF potentially relates to enhanced automaticity of atrial cardiomyocytes. The resultant triggers, in the setting of an ideal substrate such as the pulmonary veins, may be sufficient to both induce and maintain AF. Subsequent screening of LAF cohorts suggested that these channels were a rare cause of the arrhythmia[43, 44]. However, the association between Brugada's syndrome and AF supports the pathogenic rule of SCN5A[45].

These findings implied that there were likely other classes of genes that played an important role in the development of the more common sporadic form of AF. Attractive candidate genes included connexins, trans-membrane-spanning proteins that form gap junctions, which serve as intercellular pores, providing low-resistance pathways for the passage of current between adjacent cells[46]. Of the 5-connexin isoforms expressed in the heart, connexin 40 (Cx40) seemed the most intriguing in the context of AF given its high level of expression within the atria and absence from ventricular myocardium[47]. Defects in Cx40 are expected to lead to increased propensity to AF through an impaired electrical coupling between cells and decreased atrial conduction velocity. Another study[48] has highlighted the role of age-related accumulation of mitochondrial DNA mutations. The most recent culprit gene identified (NPPA) encodes a circulating hormone, the atrial natriuretic peptide (ANP) [49]. Before this work, ANP had generally been viewed as a cardio protective hormone with an important role in sodium balance and blood pressure regulation[50]. There was evidence, however, that ANP was capable of modulating the activity of various ion channels within the heart[51, 52]. Although the potential role of ANP in directly modulating atrial electrophysiology and promoting an AF substrate is intriguing, other pro-arrhythmic actions of ANP are also conceivable, an example being inflammation that could stem from the important role of ANP in the regulation of the innate immune system[53, 54]. Given that ANP is a known mediator of inflammation, long-term exposure to altered levels of ANP might induce structural changes related to inflammation that ultimately result in atrial fibrosis and subsequent development of an AF substrate. Other peptides that have been investigated are the serum B-natriuretic peptide

(BNP), whose concentration in LAF is significantly higher than in age- and sex-matched healthy subjects[55] and the Apelin, an endogenous peptide hormone that appears to have a physiological role in counter-regulation of the angiotensin and vasopressin systems, whose levels were significantly lower in patients with LAF compared with control subjects with sinus rhythm[56]. It has been demonstrated that activation of the renin-angiotensin system (RAS) with increase in Angiotensin II levels promotes formation of collagen. Therefore, pharmacological inhibition of this system could represent a novel approach to counteract the development of fibrosis and recurrence of AF[57]. Finally, it has been suggested that a specific polymorphism of matrix metalloproteinase-2 gene is a risk factor for chronic LAF, while C allele of the interleukin-10 (IL-10) polymorphism represents a protective factor[58].

Triggers

There is general agreement that AF requires a trigger usually located in the pulmonary veins and left atrium[59-63]. Haissaguerre and colleagues[64] demonstrated that paroxysmal AF originates from ectopic beats in the pulmonary veins in 94% of cases. This likely relates to the anatomical transition from pulmonary vein endothelium to left atrial endocardium; at this juncture, two types of tissue with different electric properties are juxtaposed, and this may potentiate development of AF[64, 65]. Catheter ablation of the posterior left atrium, including the antra surrounding the pulmonary veins, has proven effective at ablating both paroxysmal and permanent AF[64-67].

Other anatomical structures that may also provide ectopic beats causing LAF are the superior vena cava, the vein of Marshall, the musculature of coronary sinus and the posterior wall of the left atrium (LA). However, for LAF to become sustained the presence of an atrial substrate of sufficient mass capable of maintaining re-entrant circuits is necessary. The LA-PV junction and the posterior wall of the LA are critical structures in this regard[68].

Finally, increasing evidence suggests that sustained AF is the result of a combination of PV vein focal discharge and PV-LA re-entrant activity[69].

Modulating Factors

Currently, there is an intense research interest in the role of inflammation in the pathophysiology of AF [70,71]. Inflammatory indexes, mainly C-reactive protein (CRP) have been related to future AF development, AF recurrences after cardioversion, and to the persistence of the arrhythmia[72]. The role of inflammation in the pathogenesis of LAF remains equivocal and limited. Indeed, only the study by Frustaci et al[73] demonstrated abnormal atrial histology in most of the patients with paroxysmal LAF refractory to conventional anti-arrhythmic therapy (inflammatory infiltrates in 66% of patients).

Conversely, other investigators failed to show inflammatory changes in LA histological specimens from LAF patients[74]. Furthermore, Ellinor et al.[75] failed to demonstrate increased CRP levels in patients with LAF compared to controls while the opposite was observed in patients with AF and hypertension. It has therefore been postulated that markers of inflammation are associated with the presence of other concomitant diseases[73]. Another case-control study showed elevated CRP levels in LAF patients; however, subjects with hypertension had not been excluded[76].

An imbalance of autonomic nerve activity has been implicated in the initiation of AF[77]. Parasympathetic nerves (which slow heart rate) and sympathetic nerves (which increase heart rate) can both initiate AF, due to shortening of the atrial effective refractory period and to changes in intracellular calcium cycling[78, 79]. The pulmonary veins are a primary location for entry of vagal nerves into the left atrium[80, 81]. Depending on the branches, stimulated vagal activity can cause slowing of heart rate, slowing of atrio-ventricular nodal conduction, or heterogeneous shortening of atrial action potentials; these effects result from activation of the potassium channels coupled to muscarinic (M_2) receptors that are present at high density in atrial and nodal myocytes[82].

Results from experimental studies on isolated canine pulmonary vein preparations suggest that simultaneous sympathetic and parasympathetic (adrenergic and cholinergic) stimulation is most effective at promoting PV ectopy, by simultaneously stimulating calcium overload while abbreviating the effective refractory period[83]. In addition, Armour and colleagues[84] were the first to document the presence of an intrinsic cardiac nervous system, consisting of bundles of neurons (ganglionic plexuses, GP) located in multiple atrial and ventricular locations[83]. They noted that activity of these GP neurons could modify cardiac activity. Ganglionic plexuses are embedded in fat pads on the epicardium of the heart. Stimulation of GP located at the PV–atrial junction has been reported to convert PV focal

activity into AF[85]. On this basis, it has been suggested that selective elimination of ganglionic plexuses might attenuate the occurrence of AF.

Types of atrial fibrillation

Management of patients with AF requires knowledge of its pattern of presentation[86] (first diagnosed, paroxysmal, persistent, long-standing, and permanent AF), underlying conditions, and decisions about restoration and maintenance of sinus rhythm (SR), control of the ventricular rate, and antithrombotic therapy.

1. First diagnose AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
2. Paroxysmal AF is self-terminating, usually within 48 h.
3. Persistent AF is present when an AF episode either lasts >7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion.
4. Long-standing persistent AF has lasted for ≥1 year when it is decided to adopt a rhythm control strategy.
5. Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician).

This classification is useful for clinical management of AF patients, especially when AF-related symptoms are also considered. Many therapeutic decisions require careful consideration of additional individual factors and co-morbidities.

Treatment of atrial fibrillation

Pharmacological therapy

The efficacy of therapy has been primarily based on morbidity and mortality: for symptom control anti-arrhythmic drugs and cardioversion are used, but breakthrough arrhythmias and side effects of the drugs happen frequently[86].

Antiarrhythmic drug therapy is the first-line treatment for patients with paroxysmal and persistent AF based on current guidelines[86-87]. Prevention of AF-related complications rely on antithrombotic therapy, control of ventricular rate, and adequate therapy of concomitant cardiac diseases. However, available drug therapy has major limitations, including incomplete effectiveness, cardiac and extracardiac toxicity and risk of life-threatening proarrhythmic complications (antiarrhythmic agents), and bleeding (anticoagulants) [88-91].

According to the current guidelines amiodarone, dronedarone, flecainide, propafenone and I-sotalol are recommended for rhythm control[86]. In selected highly symptomatic patients with occasional recurrences of AF (i.e. between once per month and once per year), the 'pill-in-the-pocket' approach consisting of oral propafenone (450–600 mg) or flecainide (200–300 mg) may be used[92]. Drugs commonly used for rate control are ß-blockers, non-dihydropyridine calcium channel antagonists and digitalis. Amiodarone may be suitable for some patients with otherwise refractory rate control[86].

Antiarrhythmic drugs have low therapeutic indices and limited long-term efficacy[93] and attainment and maintenance of sinus rhythm have been suboptimal in comparative studies such as AFFIRM[94], HOT CAFÈ[95], PIAF[96], RACE[97], STAF[98] and AF-CHF[99].

RACE and AFFIRM have shown an almost significant trend towards reduced mortality and stroke by rate control, but this may have been due to inadequate anticoagulation among patients in whom AF seemed to be controlled with antiarrhythmic drugs[94,97]. Two drawbacks for treatment with antiarrhythmic drugs in the maintenance of SR are inconsistent efficacy and severe side effects. Furthermore, SR is difficult to obtain. In RACE and AFFIRM only 30-50% of patients were in SR at the end of follow-up. As a large group of patients show severe and frequent symptoms of AF (despite the use of many antiarrhythmia and rate control drugs) while being at great risk or systemic embolization, non-pharmacological approaches in the treatment of AF have gained increased interest over the last few years.

Vernakalant is a is a relatively atrial-selective antiarrhythmic agent[100] recently recommended for approval by the European Medicines Agency for rapid cardioversion of recent-onset AF to sinus rhythm in adults (≤7 days for non-surgical patients; ≤3 days for surgical patients) [101,102]. Atrial-selectivity of Vernakalant is achieved by targeting atrial specific channels: the Kv1.5 channel which carries K+ current (IKur) and the Kir3.1/3.4 channel which carries muscarinic K+ current (IKAch). Vernakalant can also work to block Ito, late Ina, with minor blockade of IKr currents.

A direct comparison with amiodarone in the AVRO trial[103] showed that Vernakalant was more effective than amiodarone for the rapid conversion of AF to SR.

Rate reduction, allowing adequate time for ventricular filling and avoiding rate-related ischemia, may result in improved haemodynamics.[92] However, the RACE II study shows that lenient-rate control < 110 bpm is not inferior to strict-

rate control < 80 bpm[104]. As lenient-rate control is generally more convenient, requiring fewer outpatient visits and examinations, it may be adopted as a reasonable strategy in patients with permanent AF.

Drugs commonly used for rate control are ß-blockers, nondihydropyridine calcium channel antagonists, and digitalis. Amiodarone may be suitable for some patients with otherwise refractory rate control[86]. Dronedarone is similar to amiodarone but lacks an iodine moiety. Possessing both rate- and rhythm-control properties, Dronedarone has proved safe and effective in preventing recurrence of AF in patients with persistent AF in the DAFNE (Dronedarone Atrial Fibrillation Study After Electrical Cardioversion) trial, the first prospective randomized trial to evaluate its efficacy and safety[105]. Nonetheless, the DIONYSOS study[106] (Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Persistent Atrial Fibrillation) suggests higher tolerability but fewer efficacies for Dronedarone than for amiodarone. In the ATHENA trial[107], Dronedarone improved the composite endpoint of cardiovascular hospitalizations and all-cause mortality in a carefully selected, high-risk, nonpermanent AF population. The new ESC 2010 AF guidelines incorporate Dronedarone into the algorithm previously recommended for therapy to maintain SR in patients with recurrent paroxysmal or persistent AF[86].

Recommendations for antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thrombo-embolism. Unless contraindicated, chronic oral anticoagulation (OAC) therapy is recommended in patients with a $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] score ≥ 2 to achieve an international normalized ratio (INR) value of 2.0–3.0. In patients with $CHADS_2$ 0–1, the $CHA2DS_2$-VASc [congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female)] score is recommended and OAC therapy is suggested if the $CHA2DS_2$-VASc score > 2[86].

Moreover, the new AF guidelines emphasize the importance of bleeding risk assessment before starting anticoagulation. In this case the HAS-BLE [Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly] bleeding risk score is recommended. A score of ≥ 3 is considered indicative of 'high-risk' patients who require caution and regular review after starting antithrombotic therapy[86].

Catheter ablation

Multiple approaches have been developed for catheter ablation, all aimed at eliminating mechanisms in the initiation and maintenance of AF. A complete isolation of the PVs and application of the lesion set proximal to the junction of the left atrium and tube-like portion of the PV are considered necessary by most techniques.

The different approaches proposed for catheter ablation include: a) Segmental/ostial PV isolation; b) Circumferential PV ablation; c) Circumferential/antral PV isolation; d) Electrogram-based ablation or complex fractionated atrial electrograms (CFAEs) ablation; e) Linear lesions; f) Autonomic ganglionated plexi ablation; g) Ablation of AF Nest; h) Sequential ablation strategy.

Segmental PV isolation requires ablation inside the vein or very close to the output into the atrium[108]. It is accepted that ablation in the PVs needs to be avoided thus an extensive atrial ablation, often circumferential is carried out with a trans-septal circular mapping catheter placed at the ostia of the four PVs [108] which creates a series of segmental lesions until isolation of the vein can be demonstrated. Circumferential PV ablation has been widely employed [109-110]. Over time the lesion set has been modified with wider circumferential lesions (1-2 cm outside PV ostia) by adding posterior lines connecting PVs and the mitral isthmus line and, finally, by abolishing the evoked vagal reflexes, in order to prevent recurrences of atrial tachycardia[111-112].

Circumferential PV isolation can be monitored by various tools, according to operator preference. Selective pulmonary venography is widely employed to define the relevant anatomy. Intracardiac echocardiography (ICE), computerized mapping and navigation techniques (Carto, NaviX, etc) help to define anatomy and catheter guidance. Registration with other techniques such as magnetic resonance (MR) or computed tomography (CT) facilitates a more accurate anatomical definition. However, the critical goal of all these techniques is to ensure that the lesion is made outside the PVs[66]. Some investigators have extended the PV isolation concept to include ablation of the PV antrum[113] which, combined with spectral mapping, has been demonstrated to improve AF success in patients with long-lasting persistent AF[114]. CFAE ablation, instead of ablating sites in the pulmonary veins, targets sites in specific areas of the atria where the electrograms break up (become fractionated) [115]. These ablation sites are determined on an individual patient basis, offering a customized and often reduced area of treatment. Linear lesions are generally deployed at the LA roof and /or at the mitral isthmus[116-117]. Their goal is to create a bidirectional block and they have been demonstrated

to be associated with conversion of AF, further demonstrating that such lesions may at least in some patients deeply modify the substrate of AF[118-119]. Based on previous experience by Pappone et al[112] four major left atrial ganglionated plexi have recently been identified in patients with AF. Plexi may be localized at the time of ablation using high-frequency stimulation delivered by a mapping catheter in the LA. For ablation, RF current (20-35W) can be applied at each site of positive vagal response to high-frequency stimulation. Pachon et al[120] have developed a system for real-time spectral mapping that identifies sites in which the unfiltered, bipolar electrograms contain unusually high frequencies, namely fibrillar myocardium or the so-called AF nest. The investigators have successfully targeted biatrial AF nests, without intentional PV isolation, as a novel approach for AF. The adjunct of AF nest ablation has shown a favourable impact on long-term outcome following a single antral PV isolation[115]. Finally, a stepwise approach has recently been developed in patients with long-lasting persistent AF with different sequences that target multiple atrial areas[121].

New ablation technologies are currently under intense investigation. Balloon-based ablation systems have been developed to create circular lesions around PVs at the atrial level. Furthermore, new software algorithms have been developed to support the various methods of image integration (from MR or CT) and to further improve the image registration process. Finally, real-time catheter-based imaging systems for on-line 3-D cardiac chamber reconstruction based on ICE technology are under investigation.

The absence of new antiarrhythmics with an improved benefit/risk profile as well as the results of several recently published clinical trials demonstrating superior outcomes with catheter ablation for AF relative to antiarrhythmic drug therapy[122-124] suggest that AF ablation may warrant consideration as first-line therapy in selected patients[125].

Indeed some authors[126] believe that first-line should at least be considered for those patients with symptomatic AF, mild to moderate structural heart disease and paroxysmal or persistent AF. Ablation might particularly benefit younger patients with LAF who are frequently symptomatic and for whom very long term antiarrhythmics and anticoagulation pose higher risks and lifestyle costs. Asymptomatic or minimally symptomatic AF patients may also benefit from ablation and SR in the long term, but until further clinical data are available, it is difficult to justify an invasive procedure to patients who may not be aware that they have a problem.

Nonetheless, there is no full consensus[127-128] about AF ablation as first-line therapy. Areas of concern are the variable short-term efficacy of catheter ablation, its unknown long-term efficacy, significant procedure-related complications and the significant variance of success among laboratories using similar ablation techniques[139].

Surgical procedures

Add-on surgery

The add-on surgery is a procedure performed to treat AF during cardiac surgery. In this technique, a number of incisions or ablations are made.

The Cox–Maze III technique

The Cox-Maze III procedure is still the gold standard to treat AF. During the procedure, a number of incisions are made on the left and right atrium to form scar tissue, which does not conduct electricity and disrupts the path of abnormal electrical impulses. The Maze procedure requires cardiopulmonary bypass and cardiac arrest and, also in experienced hands, it requires 45–60 min of cardiopulmonary bypass and cardiac arrest[130]. Thus, even with these modifications, the Maze III remains a complex procedure and this may explain why many surgeons worldwide are reluctant to perform the procedure.

The Cox–Maze IV technique

On the basis of advances in the understanding of the pathophysiology of AF, a variety of new ablation tools have been developed to facilitate surgical ablation of AF. These probes and catheters rely on alternative energy sources to create long, continuous, linear lesions that block conduction.

In 2002, a new iteration of the Cox-Maze procedure was introduced, termed the Cox–Maze IV procedure, which replaced most of the incisions with linear lines of bipolar radiofrequency ablation[131]. Conflicting results were reported after the Cox–Maze IV technique[132-133].

The Group of Damiano[134] had previously carried out a propensity analysis of matched patients undergoing the Cox–Maze III versus Cox–Maze IV procedures which showed that there was no significant difference between these two procedures in terms of the rates of freedom from AF at 3, 6 and 12 months with

the advantage of shortening operative times while maintaining the efficacy of the traditional cut-and-sew Cox–Maze III.

Minimally invasive surgery

Bilateral thoracoscopic approach

The most widely employed minimally invasive approach to LAF has been the video-assisted bilateral mini-thoracotomy or thoracoscopic PV island creation and left atrial appendage (LAA) removal or exclusion, usually with ganglionic plexus evaluation and destruction. Most surgeons prefer this approach to avoid the difficult passage of the ablation device around the PVs (through the transverse and the oblique sinus) when performing a monolateral thoracoscopic approach. The percentage of success with this technique ranged from 42 to 91% in published papers (excluding case reports) at follow-up ranging from 6 and 40 months.

Right-side thoracoscopic approach

Several authors have described a right-sided port approach with two or three ports. Initially, microwave (MW) technology was employed followed by laser and unipolar suction-assisted radiofrequency. Unfortunately, significant published assessments are lacking and the only substantial reports available are for MW technology.

This approach is promising, although a limitation potentially includes the inability to remove the LAA. For this reason, Balkhy et al.[135] combined the right thoracoscopic MW ablation with the incorporation of a new device for LAA exclusion (Surg-ASSIST computer-mediated thoracoscopic stapling system [Power Medical Intervention, New Hope, PA, USA]).

More recently, Solinas et al.[136] employed a bipolar irrigated radiofrequency (RF) source through a monolateral right thoracotomy for left atrial ablation during minimally invasive mitral surgery. No data exist in the current literature about the feasibility of bipolar RF ablation through a right-side monolateral access in patients with LAF, which would combine the benefits for patients of a less-invasive procedure with the advantages of bipolar technology.

Right-side thoracotomy approach

A full maze lesion set using a right thoracotomy and a beating heart on cardiopulmonary bypass has been performed clinically with cryotherapy. More recently, Lee et al.[137] published their results in 22 consecutive LAF patients

undergoing RF ablation through a right-side thoracotomy approach. If these results are confirmed, this approach has an important role to play in the treatment of LAF.

Left-side thoracoscopic approach

Grandmougin and Tiffet[138] presented a case of a 68-year old female with permanent LAF who, due to consequences resulting from chemotherapy and OAC, underwent left-side video-assisted thoracoscopic drainage associated with successful epicardial radiofrequency isolation of the PVs. On the basis of this experience, the authors raised the question of whether to perform ablation of both right and left PVs in the same operation rather than delaying an additional ablation of the controlateral side according to rhythmologic results.

Exclusion/excision of the left atrial appendage (LAA)

Excision or exclusion of the LAA is currently performed during surgical ablation of AF and is recommended in EHRA/HRS guidelines.

Recently, there has been great interest in development and assessment of endocardial and epicardial procedures for exclusion of the LAA[139]. Many of these approaches now use a stapler to exclude the appendage or, in some instances, endocardial suture exclusion. Nonetheless, Kanderian et al.[140], demonstrated at transoesophageal echocardiography (TEE) that only 55 of 137 (40%) closures were successful and that a LAA closure occurred more often with excision (73%) than suture exclusion (23%) and stapler exclusion (0%, $p > 0.001$). In the available literature, the ligation/exclusion of the LAA was performed in 618 (83.6%) patients undergoing minimally invasive surgical ablation for LAF. The occurrence of perioperative cerebrovascular accident was low (0.32%)[141-142] and comparable with the Cox–Maze procedure (0.5%)[143]. Alike, the occurrence of cerebrovascular accidents during the follow-up was low (0.64%) and this figure compares favourably with occurrence rates reported after the Cox–Maze operation[143-144]. However, notably, the percentage of patients with anticoagulant therapy was much lower in Cox–Maze (16.3%) compared with minimally invasive LAF patients (n = 214, 31.4%).

From our review, the procedure resulted to be safe. Indeed, among LAF patients undergoing minimally invasive surgical ablation and LAA ligation/excision, we found only one case (0.16%) of a serious complication related to tearing of the base of the LAA[145].

However, all these percentages were not the result of a meta-analysis of quantitative studies. Furthermore, the small number of patients undergoing minimally invasive surgery without a concomitant LAA procedure does not allow us to draw any conclusions. Finally, it still remains unclear whether it is better to retain the LAA, which largely contributes to left atrial booster function[146].

The hybrid approach

The concept of the 'hybrid' procedure was first published by Pak et al.[147] who combined percutaneous epicardial catheter ablation (PECA) and endocardial ablation in difficult cases of AF.

More recently, Krul et al.[148] presented their experience with thoracoscopic PV isolation and ganglionated plexus (GP) ablation guided by peri-procedural electrophysiological testing resulting in a single-procedure success rate of 86%.

Mahapatra et al.[149] have recently published their initial experience with surgical epicardial-catheter and endocardial ablation for persistent and long-standing persistent AF carried out in two sequential steps. After a mean follow-up of 20.7 ± 4.5 months, 86.7% patients were free of any atrial arrhythmia and off of antiarrhythmic drugs (AADs). This percentage was 53.3% in patients undergoing a catheter-alone procedure (p= 0.04). Our group had previously published experience with the hybrid procedure performed in two steps: 17 patients first had endocardial catheter isolation of PVs and due to recurrence of persistent AF were selected for the epicardial approach (29% in SR at 25.7 ± 12-month follow-up) whereas 20 patients first underwent an epicardial procedure with a subsequent completion of PV isolation (55% in SR at 33.4 ± 12-month follow-up) [150]. More recently, we have introduced in our practice a sequential 'one-step' approach including an epicardial procedure followed by endocardial catheter radiofrequency. One-year off-AAD success rate free of AF/atrial flutter/atrial tachycardia was 93% for patients with paroxysmal AF and 90% for patients with persistent AF[151].

The hybrid approach presents some potential advantages:

1. There is no risk of tamponade during the trans-septal puncture since the pericardium is open.
2. Since the surgical ablation device is located on the antrum of the left atrium and left as a radiopaque marker, it is almost impossible to create stenosis of the PVs.

3. Most of the ablation lines are made epicardially; therefore the number of endocardial application ablation lines employed is small with consequent reduction in the occurrence of embolic events, which may complicate endocardial ablation.

Potential disadvantages are:

1. The procedure is time consuming and significantly longer than surgery-alone techniques and
2. The heparinization of the patient after the septal puncture might cause bleeding of surgically dissected areas.

However, the efficacy of this procedure as well as its potential superiority over catheter ablation or standard surgical technique has to be proven by large comparative studies.

Health related quality of life (HrQoL) measurement in AF

Since 1948, when the World Health Organisation defined health as being not only the absence of disease, but also as the presence of physical, mental and social well-being, quality of life (QoL) has become more important in health care practice and research[152]. So in addition to purely clinical criteria such as morbidity and mortality, enhancing QoL has gradually been accepted as one of the reasons to treat patients with AF. QoL in AF will be diminished due to palpitations, dyspnoea, dizziness, syncope, fatigue and decreased exercise tolerance. Although the concept of QoL is complex and no universal definition exists, there is an emerging consensus that quality of life can be assessed on the basis of four components[153-154]: physical condition, psychological well-being, maintenance of social activities and performance of everyday activities. In this respect, the benefit of chronic SR has to outweigh the risks of a prolonged operation. In addition, cardiovascular complaints unrelated to AF may persist even after successful surgery, thus offsetting the benefit of maintaining chronic SR. At the present time we do not know whether add-on ablation surgery indeed affects morbidity and QoL, since randomised trials are lacking.

Besides enhancing QoL, as discussed above, preventing the use of oral anticoagulation (OAC) is a key-point issue in finding a definite treatment strategy for AF. Since AF is a major risk factor for stroke and trombo-embolism,

prevention of stroke is an important goal in the management of patients with AF and therefore OAC therapy is widely used. About 1 out of 6 ischaemic strokes is associated with AF and show a worse outcome than for those without AF: portraying higher mortality and morbidity, greater disability, longer hospital stay, increased costs and higher recurrence rate[155]. Long-term treatment with oral anticoagulation therapy can reduce stroke risk in AF patients by 60%[156]. Although this mainstream therapy in reduction of stroke risk has been confirmed by multiple trials, it is distressing to note that OAC therapy remains widely underutilized in high-risk patients, insufficiently protecting them against (recurrent) stroke[157-158]. On the other hand, OAC use in itself can cause serious bleeding complications: therefore OAC should only be prescribed if justified by the patient's individual stroke risk profile. As ceasing OAC therapy and therefore reducing its risk of complications might be one of the reasons for the definite treatment of AF, it has never been investigated if additional indications for OAC are present within the AF patient population. In other words, does OAC have to be continued even after AF (and its indication for OAC) is cured by ablation surgery for additional individual reasons, therefore discarding OAC-freedom as a reason for curing AF.

The impact of AF on health care consumption and its coinciding costs in the Netherlands is high: not only the direct costs of initial and ongoing treatment of AF but also indirect costs related to loss of productivity are considerable. The annual costs of AF in the Netherlands are estimated at €554 million[159]. Today, costs are an important issue in health care and may even direct options in treatment strategy. Although associated costs of add-on ablation surgery are high, restoration of SR through ablation surgery might still turn out to be cost-effective in the long run. The potential enhanced HrQoL, reduction in health care consumption due to decreased risk in stroke, lower pharmacological drug use and fewer complications due to AF, might outweigh additional surgery costs during long-term follow-up. Therefore add-on ablation surgery could well be cost saving.

AF is common in patients with heart failure (HF) and cardiomyopathy, regardless of underlying aetiology and might even predispose to the each other[160-161]. It has been thought that restoration and maintenance of sinus rhythm may be of particular importance in patients with HF and cardiomyopathy, although evidence regarding improvement in outcome as survival, trombo-embolic complications and hospitalisation for HF is conflicting[162-164]. However, patients with HF benefit from ablation surgery for atrial fibrillation with regard to improved NYHA class

enhanced exercise capacity and higher left ventricle ejection fraction in case SR conversion was successful[165-166]. Although SR conversion might seem successful, (a)symptomatic recurrences of AF after ablation surgery may occur in 2-16% of patients within the first year post-surgery[167-168]. These recurrences are thought to result from recovered pulmonary vein conduction and the pro-arrhythmic effects of ablation itself. Recurrences are generally treated with antiarrhythmic drugs or cardioversion to minimize the chance of future development of heart failure but also because of the generally accepted idea of 'AF begets AF'[169].

Aims of the thesis

The aims of the study are fourfold:

1) To assess quality of life (QoL) and cost-effectiveness of add-on surgery (Chapters 2,4) and to explore the relationship between successful normal sinus rhythm (NSR) conversion and postoperative health-related QoL (Chapter 3).
2) To compare early and mid-term outcomes of patients who underwent electrical cardioversion (ECV) for AF recurrence following add-on surgery ablation compared to those who did not undergo concomitant AF ablation. Procedural and peri-procedural variables were also considered to determine predictors of AF recurrence (Chapter 5).
3) To investigate the real-life anticoagulation treatment after add-on ablation surgery in order to examine whether this treatment adheres to current guidelines to explore all factors related to oral anticoagulation (OAC) use preoperatively and at follow-up (Chapter 6).
4) To assess the impact of lesion set and surgical technique on long-term recurrence of AF following add-on surgery (Chapter 7).

Finally, an overview will be given to summarise and discuss results from published articles about hybrid ablation for the treatment of AF to establish the efficacy of this procedure as well as its potential superiority over catheter ablation or standard surgical technique which may represent a future step also for add-on surgery (Chapter 8).

Chapter 2

A prospective randomised multicenter comparison on health-related quality of life: the value of add-on arrhythmia surgery in patients with paroxysmal, permanent or persistent atrial fibrillation undergoing valvular and/or coronary bypass surgery

Van Breugel HN[1], Nieman FH[2], Accord RE[1], van Mastrigt GA[2], Nijs JF[1], Severens JL[3], Vrakking R[4], Maessen JG[1]

[1]Department of Cardiothoracic Surgery, Maastricht University Medical Centre, The Netherlands
[2]Department of Clinical Epidemiology & Medical Technology Assessment, The Netherlands
[3]Department of Health Organisation, Policy and Economics, CAPHRI research institute, The Netherlands
[4]Department of Cardiothoracic Surgery, Amphia Hospital Breda, The Netherlands

J Cardiovasc Electrophysiol. 2010 May; 21(5): 511-20

Abstract

Introduction This was a multicentre prospective randomised controlled trial to determine the effect of add-on arrhythmia surgery on health-related quality of life during 1-year follow-up of cardiac surgery patients with atrial fibrillation.

Methods 150 patients with documented atrial fibrillation were randomly assigned to undergo cardiac surgery with or without add-on surgery. Patients completed quality of life questionnaires, comprising the RAND 36-item Health Survey 1.0 (SF-36), Multidimensional Fatigue Inventory-20 (MFI-20) and EuroQoL (EQ-5D and VAS) at baseline and 3, 6 and 12 months following surgery.

Results 132 patients completed the questionnaires at a minimum of one time point during follow-up. At baseline patient characteristics, operative data and health-related quality of life were comparable. At 12-month follow-up 62 patients were free of atrial fibrillation without significant differences between groups (p=0.28). Conversion to SR occurred in 69.8% (37/53) of patients with paroxysmal AF, in 28.2% (11/39) of patients with permanent AF and in 44.4% (12/27) of patients with persistent AF. Cardiac surgery in general resulted in an overall improvement of the RAND SF-36 and the MFI-20. However, the EQ-5D showed a significant deterioration in the subscale Pain/Discomfort for both groups (p<0.001), with a significantly worse outcome for the control group (p=0.006).

Conclusions Health-related quality of life in patients with paroxysmal, permanent and persistent atrial fibrillation improves after cardiac surgery regardless of performing add-on surgery or not, but this improvement is presumably more affected by treating the underlying heart disease than by restoring sinus rhythm.

Introduction

Chronic or paroxysmal atrial fibrillation (AF) is the most common arrhythmia in patients undergoing valvular or coronary surgery (5-40%), depending on the underlying disease and age. Historically long-term treatment for symptomatic AF consists of comprising pharmacological treatment [1] and the 'ablate and pace strategy'[1-3]. More definite treatment strategies, such as pulmonary vein (PV) isolation and limited left atrial ablation techniques (add-on surgery) have become the focus of current investigations. From 1948 onwards, when the World Health Organisation defined health as not only the absence of disease, but also as the presence of physical, mental and social well-being, health-related quality of life (HrQoL) has become an important parameter in studies evaluating new therapies[4]. Although the definition of HrQoL may vary, there is an emerging consensus that quality of life can be assessed on four domains[5,6]: physical condition, psychological well-being, social activities and every daily activity. Randomised controlled trials as the PIAF, RACE and AFFIRM have examined the impact of rate versus rhythm-control strategies on HrQoL and showed that inducing chronic sinus rhythm (SR) is not necessarily associated with an enhanced HrQoL[7-9]. One drawback of the above studies is the fact that chronic SR is difficult to obtain, as only 30 to 50% of the patients were in SR at the end of follow-up. By contrast, arrhythmia surgery is considered highly effective in restoring SR. Although improved HrQoL is one of the primary aims of add-on arrhythmia surgery, reports on successful treatment of AF are usually small non-randomised or non-controlled cohort studies with short follow-up periods and non-standardized evaluation of rhythm outcome at the end of follow-up. This study is the first multicentre randomized trial that compares the effect of add-on epicardial PV isolation and standard surgery on HrQoL in patients with paroxysmal, as well as permanent and persistent AF during one-year follow-up with standardized rhythm evaluation. The objective of this study was to evaluate the effects of add-on arrhythmia surgery up till one year postoperatively on HrQoL, compared to patients who received only standard cardiac surgery.

Methods

Study Design

The main study is a prospective, randomised, clinical, multicentre trial, comprising 150 patients enrolled to compare rhythm outcome, morbidity and mortality in two treatment strategies for patients with AF undergoing valvular and/or coronary surgery. This health related quality of life study was part of the main trial, in which 132 of the 150 patients completed a minimum of one out of three postoperative questionnaires during total follow-up (147 patients completed the pre-operative questionnaire). Patients were randomly assigned to 'surgery as usual' or 'add-on arrhythmia surgery', by a computerized randomisation program on the day before surgery. To assure an equal distribution of patients undergoing valvular and/or coronary surgery in both treatment arms, patients were stratified after inclusion but before randomisation. Patients and all medical personnel (with exception of the surgical team) were blinded to their group assignment. All AF patients undergoing cardiac surgery, who were admitted to the University hospital Maastricht or to Amphia hospital Breda in the period from October 2002 up till November 2005, were considered for inclusion in the main trial. Patients had a history of documented paroxysmal or persistent AF for at least three months prior to surgery as defined by the ACC/AHA/ESC guidelines[10]. Patients with sick sinus syndrome or contraindications for oral anticoagulant agents were excluded from the study. HrQoL and maintenance of SR at 1-year follow-up after surgery, as stated on the outpatients visit and measured on an EKG and 24-hour Holter registration, were considered as primary end points of the total study. This sub-study hypothesized that add-on surgery would improve HrQoL. The process mechanism in the hypothesis is that long-term morbidity associated with AF, would be reduced in the add-on surgery group as compared to the 'surgery as usual' group and therefore would enhance HrQoL.

Add-on arrhythmia surgery procedure

The surgical ablation procedure was performed first before institution of cardiopulmonary bypass allowing epicardial off-pump beating heart ablation. Temporary epicardial pacing wires were positioned at the transition of the right pulmonary veins to the left atrium or at the roof of the left atrium as reached from within the transverse sinus to assure positioning within the area to be isolated. Additional pacing wires were put close to the interventricular

septum and behind the right atrial appendage, which were used for evaluating the conduction block as well as for rate-control in the postoperative period. Before starting the ablation therapy, epicardial cardioversion was attempted up to three times to bring the patient into SR in order to facilitate evaluation of the ablation effect. The off-pump beating heart ablation procedure was performed according to the following protocol:

- Epicardial electrical conversion to SR
- Positioning of the temporary pacing wires
- Opening of the pericardial reflection between the inferior right pulmonary vein and the inferior caval vein into the oblique sinus
- Opening of the pericardial reflection between the superior right pulmonary vein and the superior caval vein and opening of the oblique sinus and transverse sinus
- Dissection of the intra-atrial groove and removal of fat tissue
- Removal of fat tissue at the roof of the left atrium in the transverse sinus
- Resection of the left atrial appendage
- Positioning of a sling through the transverse sinus
- Positioning of a second sling from the inferior pulmonary vein through the oblique sinus into the transverse sinus
- Surgical ablation according to the line set in Figure 1
- Verification of the conduction block

Clinical follow-up

AF during in-hospital follow-up was treated according to predefined protocols (prophylactic Sotalol for at least four weeks postoperatively, additional Digoxin for rate control, oral anticoagulants for at least 3 months depending on rhythm oucome, cardioversion after three days of persistent AF). At least for the first five postoperative days patients had continuous cardiac monitoring at the inpatient ward. Atrial arrhythmia in the follow-up period out of hospital, was treated by the patients' own cardiologist (rate control and cardioversion), instead of by a predefined protocol, who was also blinded to the allocated treatment during the 12-month study period. Oral anticoagulant therapy was started on the first postoperative day and continued for three months in case of mechanical valve implantation or other non-AF-related disease. All patients used oral anticoagulants as long as they were in AF. If none of these premises applied, patients received low-dose aspirin (100mg/daily). There were no restrictions with respect to

concomitant medications. After discharge patients were seen in our outpatient clinics at 3, 6 and 12 months after surgery. Rhythm was evaluated by an EKG and additionally at 12-month follow-up a 24-hour Holter registration was performed.

Health-related quality of life questionnaires

For a comprehensive HrQoL assessment both generic and disease specific measurements were covered. One of two generic questionnaires that was used, the EuroQoL, consists of two components: description of the respondent's own health by means of the EuroQoL thermometer (VAS, a visual analogue scale) and the EuroQoL classification (EQ-5D, mobility, self care, usual activities, pain/discomfort, and anxiety/depression)[6]. The EuroQoL has been successfully used in HrQoL and cost-effectiveness research in heart patients[11-12]. The second generic questionnaire used in this study is the RAND 36-item Health Survey 1.0 (SF-36) comprising 8 multi-item scales[13]. Both generic questionnaires are standardized, validated and frequently used in arrhythmia studies[8,10,4]. The disease-specific questionnaire used, was the Multidimensional Fatigue Inventory (MFI-20)[9]. All questionnaires were self-administered before add-on surgery (baseline) at the hospital and were then sent by post during the follow-up period of 1-year and answered at home, at 3, 6 and 12 months after surgery.

Statistical analysis

Power analysis and patient characteristics

Sample size calculation was based on the expected rhythm outcome at 12-month follow-up. It was assumed that approximately 25% of patients in the control group would show spontaneous conversion to SR after 1-year follow-up. Power calculation was based on a minimal SR improvement of 25% one year after surgery. With a power of 80% and an alpha of 5% (2 sided), it was calculated that a minimum of 65 patients was needed per group. Correcting for loss of patients during follow-up, a total study population of 150 patients was targeted for the main study. All continuous variables are presented as means and standard deviations. Group comparison between continuous variables was performed, using the Student's t-test in case of normal distribution; otherwise the Mann-Whitney-U test was applied. For all categorical data, the chi-square log-likelihood test was used.

Health-related quality of life measurements

All patients who completed the questionnaires at one time-point postoperatively, whether this was at 3, 6 or 12-month follow-up were included in the HrQoL sub-study. The RAND 36-item Health Survey (SF-36), EQ-5D, VAS and MFI-20 were measured four times. For the SF-36 higher scores define a more favourable health state. Original items scores were weighted according to the manual[13]. The EuroQol addresses the VAS and EQ-5D. Higher scores in VAS indicate a more favourable condition of the patient, while higher scores in the EQ-5D denote a more unfavourable condition. The MFI-20 consists of five scales; for each scale an overall score was calculated ranging from 0 to 20, with higher scores indicating a higher degree of (scale-specific) fatigue. At first, per questionnaire scale a repeated measure ANOVA was performed, using 'time' as a four classes within-patients factor and 'treatment group' as a dichotomous between-patients factor. Interaction between both factors was defined as treatment group differences in linear time-trend within one year. The Kolmogorov-Smirnov (K-S) test for normality of distribution was calculated for the overall linear trend in the scale measurements throughout the 1-year follow-up. By applying repeated measures ANCOVA, preliminary results were found which correct the intermediate ANOVA results for pre-operative scale scores. Other confounding factors and/or covariates at baseline, which were entered into the model were: type of operation (CABG +/-valve, other), gender, age and type of AF. These extended ANCOVA models were performed by multiple dummy-regression analysis with the 1-year linear trend in a scale as 'dependent' variable and 'treatment group' and confounding factors and/or covariates as predictors. For each scale a final regression model was computed, containing next to the effect of 'treatment group', all confounders with statistically significant effects on the linear scale trend. Variance explained in the final model is presented in the tables and the *p*-value of the treatment group effect is given. A *p*-value of less than 0.05 was considered statistically significant. All data analyses were performed with SPSS version 15.0 (SPSS Inc. Chicago IL).

Results

Background characteristics

132 patients completed the HrQoL questionnaires at a minimum of one time-point during follow-up. No statistically significant differences in demographic

data, previous medical and cardiac history was found between groups, except for baseline Ejection Fraction (Table 1). Further specification of the primary procedures and rhythm outcome are listed in Table 1.

Adverse events and mortality

During the postoperative in-hospital period the number of rethoracotomies, pulmonary complications, stroke, myocardial infarction, renal failure and infection rate showed no significant differences between either patient groups. During total follow-up the number of adverse events remained equally distributed between both groups. The overall in and out of hospital mortality rate was 5.3% (N=7); five patients in the control group versus two patients in the add-on surgery group. The mean total follow-up in days was 351.9 ± 146.7 (p= .64).

Health-related quality of life measurements

The response rate for the questionnaires was similar for both groups at each time-point during follow-up.

RAND SF-36 1.0 questionnaire

Means, standard deviations and p-values of the RAND SF-36 during total follow-up are presented in Table 2. There was an overall improvement in HrQoL for the total group of patients; ie., there were no significantly deteriorating scales during total follow-up. In ANCOVA 'physical functioning' showed no statistical difference between either groups (Table 2, p= .143), even if controlled for age and baseline measurements (beta=0.11, p= .157). A positive effect in beta indicates a higher increase in HrQoL for the add-on surgery group; a negative sign indicates a higher increase for the control group. Regarding 'Physical limitations' and ' General health' there were no differences between study groups (respectively p= .295, beta=0.04, p= .602 and p= .458). 'Physical pain' in 1-year follow-up improved (p< .001) and there appeared to be a difference in this respect between groups (p=. 032), but it was not found in the linear difference (p= .134). This effect was also found in ' Role limitations due to emotional problems' (p< .001, linear p= .157) and ' Mental Health' (p= .300). Both the 1-year follow-up for 'Vitality' and 'Social functioning' scales showed no difference (respectively p=. 246 and p= .410).

EuroQoL classification

Outcomes for the five dimensions of the EQ-5D and the VAS are listed in Table 3. 'Mobility' improved significantly during total follow-up for both treatment groups ($p< 0.001$). However without a between group difference ($p= .346$) and controlled for baseline measurements and age 'group' there was no statistically significant difference in 'Mobility' (beta=-0.08, $p=. 288$). The 1-year linear trend in 'Self-care' and 'Daily activities' improves significantly for both treatment groups during follow-up ($p< .001$), again without a difference between groups (respectively $p= .460$ and $p= .056$). The 1-year linear trend in the EuroQoL 'Pain & Discomfort' scale displayed a statistically non-normal distribution. In ANCOVA it showed a significant and considerable deterioration, not only for both treatment groups ($p< .001$), but even more so for the control surgery group ($p= 0.006$; beta=-.21). The Mann-Whitney-U test on the Studentized residuals of the 1-year pain reduction, corrected for baseline measurements, also showed a statistical significance and confirmed the above results ($p= 0.002$). The 1-year linear trend in the EuroQoL 'Anxiety-Depression' scale also displayed a statistically non-normal distribution. In ANCOVA, the EuroQoL 'Anxiety-Depression' did not show any difference between groups ($p= .267$), even after applying the Mann-Whitney-U test on the Studentized residuals of these changes corrected for baseline measurements.

EuroQoL VAS thermometer

Overall the Visual Analogue Scale of the EuroQoL improved for both groups, from an average 61.5% pre-operative, up to 69.8% at final follow-up. The VAS showed an improvement in ANCOVA during the 12-month follow-up for both treatment groups ($p< .001$), but no group difference was observed (see Table 3, $p= .488$).

MFI-20 questionnaire

The results of the MFI-20 are presented in Table 4. In ANCOVA, the 'General Fatigue' and 'Reduced Activity' scale did improve for both treatment groups ($p< .001$) during 1-year follow-up, but there was no difference between groups (respectively $p= .410$ and $p= .430$). The 'Physical Fatigue' and ' Reduced Motivation' scale also showed no difference between groups (respectively $p= .299$ and $p= .264$). Finally, the 'Mental Fatigue' scale in the 1-year follow-up improved highly for both treatment groups ($p< .001$), but again with no difference between groups ($p= .804$).

Discussion

Background characteristics

The main prospective, randomized trial of 150 patients showed that 57.1% of patients in the add-on surgery group versus 41.9% in the standard surgery group were successfully treated for AF. Several reports on rhythm outcome after similar techniques of left atrial ablation lesions showed success rates of 71-100%[10,15-17] in restoration of SR, mainly in paroxysmal atrial fibrillation (pAF) patients[18-20]. Rhythm restoration success is largely related to the type of pre-operative AF[21] and whether add-on surgery was performed on a concomitant procedure[22]. Also in our study patients with pre-operative pAF showed a significantly higher percentage of SR restoration (81.5% in the add-on surgery group versus 57.7% in the control group). These findings suggest that pAF patients benefit most of adjuvant ablation surgery as rhythm restoration is concerned. Permanent or persistent AF-patients, who have many risk factors, show significantly less resumption of SR. Therefore add-on surgery should not be offered to all AF-patients in a routine manner during cardiac surgery. No beneficial effect on morbidity and mortality of add-on surgery could be demonstrated. Particularly, there was no reduction in stroke incidence. Up till now, only one study has been able to demonstrate the beneficial role of adjuvant AF-ablation on postoperative mortality[23].

Health-related quality of life measurements

The present study confirms the outcome of previous trials: overall HrQoL improved after cardiac surgery[24-25]. The RAND SF-36 showed significant improvement in all scales during follow-up without significant differences between groups. The EuroQoL (VAS and EQ-5D) on the other hand showed no significant improvement in HrQoL. As a generic measurement the EQ-5D and VAS may be too insensitive to assess specific conditions as AF. Surprisingly, the Pain/Discomfort scale in the EQ-5D showed a significant deterioration during follow-up (p= .012). This might well be a result of a Type I error. But Lahtinen et al. showed that chest pain after cardiac surgery at 1-year follow-up ranges from pain at rest (17%) to pain upon movement (31%)[26], while others reported incidences of post-sternotomy pain ranging from 38-56%[27-28]. Furthermore, anxiety and depression are supposed to interact with chronic postoperative pain after cardiac surgery[29], although in the present study Pain/Discomfort can not be

explained by raised levels of anxiety or depression. Finally, fatigue is a common symptom in patients with valve disease and/or coronary artery disease; on the other hand fatigue is also a key symptom of AF. The MFI-20 scores revealed an overall reduction in perceived dimensions of fatigue, probably due to treatment of underlying heart disease instead of diminishing the prevalence of AF. In general this prospective randomised study reveals that successful cardiac surgery is a predictor for improvement in HrQoL in patients with paroxysmal AF as well as in patients with chronic AF. Add-on surgery did not significantly contribute to rhythm conversion and HrQoL measurements improved equally for both treatment groups. It is suggested that in this population, impaired HrQoL was predominantly caused by pre-operative underlying heart disease and not by AF.

Comparison with previous studies

Recent studies (RACE and AFFIRM) show that restoration of SR in AF patients has no effect on mortality or on major physical endpoints, which therefore would imply no benefit in attempted restoration of SR, if survival or complications alone is the reason for rate/rhythm drug therapy[7,14]. This trial confirms that add-on surgery does not have any significant benefit on morbidity and mortality. Furthermore, patients who did not convert to SR after cardiac surgery perceived sufficient rate and rhythm control (cardioversions and antiarrhythmic drugs) and therefore did not show an inter-group difference in HrQoL outcome. This is consistent with above-mentioned studies (no differences in rate versus rhythm-control on HrQoL). However, improvement in HrQoL is one of the most important reasons to treat patients with AF today, though it is highly dependant on the selected add-on surgery procedure[30]. This study also showed an improvement in HrQoL if the ablation surgery was unsuccessful, although it was not statistically significant; probably patients who undergo a prolonged invasive procedure would have some QoL benefit from the procedure itself, unrelated to the presence or absence of AF. In the study by Gerstenfeld et al.[1] focal AF ablation was pursued in 41 patients, with QoL evaluation by modified SF-36. The ablation success rate was 32% with a coinciding significant improvement in HrQoL also after AF recurrence, suggesting that the ablation modified the AF substrate without complete elimination of the AF burden. A recent study of Weerasooriya et al.[32] showed a combined PV isolation and linear atrial ablation technique, with a success rate of 86% in 63 patients with paroxysmal AF during a 12-month follow-up. Successful ablation showed a significant improvement for all eight sub-scales of

the SF-36. The important differences between the above-mentioned studies and the present study are the following: the previous studies were non-randomised, non-controlled and non-blinded, only paroxysmal AF patients were investigated, concomitant underlying heart disease was not specified nor treated and rhythm follow-up was incompletely documented and evaluated at 12-month follow-up. In other words, it cannot be determined whether improvement of HrQoL was either achieved by complete absence of arrhythmia, by asymptomatic episodes of AF, or by treating underlying heart disease.

Study limitations

Two generic questionnaires (EuroQoL and RAND SF-36) were used for HrQoL assessment. Although widely used, it is possible that important aspects or changes in HrQoL in patients with AF are not measured. Moreover, scoring was highly dependant on other physical, non-cardiac, impairments the patient perceived at that time the questionnaire was completed. Longer follow-up might mask the true picture of recovery and enhanced HrQoL after cardiac surgery, because the longer follow-up is carried out, the more non-cardiac co-morbidity will develop. Usage of AF-specific questionnaires, such as used by Badia[33] might be helpful in the future. Secondly, the high number of patients in SR in the control group has important consequences for the study design, since the sample size calculation was based on the assumption that 25% of the patients in the control group, would spontaneously convert to SR: thus a larger sample size might have been needed to detect the effect of add-on surgery on rhythm outcome. On the other hand, we believe that our follow-up was much more extensive than in previous studies. Our follow-up protocol might be considered different from the new standards described in the 2006 ACC/AHA/ESC Guidelines and by the recommendation of the Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons[10,34]. These standards were not yet available when the study was conducted. Rhythm follow-up was performed by standardized EKG and Holter registration, which is in itself an improvement in comparison to follow-up in several other studies. Meanwhile, several devices for continuous rhythm monitoring have been developed that will further improve rhythm evaluation in future intervention studies.

Conclusions

HrQoL improves after cardiac surgery with or without add-on surgery, but this improvement is probably more affected by treating the underlying heart disease than by restoring SR. Furthermore general HrQoL instruments may provide a too global insight into the patient's perception of perceived empowerment; they are not specifically designed for the heterogeneity of the patient case mix. It would be useful to construct and evaluate more specific tools to capture HrQoL changes in AF patients more accurately in the future.

Acknowledgements:
B. van Ginneken
Research nurse, Amphia Hospital Breda

References

1. Levy S. Pharmacologic management of atrial fibrillation: current therapeutic strategies. *Am Heart J* 2001; 141(2 Suppl): S15-21.
2. Jordaens L, Szili-Torok T. Between Scylla and Charybdis: a choice between equally dreadful alternatives. *Europace* 2002; 4(3): 215-8.
3. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, et al. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol* 2003; 41(10): 1697-702.
4. Luderitz B, Jung W. Quality of life in atrial fibrillation. *J Interv Card Electrophysiol* 2000; 4 Suppl 1:201-9.
5. Schumacher M, Olschewski M, Schulgen G. Assessment of quality of life in clinical trials. *Stat Med* 1991; 1 0(12): 1915-30.
6. Brooks R. Quality of life measures. *Crit Care Med* 1996; 24(10): 1769.
7. Hagens VE. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol* 2004; 43(2): 241-7.
8. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation--Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 2000; 356(9244): 1789-94.
9. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; 39(3): 315-25.
10. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006; 48(4): 854-906.
11. Beck LB. The role of outcomes data in health-care resource allocation. *Ear Hear* 2000; 21(4 Suppl): 89S-96S.
12. Kuilman M, Bleeker JK, Hartman JA, Simoons ML. Long-term survival after out-of-hospital cardiac arrest: an 8-year follow-up. *Resuscitation* 1999; 41(1): 25-31.
13. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; 31(3): 247-63.
14. Jenkins LS, Brodsky M, Schron E, Chung M, Rocco T, Jr., Lader E, et al. Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005; 149(1): 112-20.
15. Ruchat P, Schlaepfer J, Delabays A, Hurni M, Milne J, Von Segesser LK. Left atrial radiofrequency compartmentalization for chronic atrial fibrillation during heart surgery. *Thorac Cardiovasc Surg* 2002; 50(3): 155-9.
16. Schuetz A, Schulze CJ, Sarvanakis KK, Mair H, Plazer H, Kilger E, et al. Surgical treatment of permanent atrial fibrillation using microwave energy ablation: a prospective randomized clinical trial. *Eur J Cardiothorac Surg* 2003; 24(4): 475-80; discussion 480.
17. Deneke T, Khargi K, Grewe PH, von Dryander S, Kuschkowitz F, Lawo T, et al. Left atrial versus bi-atrial Maze operation using intraoperatively cooled-tip radiofrequency ablation in patients undergoing open-heart surgery: safety and efficacy. *J Am Coll Cardiol* 2002;39(10):1644-50.
18. Sueda T, Imai K, Ishii O, Orihashi K, Watari M, Okada K. Efficacy of pulmonary vein isolation for the elimination of chronic atrial fibrillation in cardiac valvular surgery. *Ann Thorac Surg* 2001; 71(4): 1189-93.
19. Starck C, Botha CA, Roser D, Paula J, Rein JG, Hemmer W. Results of a modified left atrial maze procedure as a combined procedure. *Thorac Cardiovasc Surg* 2003; 51(3): 147-53.
20. Suwalski P, Suwalski G, Doll N, Majstrak F, Kurowski A, Suwalski KB. Epicardial beating heart "off-pump" ablation of atrial fibrillation in non-mitral valve patients using new irrigated bipolar radiofrequency technology. *Ann Thorac Surg* 2006; 82(5): 1876-9.

21. Yamada T, Murakami Y, Okada T, Yoshida N, Toyama J, Yoshida Y, et al. Plasma brain natriuretic peptide level after radiofrequency catheter ablation of paroxysmal, persistent, and permanent atrial fibrillation. *Europace* 2007; 9(9): 770-4.

22. Khargi K, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation; a systematic review. *Eur J Cardiothorac Surg* 2005; 27(2): 258-65.

23. Knaut M, Tugtekin SM, Spitzer S, Jung F, Matschke K. Mortality after cardiac surgery with or without microwave ablation in patients with permanent atrial fibrillation. *J Heart Valve Dis* 2005; 14(4): 531-7.

24. Rumsfeld JS, Ho PM, Magid DJ, McCarthy M, Jr., Shroyer AL, MaWhinney S, et al. Predictors of health-related quality of life after coronary artery bypass surgery. *Ann Thorac Surg* 2004; 77(5): 1508-13.

25. Thornton EW, Groom C, Fabri BM, Fox MA, Hallas C, Jackson M. Quality of life outcomes after coronary artery bypass graft surgery: relationship to neuropsychologic deficit. *J Thorac Cardiovasc Surg* 2005; 130(4): 1022-7.

26. Lahtinen P, Kokki H, Hynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 2006; 105(4): 794-800.

27. Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery--a prospective study. *Acta Anaesthesiol Scand* 2001; 45(8): 940-4.

28. Eisenberg E, Pultorak Y, Pud D, Bar-El Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). *Pain* 2001; 92(1-2): 11-7.

29. Taillefer MC, Carrier M, Belisle S, Levesque S, Lanctot H, Boisvert AM, et al. Prevalence, characteristics, and predictors of chronic nonanginal postoperative pain after a cardiac operation: a cross-sectional study. *J Thorac Cardiovasc Surg* 2006; 131(6): 1274-80.

30. Erdogan A, Carlsson J, Neumann T, Berkowitsch A, Neuzner J, Hamm CW, et al. Quality-of-life in patients with paroxysmal atrial fibrillation after catheter ablation: results of long-term follow-up. *Pacing Clin Electrophysiol* 2003; 26(3): 678-84.

31. Gerstenfeld EP, Guerra P, Sparks PB, Hattori K, Lesh MD. Clinical outcome after radiofrequency catheter ablation of focal atrial fibrillation triggers. *J Cardiovasc Electrophysiol* 2001; 12(8): 900-8.

32. Weerasooriya R, Jais P, Hocini M, Scavee C, MacLe L, Hsu LF, et al. Effect of catheter ablation on quality of life of patients with paroxysmal atrial fibrillation. *Heart Rhythm* 2005; 2(6): 619-23.

33. Badia X, Arribas F, Ormaetxe JM, Peinado R, de Los Terreros MS. Development of a questionnaire to measure health-related quality of life (HRQoL) in patients with atrial fibrillation (AF-QoL). *Health Qual Life Outcomes* 2007; 5:37.

34. Shemin RJ, Cox JL, Gillinov AM, Blackstone EH, Bridges CR. Guidelines for reporting data and outcomes for the surgical treatment of atrial fibrillation. *Ann Thorac Surg* 2007; 83(3): 1225-30.

Figure 1: box lesions

Posterior view of the heart. The bold lines illustrate the six epicardial ablation lesions, encircling all four pulmonary veins.

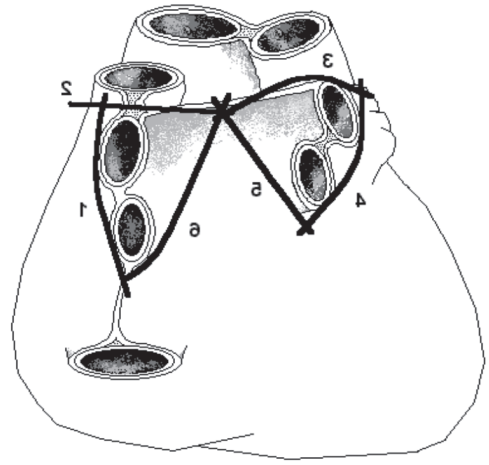


Table 1. Comparison of baseline characteristics and rhythm outcome between control and add-on surgery patients (N=132).

	Study Population	Control (N=67)	Add-on surgery (N=65)	p-value
Demographic data				
Age (Years)	68.2 ± 9.1	71.0 (38.8 – 85.0)	61.9 (46.6 – 81.0)	.17
Weight (Kg)	77.9 ± 16.4	77.7 (50 – 170)	78.1 (49 – 111)	.89
Sex (male)	85 (64.4%)	39 (58.2%)	46 (70.8%)	.13
Previous cardiac history (N=132)				
Atrial Fibrillation:				.99
Paroxysmal AF	57(43.2%)	30(44.8%)	27(41.5%)	
Permanent AF	43 (32.6%)	21(31.3%)	22(33.8%)	
Persistent AF	30 (22.7%)	15(22.4%)	15(23.1%)	
Atrial flutter	2 (1.5%)	1(1.5%)	1(1.5%)	
Total months of AF	81.0 ± 102.4	84,1 (3 – 618)	78,0 (33 – 403)	.73
Left Atrial Dimension (mm)	50.6 ± 7.5	50.4 (33-70)	50.7 (40-67)	.38
Left Ventrical Ejection Fraction (%)	52.6 ± 13.5	56.5 (30-80)	48.8 (18-79)	.01
Pre-operative complaints (N=132)				
Palpitations	58 (39.2%)	34 (44.7%)	24 (33.3%)	.16
Dyspnea	120 (81.1%)	61 (80.3%)	59 (81.9%)	.79
Angina	60 (40.8%)	33 (44%)	27 (37.5%)	.42
(Pre-) Syncope	7 (4.7%)	3 (3.9%)	4 (5.6%)	.65
Dizziness	41 (27.7%)	23 (30.3%)	18 (25%)	.47
Fatigue	76 (51.4%)	41 (53.9%)	35 (48.6%)	.52
Other complaints	12 (8.2%)	7 (9.2%)	5 (7.0%)	.63

Table 1. continued

	Study Population	Control (N=67)	Add-on surgery (N=65)	p-value
Operative data (N=132)				
Coronary Artery Bypass Grafting (CABG)	41 (31.1%)	23 (34.3%)	18 (27.7%)	
Valve replacement	53 (40.2%)	21 (31.3%)	32 (49.2%)	
CABG and Valve replacement	30 (22.7%)	20 (29.9%)	10 (15.4%)	
Other cardio-surgery	8 (6.1%)	3 (4.5%)	5 (7.7%)	
				.08
Postoperative rhythm				
Atrial fibrillation	113 (85.6%)	55 (82.1%)	58 (89.2%)	.24
Atrial flutter	7 (5.3%)	0 (0%)	7 (10.8%)	.01
Atrioventricular block	18 (13.6%)	13 (19.4%)	5 (7.7%)	.05
Temporary Pacemaker	56 (42.4%)	29 (43.3%)	27 (41.5%)	.84
Definite Pacemaker	3 (2.3%)	1 (1.5%)	2 (3.1%)	.54
Postoperative Cardioversions				
Electrical	10 (7.6%)	3 (4.5%)	7 (10.8%)	.17
Pharmacological	23 (19.5%)	8 (13.6%)	15 (25.4%)	.10
Rhythm Outcome				
SR at discharge (N=126)	50 (39.7%)	27 (42.2%)	23 (39.7%)	.56
SR at 1 month (N=110)	54 (49.1%)	26 (45.6%)	28 (52.8%)	.45
SR at 6 months (N=115)	69 (60.0%)	31 (53.4%)	38 (66.7%)	.15
SR at 12 months (N=125)	62 (47.0%)	26 (41.9%)	36 (57.1%)	.09
Rhythm outcome at 12 months (N=125)				
Sinus rhythm	62 (49.6%)	26 (41.9%)	36 (57.1%)	
Paroxysmal AF	6 (4.8%)	5 (8.1%)	1 (1.6%)	
Persistent AF	7 (5.6%)	3 (4.8%)	4 (6.3%)	
Permanent AF	34 (27.2%)	18 (29.0%)	16 (25.4%)	
Atrial flutter	5 (4.0%)	2 (3.2%)	3 (4.8%)	
Pacemaker rhythm	1 (0.8%)	1 (1.6%)	0 (0.0%)	
Lost in follow-up (including death)	10 (8.0%)	7 (11.3%)	3 (4.8%)	
				.28
Conversion to SR at 12 months follow-up compared to type of AF	SR:	SR:	SR:	
Pre-operative paroxysmal AF	37 (69.8%)	15 (57.7%)	22 (81.5%)	
Pre-operative permanent AF	11 (28.2%)	4 (21.1%)	7 (35.0%)	
Pre-operative persistent AF	12 (44.4%)	6 (42.9%)	6 (46.2%)	
Pre-operative atrial flutter	2 (100.0%)	1 (100%)	1 (100%)	
	<.01			.01

Table 2. Means and standard deviations of SF-36 scores for 1-year follow-up in total and for both treatment groups (N=132). First *p*-value per scale tests linear 1-year trend for total group, second *p*-value tests overall interaction time*group effect (i.e. difference in 1-year trend between groups).

	Physical Functioning							
	Total group (N=132)			**Control (N=67)**		**Add-on (N=65)**		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	50.12	24.05		50.12	24.23	50.23	24.05	
3 months Postoperative (M2)	65.13	23.10		61.14	25.06	69.24	20.25	
6 months Postoperative (M3)	64.60	23.15		61.36	24.13	67.94	21.78	
12 months Postoperative (M4)	64.78	23.72		61.24	23.86	68.42	23.21	
P-value			<.001					.143

	Mental Health							
	Total group (N=132)			**Control (N=67)**		**Add-on (N=65)**		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	70.82	20.99		72.01	22.04	69.60	19.96	
3 months Postoperative (M2)	74.41	19.63		74.29	20.52	74.52	18.84	
6 months Postoperative (M3)	78.02	14.83		77.91	15.80	78.13	13.87	
12 months Postoperative (M4)	75.81	15.50		73.99	17.46	77.69	13.04	
P-value			<.001					.300

	Physical Pain							
	Total group (N=132)			**Control (N=67)**		**Add-on (N=65)**		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	74.15	24.76		72.31	24.55	76.04	25.02	
3 months Postoperative (M2)	75.00	22.95		75.75	21.62	74.23	24.40	
6 months Postoperative (M3)	77.88	22.50		73.27	24.40	82.63	19.43	
12 months Postoperative (M4)	75.21	22.32		72.77	21.94	77.74	22.59	
P-value			<.001					.032

	Vitality							
	Total group (N=132)			**Control (N=67)**		**Add-on (N=65)**		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	50.89	22.02		51.31	21.83	50.46	22.37	
3 months Postoperative (M2)	59.24	20.60		57.96	21.87	60.56	19.30	
6 months Postoperative (M3)	61.19	20.16		58.39	21.62	64.09	18.27	
12 months Postoperative (M4)	60.67	17.33		59.99	17.80	61.36	16.95	
P-value			<.001					.246

Table 2. continued

	Role limitations due to emotional problems							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	68.48	42.27		69.24	41.97	67.69	42.89	
3 months Postoperative (M2)	66.38	39.40		66.63	38.93	66.13	40.18	
6 months Postoperative (M3)	75.52	35.91		69.48	40.87	81.74	28.97	
12 months Postoperative (M4)	70.79	36.07		69.52	36.64	72.11	35.71	
P-value			<.001					.157

	Role limitations due to physical limitations							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	33.33	39.96		42.91	42.08	23.46	35.32	
3 months Postoperative (M2)	41.53	37.48		42.89	37.89	40.12	37.29	
6 months Postoperative (M3)	54.42	40.77		51.41	40.84	57.53	40.79	
12 months Postoperative (M4)	50.48	38.83		47.86	38.13	53.17	39.65	
P-value			<.001					.295

	Social Functioning							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	66.96	25.42		66.99	25.78	66.92	25.24	
3 months Postoperative (M2)	74.26	23.49		73.41	24.37	75.14	22.70	
6 months Postoperative (M3)	79.65	23.02		76.63	26.97	82.76	17.76	
12 months Postoperative (M4)	78.10	22.21		76.21	24.68	80.04	19.34	
P-value			<.001					.410

	General Health							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P-time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/ Baseline)	56.74	18.86		60.23	17.43	53.15	19.72	
3 months Postoperative (M2)	60.00	18.62		59.93	19.43	60.08	17.89	
6 months Postoperative (M3)	60.31	18.60		59.52	19.52	61.12	17.71	
12 months Postoperative (M4)	55.43	17.71		54.87	17.35	56.01	18.19	
P-value			<.001					.458

Table 3. Means and standard deviations for EuroQoL scores for 1-year follow-up in total and for both treatment groups (N=132). First *p*-value per scale tests linear 1-year trend for the total group, second *p*-value tests overall interaction time*group effect (i.e. difference in 1-year trend between groups).

	Mobility							
	Total group (N=132)			**Control (N=67)**		**Add-on (N=65)**		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	1.50	.50		1.49	.49	1.52	.50	
3 months Postoperative (M2)	1.50	.51		1.56	.50	1.44	.51	
6 months Postoperative (M3)	1.47	.48		1.52	.50	1.42	.46	
12 months Postoperative (M4)	1.50	.46		1.55	.48	1.44	.45	
P-value			<.001					.346
	Self Care							
	Total group (N=132)			**Control (N=67)**		**Add-on (N=65)**		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	1.11	.31		1.11	.31	1.11	.31	
3 months Postoperative (M2)	1.16	.41		1.20	.49	1.12	.31	
6 months Postoperative (M3)	1.09	.26		1.09	.26	1.09	.267	
12 months Postoperative (M4)	1.14	.34		1.15	.37	1.14	.31	
P-value			<.001					.460
	Usual activities							
	Total group (N=132)			**Control (N=67)**		**Add-on (N=65)**		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	1.63	.59		1.64	.59	1.62	.60	
3 months Postoperative (M2)	1.53	.68		1.65	.75	1.41	.59	
6 months Postoperative (M3)	1.49	.59		1.62	.67	1.34	.47	
12 months Postoperative (M4)	1.52	.57		1.59	.59	1.46	.54	
P-value			<.001					.056

Table 3. continued

	Pain/Discomfort							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	1.26	.44		1.28	.44	1.25	.43	
3 months Postoperative (M2)	1.47	.52		1.53	.50	1.42	.54	
6 months Postoperative (M3)	1.46	.57		1.59	.60	1.33	.50	
12 months Postoperative (M4)	1.51	.54		1.64	.52	1.38	.53	
P-value			<.001					.006

	Anxiety/Depression							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	1.37	.59		1.43	.65	1.31	.53	
3 months Postoperative (M2)	1.28	.52		1.28	.54	1.28	.50	
6 months Postoperative (M3)	1.18	.35		1.19	.37	1.16	.34	
12 months Postoperative (M4)	1.20	.40		1.27	.47	1.13	.29	
P-value			<.001					.267

	VAS							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	61.54	17.62		61.60	16.13	61.47	19.16	
3 months Postoperative (M2)	68.42	14.90		67.89	15.77	68.96	14.06	
6 months Postoperative (M3)	71.51	16.71		69.61	18.17	73.47	14.95	
12 months Postoperative (M4)	69.81	16.09		68.60	16.64	71.05	15.52	
P-value			<.001					.488

Table 4. Means and standard deviations of Multidimensional Fatigue Inventory (MFI) scores for 1-year follow-up in total and for both treatment groups (N=132). First *p*-value per scale tests linear 1-year trend for the total group, second *p*-value tests overall interaction time*group effect (i.e. difference in 1-year trend between groups).

	General Fatigue							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	3.56	1.11		3.51	1.12	3.62	1.10	
3 months Postoperative (M2)	2.87	1.13		2.93	1.20	2.81	1.06	
6 months Postoperative (M3)	2.67	1.13		2.76	1.19	2.58	1.07	
12 months Postoperative (M4)	2.85	1.01		2.82	1.03	2.88	.99	
P-value			<.001					.410
	Physical Fatigue							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	3.45	1.10		3.33	1.04	3.57	1.16	
3 months Postoperative (M2)	2.89	1.16		2.96	1.17	2.82	1.15	
6 months Postoperative (M3)	2.69	1.16		2.79	1.24	2.58	1.08	
12 months Postoperative (M4)	2.85	1.04		2.96	1.06	2.74	1.01	
P-value			<.001					.299
	Reduced Activity							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	3.32	1.15		3.31	1.13	3.33	1.19	
3 months Postoperative (M2)	2.90	1.08		3.02	1.06	2.78	1.09	
6 months Postoperative (M3)	2.64	1.18		2.72	1.23	2.55	1.13	
12 months Postoperative (M4)	2.71	1.08		2.72	1.11	2.71	1.05	
P-value			<.001					.430

Table 4. continued

	Reduced Motivation							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	2.64	1.09		2.73	1.11	2.55	1.07	
3 months Postoperative (M2)	2.54	1.13		2.70	1.14	2.39	1.10	
6 months Postoperative (M3)	2.30	1.03		2.48	1.14	2.11	.87	
12 months Postoperative (M4)	2.36	.93		2.50	1.00	2.22	.82	
P-value			<.001					.264

	Mental Fatigue							
	Total group (N=132)			Control (N=67)		Add-on (N=65)		
	Mean	Std. Deviation	P- time* group *)	Mean	Std. Deviation	Mean	Std. Deviation	P-linear* group ^)
Pre-operative (M1/Baseline)	2.30	1.07		2.37	1.11	2.23	1.02	
3 months Postoperative (M2)	2.10	1.05		2.14	1.14	2.05	.95	
6 months Postoperative (M3)	2.08	.97		2.05	1.01	2.11	.94	
12 months Postoperative (M4)	2.15	.99		2.19	1.04	2.12	.95	
P-value			<.001					.804

Chapter 3

Sinus rhythm conversion after cardiac surgery in patients with pre-operative atrial fibrillation; does it affect postoperative health-related quality of life?

[1]Henrica N.A.M. van Breugel, MD, [2]Fred H.M. Nieman, PhD,
[1]Ryan E. Accord, MD, [1,3]Sandro Gelsomino, MD, Ph.D, [1,4]Fabiana Lucà, MD,
[1]Pieter Lozekoot, MD, [3]Orlando Parise MSc, [1]Ghislaine A.P.G. van Mastrigt, PhD,
[1]Jan F.M.A. Nijs, MD, [5]Ries Vrakking, MD, [1]Jos G. Maessen, MD, PhD.

[1]Department of Cardiothoracic Surgery, Maastricht University Medical Centre, The Netherlands
[2]Department of Clinical Epidemiology & Medical Technology Assessment University Hospital of Maastricht, The Netherlands
[3]Department of Heart and Vessels, Careggi Hospital, Florence, Italy
[4]Department of Cardiology, Paolo Borsellino Hospital, Marsala, Italy
[5]Department of Cardiothoracic Surgery, Amphia Hospital Breda, The Netherlands

Under review: Eur J Cardiothoracic Surg.

Table 2. Surgery (n=685).

Unipolar		166 (24.2)
Bipolar		371 (54.2)
Combined Bipolar/Unipolar		148 (21.6)
LA Connecting Lesions		
Roof Line		552 (80.5)
Inferior Line		483 (70.5)
Mitral Isthmus Line		437 (63.7)
LAA to LPV Line		453 (66.1)
RA Ablation		318 (46.4)
LAA Isolation		212 (30.9)
LAA Ligation/Stitching		
Ligation		534 (77.9)
Stitching		151 (22.1)
Cardio Ablate System		531 (77.5)
Atricure System		154 (22.4)
GP Ablation		279 (40.7)
CPB Time		96.4±14.3
CCT		74.2±13.1
Main Procedure		
MV Repair		316 (46.1)
MV Replacement		
	Biological	247 (36.0)
	Mechanical	122 (17.9)
Concomitant Procedures		
AV Repair		34 (4.9)
AV Replacement		
	Biological	74 (10.8)
	Mechanical	37 (5.4)
TVR		264 (38.5)
CABG		97 (14.1)
Other		22 (3.2)

Values are shown as mean ± standard deviation for normally distributed data or number (percentage) for categorical data.

Abbreviations: PVs, Pulmonary Veins; LA, Left Atrium; LAA, Left Atrium Appendage; LPV, Left Pulmonary Veins; RA, Right Atrium; GP, Ganglionated Plexi; CPB, Cardiopulmonary bypass; CCT, Cross Clamp Time; MV, Mitral Valve; AV, Aortic Valve; TVR, Tricuspid Valve Repair; CABG, Coronary Artery Bypass Graft.

Table 3. Rhythm at follow-up by surgery.

	NSR	*p*	NSR Off-AAD	*p*
Unipolar	101 (74.2)	*	86 (63.2)	**
Bipolar	307 (96.2)		271 (85.1)	
Combined Bipolar/Unipolar	105 (84.6)		90 (72.5)	
Roof Line (yes/no)	363/96 (79.0/80.0)	0.7	289/74 (62.9/61.6)	0.6
Inferior Line (yes/no)	323/139 (80.5/78.0)	0.2	252/113 (62.8/63.4)	0.6
Mitral Isthmus Line (yes/no)	295/178 (78.4/82.7)	0.07	237/126 (63.0/62.0)	0.7
LAA to LPV (yes/no)	311/155 (80.8/79.8)	0.7	235/124 (61.0/63.9)	0.3
RA Ablation (yes/no)	206/246 (86.1/72.3)	0.001	172/215 (71.9/63.2)	0.03
LAA Isolation (yes/no)	144/312 (80.0/78.1)	0.5	116/242 (64.4/60.6)	0.1
LAA Ligation/ Stitching	357/101 (78.1/82.7)	0.06	275/77 (60.1/63.1)	0.1
GP Ablation (yes/no)	190/267 (80.1/78.0)	0.3	148/217 (62.4/63.4)	0.7
Cardio Ablate/ Atricure System	364/99 (80.3/78.5)	0.6	287/79(63.3/62.6)	0.7
MV Repair/ Replacement	214/246 (80.4/78.6)	0.6	165/197 (62.0/63.9)	0.5
Concomitant Procedures (yes/no)	330/129 (78.7/80.6)	0.5	257/102 (61.3/63.7)	0.2

Values are shown as number (percentage) for categorical data. **Abbreviations:** NSR: Normal sinus rhythm; AAD: Antiarrhythmic Drugs; LAA, Left Atrium Appendage; LPV, Left Pulmonary Veins; LAA, Left atrial appendage; RA, Right Atrium; GP, Ganglionated Plexi; LA, Left Atrium; MV, Mitral Valve.

* Unipolar vs Bipolar, $p<0.001$; Unipolar vs Combined Bipolar/Unipolar $p=0.003$; Bipolar vs Combined Bipolar/Unipolar $p=0.001$

** Unipolar vs Bipolar $p=0.001$; Unipolar vs Combined Bipolar/Unipolar $p=0.005$; Bipolar vs Combined Bipolar/Unipolar $p=0.001$

Table 4. Competing risk regression

	SHR (95% CI)	*p*
Unipolar	7.41 (5.22-12.43)	<0.001
Combined Bipolar/Unipolar	3.93 (2.89-5.87)	0.003
Bipolar	0.75 (0.36-1.72)	0.547
Lack of Roof Line	1.69 (0.87.4.25)	0.172
Lack of Inferior Line	1.47 (0.79-3.98)	0.131
Lack of Mitral Isthmus Line	1.32 (0.54-2.27)	0.114
Lack of LAA to LPV line	1.25 (0.79-4.02)	0.205
Lack of RA Ablation	2.79 (1.27-6.48)	0.011
Lack of GP Ablation	0.97 (0.44-2.87)	0.684
Lack of LAA Isolation	1.61 (0.58-4.32)	0.517
Lack of LAA Ligation/Stitching	2.10 (1.02-4.62)	0.328
Ablation system	1.05 (0.58-2.57)	0.896
MV Repair	0.89 (0.39-1.79	0.393
MV Replacement	1.75 (0.81-3.98)	0.213
Concomitant Procedures	0.98 (0.43-4.68)	0.913

Abbreviations: SHR, Sub- Hazard Ratio; CI, Confidence Interval; LAA, Left Atrium Appendage; LPV, Left Pulmonary Veins; RA, Right Atrium; GP, Ganglionated Plexi; MV, Mitral Valve.

Table 5. Echocardiographic results by rhythm at follow-up.

	Sinus Rhythm	AF Recurrence	*p*
LA diameter (mm)	51.8±9.4 *	55.3±8.1 *	< 0.001
LA area (cm^2)	30.4±7.1 *	33.7±8.5 *	< 0.001
RA area (cm^2)	20.8±4.4 *	22.2±6.4 *	0.001
Systolic PAP (mmHg)	40.2±11.4 *	44.7±14.6	< 0.001
LVEDD (mm)	50.0±8.8	51.0±9.0	0.09
LVESD (mm)	38.0±7.9	39.0±7.4	0.1

Values are shown as mean ± standard deviation.
Abbreviations: AF, Atrial Fibrillation; LA, Left Atrium; RA, Right Atrium; PAP, Pulmonary Artery Pressure; LVEDD, Left Ventricular End-Diastolic Diameter; LVESD, Left Ventricular End-Systolic Diameter. *Significance versus baseline.

Figure 1. Cumulative survival

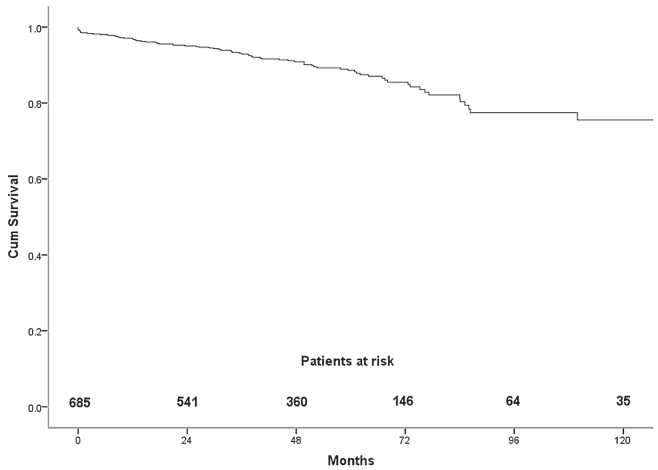


Figure 2. A-D
Ten-year cumulative cncidence of recurrent atrial fibrillation by type of radiofrequency ablation and left atrial lesion lines. The cumulative incidence was reported with the 95% confidence interval (parentheses) and the standard error (SE).
Abbreviations: RF, Radiofrequency; AF, Atrial Fibrillation; LAA, Left Atrial Appendage; LPVs, Left Pulmonary Veins.

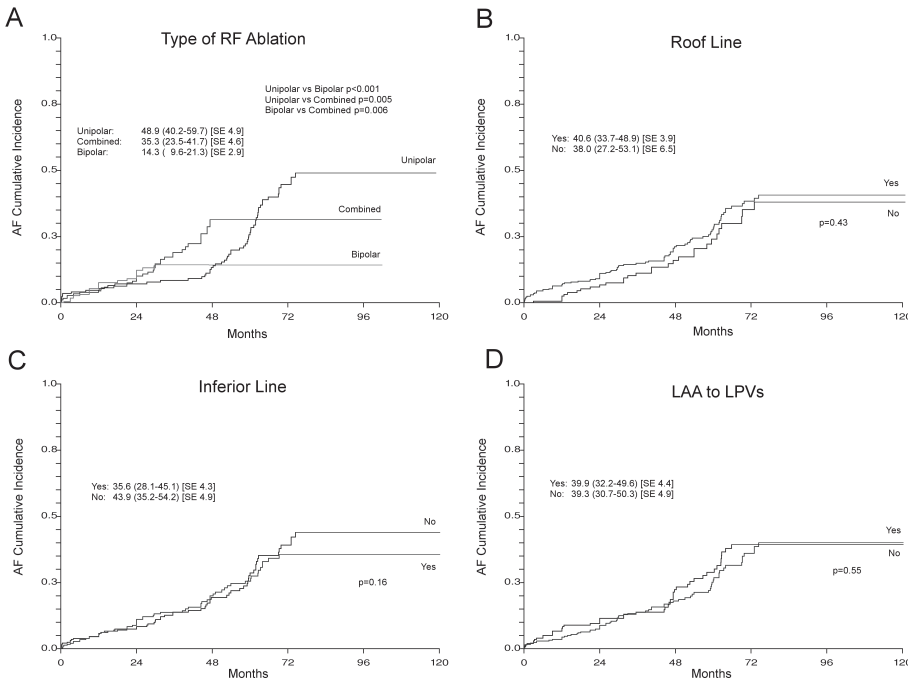


Figure 3.A-D
Ten-year cumulative incidence of recurrent atrial fibrillation by performance of mitral isthmus line, right atrial ablation, left atrial appendage isolation and left atrial appendage ligation/stitching. The cumulative incidence was reported with the 95% confidence interval (parentheses) and the standard error (SE). **Abbreviations:** AF, Atrial Fibrillation; MI, Mitral Isthmus; RA, Right Atrium; LAA, Left Atrial Appendage.

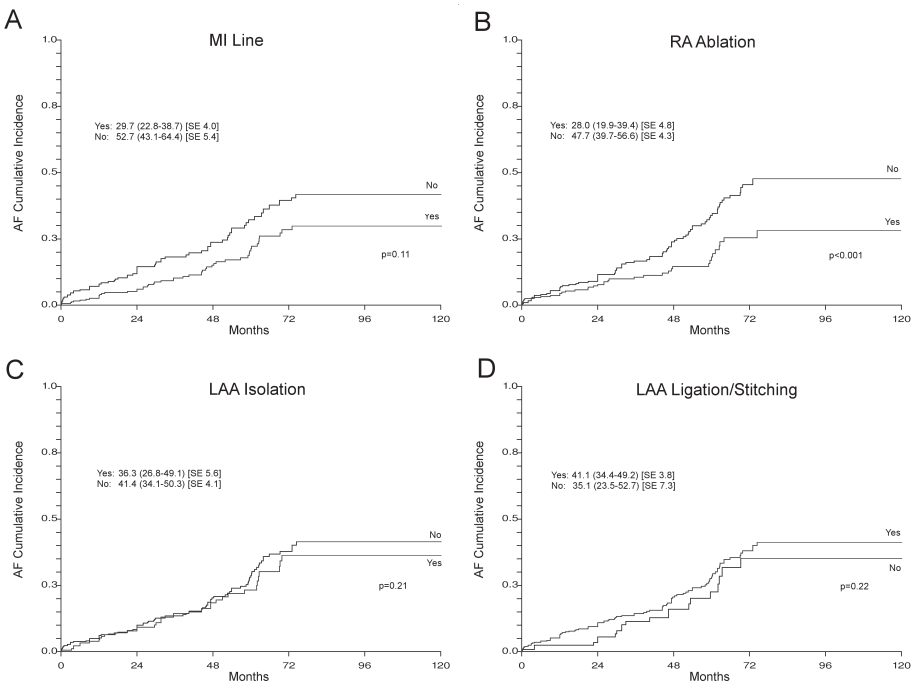


Figure 4.A-D
Ten-year cumulative incidence of recurrent atrial fibrillation by ganglionated plexi ablation, type of ablation system employed, type of main procedure performed on mitral valve and performance of concomitant heart procedures. The cumulative incidence was reported with the 95% confidence interval (parentheses) and the standard error (SE).
Abbreviations: AF, Atrial Fibrillation; GP, Ganglionated Plexi; MV, Mitral Valve;

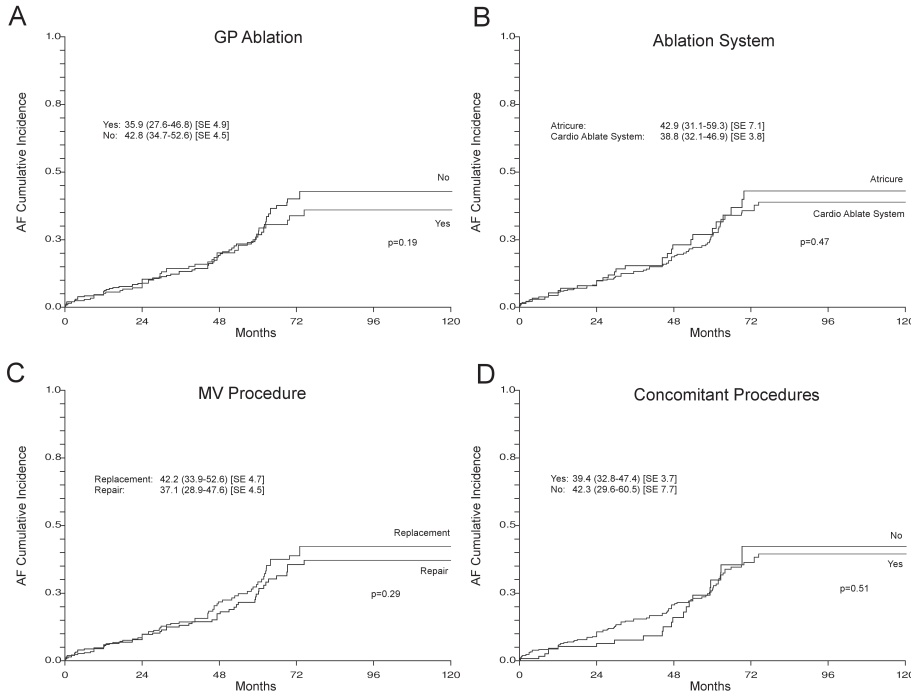
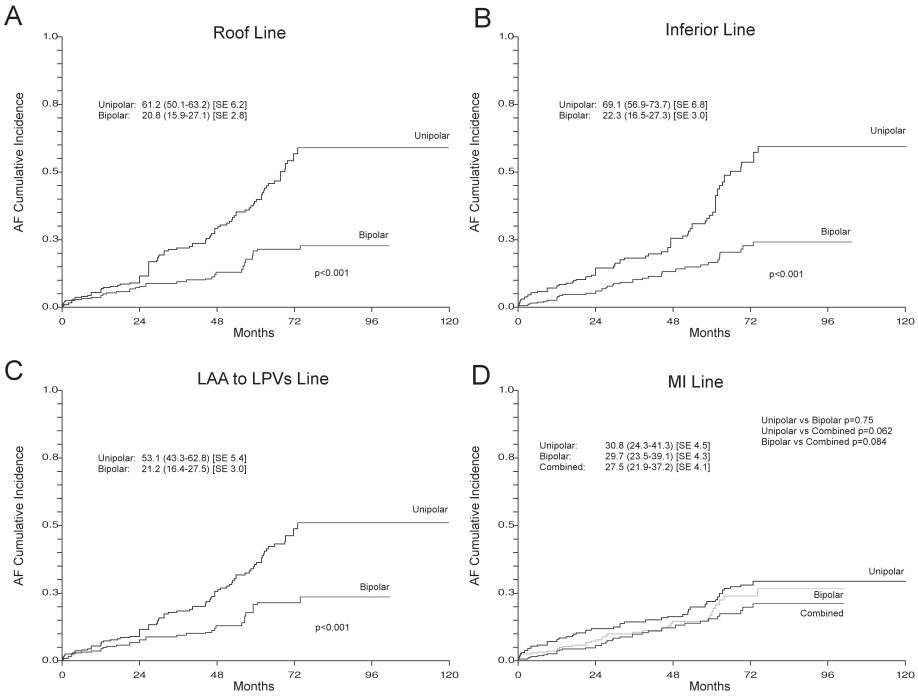


Figure 5.A-D
Ten-year cumulative incidence of recurrent atrial fibrillation by RF source employed for left atrial linear lesions. The cumulative incidence was reported with the 95% confidence interval (parentheses) and the standard error (SE).
Abbreviations: LAA, Left Atrial Appendage; LPVs, Left Pulmonary Veins; MI, Mitral Isthmus;



Appendix 1

Patients available for rhythm analysis at follow-up (n=579)	
Unipolar	136 (23.4)
Combined Bipolar/Unipolar	319 (55.0)
Bipolar	124 (21.4)
Roof Line	459 (79.2)
Inferior Line	401 (69.2)
Mitral Isthmus Line	376 (64.9)
LAA to LPV line	385 (66.4)
RA Ablation	239 (41.4)
LAA Isolation	180 (31.0)
LAA Ligation	457 (78.9)
LAA Stitching	122 (21.1)
Ablation system: Cardioablate	453 (78.2)
Ablation system: Atricure	126 (21.8)
GP Ablation	237 (40.9)
MV Repair	266(45.9)
MV Replacement	313 (54.0)
Concomitant Procedures	419 (72.3)

Values are shown as number (percentage)

Abbreviations: LAA, Left Atrium Appendage; LPV, Left Pulmonary Veins; RA, Right Atrium; GP, Ganglionated Plexi; MV, Mitral Valve.

Chapter 8

Hybrid thoracoscopic and transvenous catheter ablation of atrial fibrillation

[1]Sandro Gelsomino*, MD, PhD,[1] Henrica N.A.M.van Breugel*,MD,
[1]Laurant Pison, MD, [1]Orlando Parise, MSc,[1]Harry J G M Crijns, MD, PhD,
[2]Francis Wellens, MD, PhD, [1]Jos G Maessen, MD, PhD,
and [2]Mark La Meir, MD PhD.

***The first two authors equally contributed to the paper.**
[1]Department of cardiology and cardiothoracic surgery, Maastricht University Hospital, Maastricht, The Netherlands
[2]Department of cardiothoracic surgery, University Hospital, Brussels, Belgium

Eur J Cardiothorac Surg. 2014 Mar; 45(3): 401-7

Table 2. Surgery

First Author	Source	Method	Access	Roof	Inf	A-LA	IL	RA	LAA	GP	CTL	CSL
Mahapatra S.[17]	RF (b)I	VATS	B-Thor	Y	-	Y	-	Y	14/15	Y	Y	Y
Krul S.P.J[18]	RF(b) I	VATS	B-Thor	13/31	8/31	13/31	-	-	29/31	Y	ns	-
La Meir M.[19]	RF (b)I	VATS	B-Thor	31/35	32/35	Y	7/35	23/35	15/35	Y	3/35	-
Pison L.[20]	RF(b) I	VATS	B-Thor	23/26	22/26	Y	3/26	8/26	Y	Y	2/26	-
La Meir M.[21]	RF(u) I	VATS	R-Thor	-	Y	3/19	-	-	-	Y	2/19	-
Zembala M.[22]	RF(u) I	VALS	LAP	Y	Y	-	-	-	Y	-	Y	-
Muneretto C.[23]	RF(u)	VATS	R-Thor	Y	Y	-	-	-	-	Y	ns	-
Gehi A.K[24].	RF(u) I	VATS	SubX	90/101	97/101	Y	84/101	-	-	-	99/101	73/101
Bisleri G.[25]	RF(u)	VATS	R-Thor	Y	Y	-	-	-	-	-	ns	-

Studies were presented by year of publication. **Abbreviations:** Source: RF: Radiofrequency; b: bipolar; u: unipolar; I. Irrigated; Method:VATS: video assisted thoracoscopic surgery;VALS:Video assisted Laparoscopy ;Access: R-Thor: Right Thorachoscopy; B-Thor:Bilateral Thorachoscopy; LAP: Laparoscopy; SubX: Subxiphoid; Roof: Roof line; Inf: Inferior line;A-LA:Additional Left Atrial lines; IL: Isthmus line.Y: RA: Right atrial and caval lines, LAA: Left atrial appendage excision/closure; GP: Ganglionated plexi ablation; CTL Cavo-tricuspid line; CSL: Coronary sinus line;Y:Yes; ns: not specified

Table 3. End-points and rhythm monitoring

First Author	F-Up (m)	Completeness	F-Up type	End-point	Rhythm Monitoring	AAD	OA
Mahapatra S.[17]	20.4±4.5	15/15 (100%)	OC	1	EKG; 7d CAT; 24h HM	6.6%	ns
Krul S.P.J[18]	24	22/31 (70.9%)	OC	2	EKG; 24h HM	ns	48.3%
La Meir M.[19]	24	35/35 (100%)	OC;CV	3	EKG; 7d HM	26%**	29%**
Pison L.[20]	*	24/26 (92.3%)	OC ;CV	3	EKG; 7d HM	ns	ns
La Meir M.[21]	24	19/19 (100%)	OC;CV	4	EKG; 7d HM	26%**	48.2%**
Zembala M.[22]***	24	18/27 (66.6%)	OC	5	24h HM	ns	ns
Muneretto C.[23]	30	36/36 (100%)	OC	6	ICM	22.2%	ns
Gehi A.K[24].	12	101/101 (100%)	OC	7	24h HM	37%	ns
Bisleri G.[25]	28.4±1.7	45/45 (100%)	OC	6	ICM	ns	ns

Studies were presented by year of publication. **Abbreviations**: F-Up: Follow-up; m=months;AAD: (%patients taking) Antiarrhythmic Drugs; OA: (%patients taking) Oral Anticoagulants. **Endpoint**: 1: Event-free survival of any atrial arrhythmia longer than 30 seconds off AAD; 2: Freedom from episodes of AF, atrial flutter or tachycardia, without the use of AAD after 12 months;3: No AT, AF or Atrial Flutter lasting >30 seconds off antiarrhythmic drugs;4.AF prevalence; 5: Patients in AF; 6 Absence of AF

lasting more than 5 minutes and an overall burden of 0.5% of time spent in AF on a monthly basis;7:Any asymptomatic or symptomatic episode of AF lasting >30 seconds noted on ECG, 24-h monitoring or pacemaker/implantable cardiac defibrillator interrogation.**Follow-Up type**: OC: Outpatient Clinic; CV: Cardiologic Visits. **Rhythm Monitoring**: EKG: Electrocardiograms, HM: Holter Monitoring, CAT: Continuous autotriggered monitor; ICM: Insertable Cardiac Monitor. *Fup: 6 months (n=2), 12 months (n=21), 24 months n=3. Ns: not specified. **Estimated prevalence. ***This author reports 3-6-12 and 24- month results (see text)

Table 4. Results according to HRS/EHRA/ECAS Consensus*

	ALL			Paroxysmal			Persistent			LS-Persistent		
First Author	**n**	**AF**	**AF-AAD**	**n**	**AF**	**AF-AAD**	**n**	**AF**	**AF-AAD**	**n**	**AF**	**AF-AAD**
Mahapatra S.[17]	2	93.3%	86.7%	-	-	-	ns	ns	ns	ns	ns	ns
Krul S.P.J[18]	3	ns	86%	1	ns	91.6%	2	ns	77.7%	0	ns	100%
La Meir M.[19]	5	ns	85.7%	2	ns	87.5%	1	ns	87.5%	2	ns	81.8%
Pison L.[20]	2	ns	92%	1	ns	93%	1	ns	90%	0	ns	100%
La Meir M. [21]	12	63.1%	36.8%	2	ns	60%	2	ns	50%	8	ns	20%
Zembala M.[22*]	5	72.2%	66.5%	-	-	-	ns	ns	ns	ns	ns	ns
Muneretto C.[23]	8	91.6%	77.7%	-	-	-	ns	ns	ns	ns	ns	ns
Gehi A.K[24].	34	73.3	60.7%	ns	ns	ns	ns	ns	ns	ns	ns	ns
Bisleri G.[25]	5	ns	88.9%	-	-	-	-	-	-	5	ns	88.9%

Studies were presented by year of publication. **Abbreviations:** HRS: Heart Rhythm Society; EHRA: European Heart Rhythm Association; ECAS: European Cardiac Arrhythmia Society; AF: (patients free of) Atrial fibrillation; AF-AAD (Patients free of) Atrial Fibrillation and Antiarrhythmics, Ns: not specified. * Freedom from AF, off antiarrhythmic drugs (ADD) at 6 months (see text).

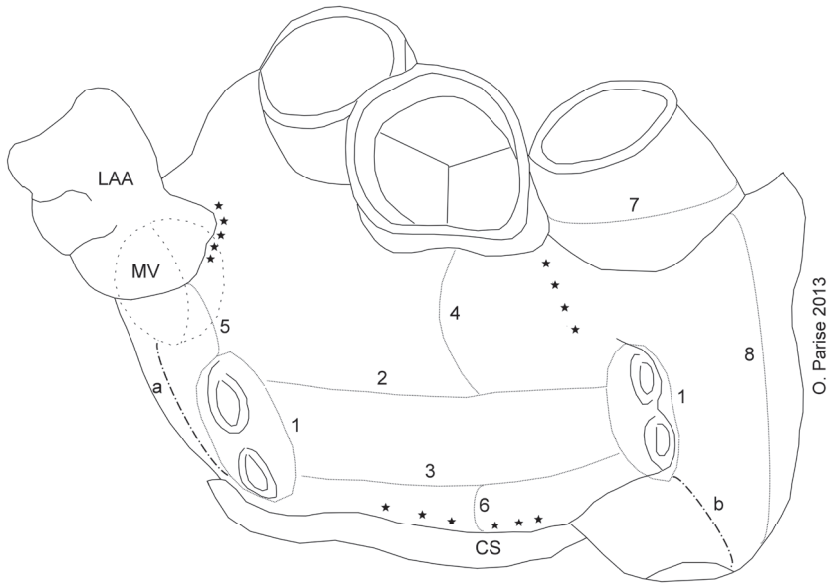
Table 5. Early and late outcome

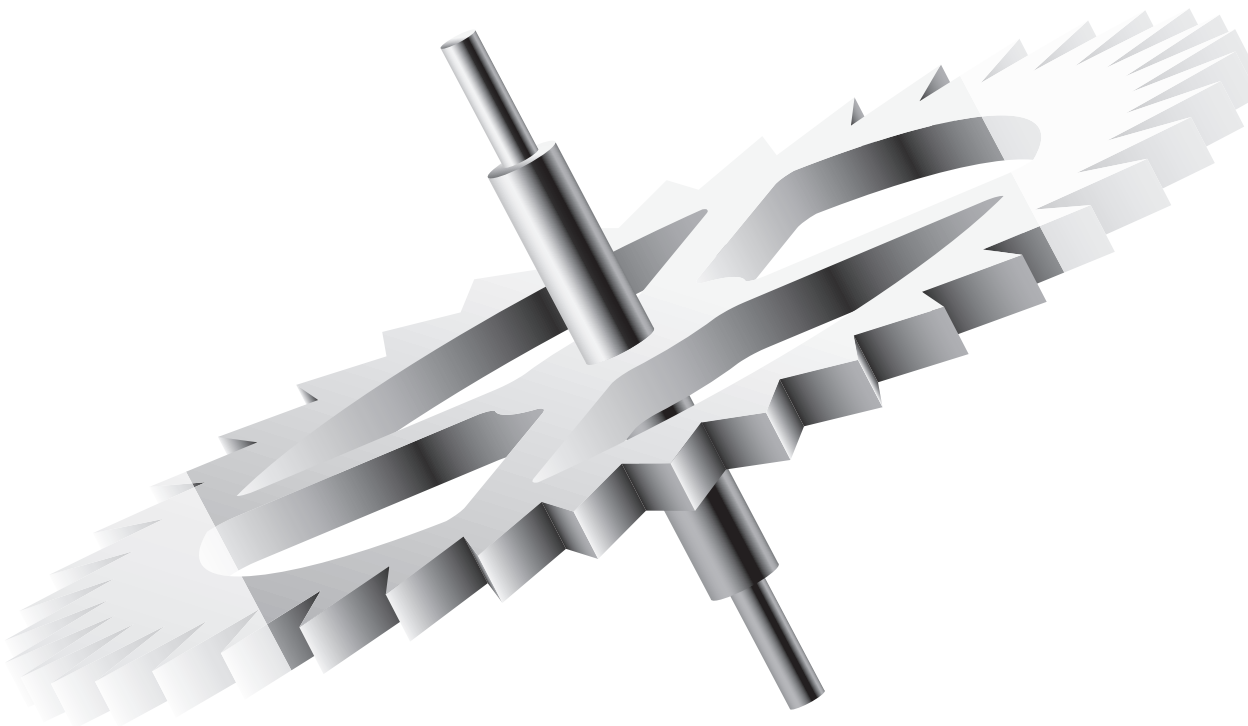
First Author	Early death	Conversion*	Complications	Late death	Repeated ablation	ECV	TEs
Mahapatra S.[17]	0	0	T	0	0	2	0
Krul S.P.J[18]	0	3	B(3) HeTX PNX PN	0	0	0	0
La Meir M.[19]	0	0	0	0	0	2	0
Pison L.[20]	0	0	PLE	0	0	0	0
La Meir M. [21]	0	0	0	0	0	0	0
Zembala M.[22]	1	0	T B	0	0	0	0
Muneretto C.[23]	0	0	0	0	0	0	0
Gehi A.K[24].	2	0	B(2) T(2)	0	0	0	0
Bisleri G.[25]	0	0	0	0	0	0	0

Studies were presented by year of publication. *Conversion: Conversion to sternotomy and cardiopulmonary bypass. ECV: Electric Cardioversion. TEs: Thromboembolic events. T: Tamponade; B: Bleeding; HeTX: Hemothorax; PNX: Pmeumothorax, PN: Pneumonia; PLE: Pleural effusion; B: Bleeding

Figure 1.

Schematic drawing of ablation lines performed in the LA during a hybrid approach. **Epicardial lines**. 1: pulmonary vein isolation; 2: roof line; 3: inferior line; 4: line between the superior line and the left fibrous trigone; 5: connecting line from the superior PV and the LAA; 6: line from the right inferior PV to the CS.7: superior vena cava isolation; 8:intercaval line. **Endocardial lines.** a: mitral isthmus line; b: cavo-tricuspid line; Ablation of complex fractionated atrial electrogram (CFAE). Abbreviations: LAA: left atrial appendage; MV: mitral valve; CS: coronary sinus.





Chapter 9

General discussion

Discussion

Background

Atrial Fibrillation (AF) is a frequent and important contributor to symptoms and morbidity in patients with cardiac diseases. More than 40% of patients referred for mitral valve surgery

have continuous AF[1-3]. Patients who remain in AF following mitral valve surgery may have lower survival three to five years later[4] compared with those in sinus rhythm (SR), although this has not been observed in all studies[5].

In the presence of AF the likelihood of normal sinus SR recovery after a conventional heart operation alone ranges from 4.5 to 36% and is even more unlikely in patients with left atriomegaly[6]. The first-line use of antiarrhythmic drugs to control AF resulted not to be an effective strategy due to reports of limited efficacy, poor patient compliance and contraindications[7]. As such, AF treatment has primarily been focused on treating the underlying rhythm pathology[8]. Therefore, intraoperative ablation of concurrent AF during open-heart surgery (add-on surgery) is today advised in most cases[9] and the so called Cox-Maze III procedure resulted to be the most effective surgical technique for treating AF and its adverse consequences of altered hemodynamics, and increased thromboembolic risk[10]. Nonetheless, due to its high complexity, many surgeons are reluctant to perform the full "cut and sew" Maze III operation. As a result, the newest iteration is a Maze operation using surgical ablation rather than incisions replaced by lesions being performed employing different energy source and ablation technologies. This version is sometimes called Cox maze IV[11]. Using a variety of energy sources and lesion sets, most groups report ablation success in 70 to 80% of mitral patients[12-20].

Nonetheless, there are many aspects of add-on ablation surgery that have been poorly investigated and are the maim aims of this thesis.

First, controversy exists as to whether the considerable proportion of health care resources spent on these patients represents a cost-effective approach in an attempt to maintain a meaningful quality of life (QoL). To answer this question, we evaluated QoL and cost-effectiveness of add-on surgery. We also explored the relationship between successful SR conversion and postoperative health-related QoL.

Furthermore, electrical cardioversion (ECV) is commonly recommended for patients with recurrent AF following an initial ablation procedure. Nonetheless, although the long-term effect of ECV might be promising under these

circumstances, it has been reported that > 80% of patients who undergo ECV for persistent AF or atrial flutter after catheter ablation have recurrence[21]. However, little is known about the benefit of ECV, with or without additional pharmacological pre-treatment, after unsuccessful add-on ablation surgery.

Therefore, we report early and mid-term outcomes of patients who underwent ECV for AF recurrence following add-on surgery ablation compared to those who did not undergo concomitant AF ablation. We also examined multiple pre-procedural and peri-procedural variables to determine predictors of AF recurrence after cardioversion.

Moreover, the current management of anticoagulation following add-on ablation surgery is inconsistent and challenging and no guidelines were put in place until recently[22] and little work has been done investigating the best anticoagulation treatment strategies after surgical ablation. Indeed, if on one hand interruption of oral anticoagulation (OAC) after a successful procedure may be a safe approach even in patients who are considered to be at high-risk for stroke, on the other hand, due to the large number of a asymptomatic episodes, many centres avoid interruption of OAC in high-risk patients, even after successful surgery. Therefore, it is still uncertain whether real-life OAC following ablation surgery is guided by current guidelines[22] and what factors drive the decision to anticoagulate or not these patients in daily clinical practice.

Therefore we investigated the real-life anticoagulation treatment after ablation surgery to examine whether this treatment adheres to current guidelines and we explored all factors related to OAC use pre-operatively and at follow-up.

In addition, the long-term efficacy of add-on surgical ablation has not yet been fully determined and the role of lesion sets on long-term outcome has been poorly defined[10].

Hence, we analysed the late outcomes of patients undergoing add-on surgery. Our main objective was to assess the impact of lesion set and surgical technique on long-term recurrence of AF.

Finally, because of suboptimal results of both catheter ablation and surgery especially in long-standing persistent AF[23, 24]. A so-called hybrid approach has recently been introduced by our group in the clinical scenario. This procedure combines an epicardial and an endocardial ablation; either staged or as a single procedure, through a partnership between the surgeon and the electrophysiologist and it may represent a future step also for add-on surgery.

Data related to this approach are still scarce thus we gave an overview is given to summarize and discuss results from published articles about hybrid ablation for the treatment of AF to establish the efficacy of this procedure as well as its potential superiority over catheter ablation or standard surgical technique.

Add-on surgery: Quality of life and cost-effectiveness.

EuroQoL, RAND 36-item Health Survey and Multidimensional Fatigue Inventory (MFI) have been widely employed in clinical practice[25-32]. The EuroQoL consists of two components: description of the respondent's own health by means of the EuroQoL thermometer (visual analogue scale [VAS]) and the EuroQoL classification (EQ-5D, mobility, self care, usual activities, pain/discomfort, and anxiety/depression) [25]. The RAND 36-item Health Survey 1.0 (SF-36) comprises eight multi-item scales (Physical functioning, Mental health, Physical pain, Vitality, Role limitations due to emotional problems, Role limitations due to physical limitations, Social functioning, General health) [30]. The MFI is a 5-item self-report (General fatigue, Physical fatigue, Reduced activity, Reduced motivation, Mental fatigue)[32].

In our clinical trial (Chapter 2) all the above questionnaires were self-administered before add-on surgery (baseline). They were then mailed to patients' home 3, 6, and 12 months after surgery.

In our experience, add-on ablative surgery performed using microwave energy. After one year led to successful 1-year SR conversion in 57% of cases. On the contrary, 42% of patients in the control group (no additional ablation surgery) converted to NSR, which did not result in a significant difference in either treatment group. At 6-month follow-up differences in rhythm outcome were even smaller between the both groups. These findings suggest that microwave ablation surgery does not significantly induce SR conversion.

Health-related quality of life showed an overall linear enhancement after cardiac surgery: indeed there was a steady gradual improvement in resumption of activities and a gradual diminishing of physical symptoms. This finding confirms traditional expectations of recovery following surgery. In contrast to cardiac surgery, additional ablation surgery did not affect QoL. Since rhythm outcome also did not significantly differ between treatment groups, we could not actually demonstrate that induced SR does not affect HrQoL. To investigate whether overall improvement in QoL in both treatment groups was due to treatment of underlying heart disease by cardiac surgery itself or due to SR conversion further larger studies are necessary to confirm our findings.

However these unsatisfactory results may be explained by the use of microwave energy to make lesions. Indeed, there are potential advantages of this energy source (MW probes can create a linear lesion easily, it can penetrate tissue more deeply than other energy sources, the lesion is more likely to be transmural with a greater volume of heated tissue for the same tissue surface temperature, its unidirectional focused energy avoids collateral damage, and there is lower risk of thromboembolism), it has important drawbacks (unfocused heat energy, no way to judge transmurality of ablation during surgery, and it is not capable of making transmural lesions on the beating heart) which limit its wide use in clinical practice. The major challenge to using microwaves is controlling the heating zone for a desired clinical outcome without incidentally heating nearby tissues or causing complications. Primary focus has been given to antenna cooling and arrays as a means to safely deliver more power and produce larger ablations, but research has also continued in antenna design, frequency comparisons, and power application algorithms[34]. However a review recently published has demonstrated that microwave ablation, as an intervention for the treatment of AF during concomitant surgery, is not currently recommended on the limited available evidence[35].

Another critical point in our study is that only pulmonary vein isolation was carried out without making additional left atrial and right atrial lesions, which are necessary for a successful ablation as widely discussed before.

However, starting from comparable 1-year SR conversion with or without add-on surgery, we wanted to further investigate whether SR conversion after cardiac surgery was associated with enhanced QoL. For this purpose, a retrospective analysis was performed (Chapter 3). Based on patients' rhythm outcome at 6- and 12-month follow-up, a dummy regression analysis was carried out with each questionnaire sub-scale as a dependant outcome variable. SR conversion at discharge, between 3 and 6 months follow-up and between 6 and 12 months of follow-up were tested for their significance. Overall, QoL was not influenced by SR conversion nor by possible confounders such as age, gender and type of AF. In addition, the relationship between SR conversion and QoL tended to attenuate and wear off with post-operative time.

In conclusion, the results of these two studies with respect to QoL indicate that QoL does not improve in case SR restoration is achieved, regardless of whether this restoration was brought about by ablation surgery or the corrective effect of cardiac surgery on underlying heart disease.

Apart from the above-mentioned limitations regarding the energy source employed, general limitations on QoL research in AF patients should be addressed as well, as QoL measurements might not appropriately reflect the disease specific burden. For a HrQoL or subjective assessment measure to be valid, it must accurately measure its target construct. Life events and other chronic diseases, besides in our case AF, also influence HrQoL: this clouding effect enhances while follow-up extends over time. As these additional individual influences are usually not known by researchers, it is unclear how respondents interpret questions. Respondents impute their overall subjective health considerations, not just from a perspective regarding their AF burden, in questionnaire scale responses. Furthermore, data from QoL questionnaires are often used for purposes different from which they were originally designed. Since validated disease specific questionnaires for AF are lacking, it is appealing to use a generic QoL questionnaire as a core module with a disease-specific module added to it, in order to assess proper QoL evaluation. In this way, measurements would be maximally valid and responsive to change in health status for AF patients. In our HrQoL study, we used two generic questionnaires: SF-36 and EuroQoL. Although these questionnaires have been widely used in arrhythmia studies and even in ablation surgery trials, they have not been designed to detect HrQoL changes in the specific AF patient population[28, 31, 36, 37]. The MFI-20 was considered as being a disease-specific questionnaire since it addresses different aspects of fatigue, which is one of the key symptoms of AF. Although the MFI-20 seemed to be more subtle in detecting changes in QoL through SR conversion, a validated AF-specific questionnaire will be indispensable in future QoL research.

A further step of our research was to assess cost-effectiveness of add-on surgery and to compare it to isolated cardiac surgery procedures.

The costs of AF were collected during one year, at baseline and at two to six weeks, three to four months, six to seven months and 11-12 months postoperatively, by means of the cost diary method in which participants continuously recorded volumes of healthcare utilization[38].

The diary contained questions regarding three categories of costs, which were evaluated from a societal perspective: direct healthcare costs (costs of visits to the general practitioner, prescribed medication, etc.), direct non-healthcare costs (counter medication and informal help) and indirect costs (work status and absence, voluntary work, informal care etc.). To calculate the incremental cost-effectiveness ratio (ICER), the difference in costs between two treatment

options is divided by the gain in QoL. The result of this calculation was defined as the incremental costs per QALY. Furthermore, to test the robustness of the cost analysis and to obtain uncertainty intervals (UIs) around the mean difference of the costs and the QALYs, the bootstrap method was used (1000 replications), based on random sampling with replacement based on original individual data of the participants through a large number of simulations[39]. To account for the uncertainty surrounding the ICERs, a bootstrap analysis was also performed.

The Dutch Council for Public Health and Health Care argues that thresholds can vary from €16,000 to a maximum of € 80,000 for a condition with a high disease burden[40]. Hence, based on this information, assuming a threshold value of €60,000 for the treatment of AF seems acceptable.

Total costs of the add-on ablation surgery group were significantly higher compared to the regular cardiac surgery group (cost difference bootstrap: €4,724; 95% uncertainty interval (UI), €2,770–€6,678). The bootstrapped difference in QALYs was not statistically significant (0.06; 95% UI: –0.024 to 0.14). The incremental cost-effectiveness ratio is €73,359 per QALY. The acceptability curve showed that, even in the case of a maximum threshold value of €80,000 per QALY gained, the probability of add-on surgery being more cost-effective than regular cardiac surgery did not reach beyond 50%. Hence, based on the data of a 1-year follow-up, AS cannot be considered a cost-effective treatment.

Apart from the employment of a microwave energy source the short follow-up is a limitation of our study. Indeed, it seems reasonable to suppose that longer follow-up would more accurately define differences in health care consumption. On the other hand, QoL outcomes may become confounded by additional co-morbidity as follow-up extends therefore affecting the QALY calculation and coinciding ICER. Furthermore, longer follow-up might result in a higher dropout rate as the participants' burden increases over time.

A solution would be to build a decision-model to test cost-effectiveness of the intervention over a longer period than the time horizon of the trial. However, decision models might not reflect clinical practice. Another limitation in this study is that our analyses in health care consumption were not constricted to costs related to AF only. Because cardiac surgery is predominantly performed in the elderly, other co-morbidity may cause significant costs during follow- up. Differences in costs due to rhythm-related health care consumption might not have been observable in this case. However, this limitation is shared with the other studies available in the literature. Larger randomized studies are warranted

to establish the cost-effectiveness of add-on surgery also employing different energy sources.

Add-on surgery: Effectiveness of electrical cardioversion after unsuccessful surgery

We reported early and mid-term outcomes in patients who underwent cardioversion for persistent AF occurring after RF ablation associated with mitral valve surgery and we compared these outcomes to patients undergoing ECV after mitral surgery without concomitant AF ablation (Chapter 5).

After successful ECV, more than 78% of patients in the ablation group were in stable SR off- antiarrhythmic drugs at follow-up whereas only 21.4% of patients in the no-ablation group did not show recurrent AF ($p<0.001$). In addition, omission of the ablation procedure ($p<0.001$) was the strongest predictor of AF recurrence after ECV.

We can postulate that some kind of substrate modification occurred after surgical ablation, which made patients more susceptible to the treatment of ECV. Indeed, intra-operative radiofrequency ablation methods limited to the left atrium have proven to be efficacious for modification of the AF substrate[41].

Nevertheless, the surgical procedure did not result in higher early post-operative stable conversion to SR and this might be explained by the demonstration of a bidirectional block which could be only transient requiring further "maturation" of the ablative lesions[42] to alter the arrhythmia substrate sufficiently to be responsive to ECV.

In addition, left atrial LA dimensions < 45 mm ($p=0.005$) before ECV predicted mid-term maintenance of SR. Atrial size was more markedly reduced in patients with associated ablation than in those with isolated mitral valve surgery (40.5 ± 5.8 mm vs. 48.9 ± 8.1 mm, $p<0.001$) as result of a significantly higher reverse remodelling in the left atrium following surgical linear endocardial RF lesions. Enlarged left atrium LA with over-stretched myocardium and residual high wall stress might not achieve significant reverse remodelling because of the progression of myocardium damage. Nonetheless the lower atrial size in the ablation group might also be due to scarring along the ablation lines.

From our analysis it also merges that the timing between surgery and the cardioversion procedure is a matter of utmost importance. Early AF recurrence after a Maze procedure is explained by changes induced in atrial electrophysiology by myocardial edema and inflammatory response to cardiac surgery[43]**.** There

is evidence that this condition tends to resolve within the first post-operative month when the myocardial edema tends to disappear[22, 44]. In contrast, the genesis of late recurrence might be attributed to lesion incompleteness[45] Since early recurrences are thought to be inflammatory-mediated, we could expect that ECV performed after a 3-month blanking period might be associated with a lower recurrence rate. In contrast, the time from surgery to ECV was significantly longer in patients with AF recurrence and time from surgery to ECV resulted to be a multivariate predictor of recurrence with a cut-off ≥ 88 days (p=0.005). This finding strongly supports the hypothesis that cardioversion should be performed within 90 days from surgery. We can postulate that this effect might be related to irreversible anatomical and electrophysiological changes in the atrial conduction tissue after this period, which might render the ECV ineffective.

Also, we failed to find any interaction between surgical ablation time-to-surgery and LA dimension, which demonstrates that surgical ablation is a primary predictor of AF recurrence and its effect is not secondary to increased left atrial size and time to ECV.

Remarkably, the use of amiodarone and other antiarrhythmics at the time of cardioversion did not influence AF recurrence after add-on surgery whereas in isolated cardiac surgery, among patients showing AF recurrence at follow-up, the number of those who were not in treatment with amiodarone was significantly higher. From our data, it seems that the pre-treatment with oral amiodarone before cardioversion improves the reversion rate in patients with AF recurrence after mitral surgery without ablation referred for ECV. Consequently, the use of amiodarone should be, in our opinion, highly recommended in these patients.

Amiodarone, by prolonging atrial refractoriness[46-48]may reverse the electrophysiological effect of the electrical remodelling, thus affecting the efficacy of direct-current cardioversion. We can postulate that the effect of amiodarone results not to be important in patients undergoing an associated ablation procedure since the epicardial radiofrequency ablation leads itself to attenuated shortening of atrial refractoriness[49].

However, our data do not allow us to draw any final conclusion on the impact of amiodarone on AF recurrence since drug therapy discontinuation was not based according to a study protocol but left to investigators' decisions and this has the potential to introduce a selection bias into the study. In addition, when examining our results it is important to also consider that the decision to perform an additional ablation procedure was left to the surgeon's preference and surgical

ablation was not executed according to a predefined protocol. The high number of AF patients undergoing mitral surgery without an associated Maze procedure may be explained in part by surgeons' hesitation to extend the cardiopulmonary bypass time, by the still existing concerns about the effectiveness of the procedure, by the lack of surgeons' experience and little knowledge of the surgical lesion sets. Nonetheless, this drawback is shared by most of the published studies on this topic[50].

Add-on surgery and oral anticoagulation: A still unanswered matter.

We investigated the real-life anticoagulation treatment after ablation surgery and examined whether this treatment adhered to current guidelines. Additionally, we explored factors related to oral anticoagulation (OAC) use preoperatively and at follow-up (Chapter 6).

The main finding of the study was that OAC before and after AF surgical ablation is hardly guided by the patient's individual stroke risk. Contrary to current recommendations, the rate of OAC remains high even in patients with a low stroke risk. The most important factor that influences the use of anticoagulants seems to be age > 75 years and type of AF > paroxysmal at inclusion and "preoperative OAC use" and "other indications for OAC use than AF" at follow-up. This results in possible over-treatment of low-risk patients and under-treatment of high-risk patients. Indeed, one year after the procedure, 96% of patients (47/49) with a low stroke risk ($CHADS_2$ [51,52] [congestive heart failure, hypertension, age ≥ 75 years, diabetes {1 point each}, and prior stroke or transient ischaemic attack {2 points}) score ≤ 1) were still receiving OAC. In addition, this is in contrast with the current guidelines, which advocate basing decisions regarding OAC treatment after surgical and catheter ablation on the patient's risk factors, and not on the presence or type of AF[53,54], and to continue anticoagulation treatment in patients with a high stroke risk as expressed by a $CHADS_2$ score ≥ 2. Indeed, the results of our study show that real-life anticoagulation practice does not adhere to these recommendations and the rate of anticoagulation remained very high at 12-month follow-up irrespective of the patient's stroke risk. Indeed, we found only a moderate overall guideline adherence of 62% at inclusion with an even distribution in low- and high-risk AF patients (p=. 13). Total guideline adherence for patients still in AF follow-up fell to 55% at 12-months with no statistical difference between high-risk and low-risk groups (p=0.12). In addition, a high percentage of low-risk patients were over-treated (41% at inclusion 42% at 12

months) whereas there was a propensity to under-treat high-risk patients (31% at inclusion 40% at 12 months).

These results are in agreement with previous findings regarding over- and under-treatment of OAC in AF patients[55, 56]. Similarly, Dagres et al.[57] demonstrated that OAC after catheter ablation was not guided by the patient's individual stroke risk with resulting over-treatment of low-risk patients and under-treatment of high-risk patients. These authors found that the most important factor influencing the use of OAC was the detection of AF recurrences during follow-up. However, to the best of our knowledge, our study is the first to explore OAC appropriateness following surgical ablation and our findings may have important clinical consequences since the guideline-deviant management has been shown to be associated with a worse outcome in daily practice[58].

One major reason for the inappropriate antithrombotic therapy is possibly due to lack of education, but also insufficient communication between cardiac surgeons and general practitioners/referring cardiologists. Indeed, it should be emphasised that in the patients of this study, the final decision on anticoagulation treatment was made by the general practitioner or by the referring cardiologist in consultation with the patient, and not by the tertiary centre that gave only a recommendation.

In addition, appropriate treatment is further hampered by the introduction of different stroke risk stratification models in clinical practice which, although widely applied, have shown a suboptimal predictive value leading to misclassification of the individual patient risk, as shown recently for the $CHADS_2$ scheme[59, 60]. This has undoubtedly contributed to making some physicians reluctant to prescribe OAC only on the basis of these risk-score schemes. Moreover, there are conflicting data regarding the risk conferred by certain factors that are included in some of the risk models but not in others[61]. Finally, the lack of large randomised trials regarding the necessity and efficacy of anticoagulation after a presumably successful surgical procedure might also be responsible for poor guideline-adherence of antithrombotic treatment following ablation surgery.

As a result, the choice of appropriate antithrombotic therapy for the individual AF patient is still debated[62, 63] and it is not clear whether the standard scheme of OAC therapy is optimal for all patients after surgical ablation or if this scheme should be modified according to other factors rather than $CHADS_2$ score. This is confirmed, in our study by multivariate analysis, which showed that the effect of the $CHADS_2$ score on anticoagulation at admission was not significant. In

contrast, age >75 years (p=0.01) and type of AF > paroxysmal (p=0.01) played a significant role in the decision-making process for OAC use at inclusion.
Finally, in our study complications during follow-up were present in 6% of the patients. We could not demonstrate that these adverse events played a role in the decision-making of OAC prescription, although some studies suggest that complications might influence the employment or avoidance of OAC in AF patients[64]. In this study over-treatment or under-treatment did not show any significant differences in stroke or bleeding risk, and, in addition, we failed to show any correlation between OAC-related complications and guideline adherence, over-treatment or undert-reatment. This finding is in contrast with Nieuwlaat et al[58] who showed that especially high-risk patients who are under-treated are at great risk of developing stroke. This aspect requires further investigation and it will be the subject of an ongoing study.

Add-on surgery: The importance of lesion sets

The multicentre study in Chapter 7 analysed the long-term follow-up outcomes of patients undergoing add-on radiofrequency (RF) ablation. Our main objective was to assess the impact of lesion set and surgical technique on long-term recurrence of AF.
Briefly, this study showed favourable long-term results following RF add-on surgical AF ablation with a percentage of patients in NSR and off-antiarrhythmic drugs (AAD) of 62.3% at a median follow-up of 49.8 months (Inter Quartile Range [IQR] 27.0. - 86.5).
Data from transcatheter ablation[65, 66] and AF surgery[67] have demonstrated that clinical outcome is strongly influenced by completeness, transmurality and continuity and of the lesion set. Continuity and transmurality of the lesions are strongly related to the ablation tool employed and different studies have confirmed that bipolar RF clamps are reliable and effective in creating transmural scars[68].
Our findings confirm the superiority of the bipolar source. Indeed, the complete bipolar RF lesion set resulted to be the technique with the highest number of patients in NSR-off antiarrhythmic drugs (AAD) at follow-up (p<0.001 vs. unipolar, p=0.001 vs. combined bipolar/unipolar lesions). Furthermore, at multivariate analysis using competing risk regression the use of unipolar RF (SHR 7.41, p<0.001) or combined unipolar/bipolar ablation (sub-hazard ratios [SHR] 3.93, p=0.003) were independent predictors of AF recurrence.
In addition to the uncertainty of transmurality of the lesions of unipolar sources[69],

the bipolar RF has the advantage of limiting the burn to the width of the clamp whereas the unipolar pen produces a burn several millimetres wider and releases hot energy which is not confined entirely to the myocardial tissue thus increasing the odds of damage to extracardiac structures. Therefore, due to these limitations of unipolar energy sources, there is an apparent trend towards the implementation of the Cox-Maze IV through the application of the bipolar RF clamp on a pattern of LA lesions[70].

The importance of completeness of lesion set has been demonstrated by Gaita et al[71] who showed that the final set of lines is a key point in patients with permanent AF and valvular heart disease. Furthermore, Gillinov and coworkers[67] confirmed the value of left atrial lesion sets in the surgical management of permanent AF. In contrast, in our experience there was no difference in AF recurrence in patients who received or not a roof line, an inferior line or a left atrial appendage (LAA) to left pulmonary veins (LPVs) line and the absence of these lesions was not associated with a higher incidence of AF recurrence at multivariate competing risk analysis, independent of the type of preoperative AF. However our results could be explained by the higher number of patients at follow-up receiving a connecting line with a unipolar RF device applied from the endocardial surface, which could have had limited efficacy in creating transmural connecting lesions. This is also confirmed by the sub-analysis carried out on patients having LA linear connecting lines either with the unipolar pen or bipolar clamp which showed that a higher percentage of patients having LA lines performed with the bipolar clamp were in NSR off-AAD with cumulative incidences significantly lower compared to those who had additional LA lesions made with the unipolar pen.

Another key point of our study is that right atrial ablations in addition to left-sided lines led to better long-term rhythm outcome.

Based on the study findings of Haïssaguerre et al[72], who documented focal ectopies arising from the pulmonary veins, and of Sueda et al.[73] who demonstrated the presence of left atrial foci during intraoperative AF, the concept of approaching only the left atrium during anti-arrhythmic surgery was developed. Nonetheless, Chauvin et al[74] observed in explanted hearts, some striated muscle cells around the coronary sinus connecting the inferior right atrium. Furthermore, Lin et al[75] showed some specific right atrial "trigger zones" where paroxysmal AF may be induced and these authors found that the ablation of these sites may eliminate AF and that recurrent atrial flutter or tachycardia is a complication of performing isolated left atrial lesions.

Hereafter, these anatomic and electrophysiological features may be the basis for the inconsistent results reported for left atrial isolation and Cox-Maze operations[76] and it may suggest that a right-side ablation should always be performed to interrupt the interatrial connections and to improve clinical results. However, the importance of the right atrial lesions included in the add-on procedure is difficult to define, as biatrial versus left atrial surgical ablation has never been compared in a randomised clinical trial and it is, therefore, still matter of debate. Indeed, whereas some studies found no significant difference between left-side and biatrial ablation[77]or achieved comparable results to those of Maze III with the simple isolation of pulmonary veins[78], other studies confirmed the superiority of the biatrial approach compared to isolated left atrial ablation[79].

We found that a higher number of patients undergoing the biatrial approach were in NSR off-ADD ($p<0.001$) with a lower 10-year cumulative incidence of AF recurrence compared to patients undergoing LA ablation ($p<0.001$). Onorati et al[80] postulated that whereas left side procedures can succeed in patients with normal atria due to the shorter refractory periods of LA, patients with enlarged atria may require additional right ablation lines. This conclusion did not come out from our results: indeed, at competing risk regression, corrected by preoperative LA diameter and area, the absence of right atrial ablation (SHR 2.7, $p=0.011$) was an independent predictor of AF recurrence. In other words, from our data, the performance of additional right ablation lines seems to be indicated even in patients with normal atria. A strength of our findings is that all patients having a biatrial ablation underwent the same right lesion set including intercaval ablation, cavo-tricuspid isthmus line and isolation of right atrial appendage and terminal crest.

Another important finding of our study is that among LA lines, only the MI ablation was not a significant predictor of AF recurrence at multivariate analysis which is in contrast with previous reports that have shown the significance of the left atrial isthmus lesion in patients with permanent AF[81,82].

The mitral isthmus refers to the atrial myocardium between the MV annulus and the left-sided PVs[83]. Anatomically, since this isthmus extends into the left inferior pulmonary vein, the width of the isthmus will depend on the extent of the myocardial sleeves associated with this vein. The wall of the isthmus ranges from 2-8 mm in myocardial thickness[84] and its endocardial surface may contain pits and troughs where the atrial wall becomes exceptionally thin[85]. Finally, the presence of crevices in the isthmus area which may hinder safe and efficient radiofrequency energy delivery, the continuation of atrial myocardium onto the

atrial aspect of the mitral valve leaflet and the epicardial connections (e.g. the Ligament of Marshall) across the mitral isthmus line further make this line uneasy to perform and they may represent a possible obstacle to successful MI ablation. At the beginning of our experience, we employed only monopolar ablation. With the introduction of the bipolar clamp, we started using bipolar RF to ablate the complex anatomy of this area in combination with the unipolar pen or, more recently, only with the bipolar clamp.

From sub-analysis these three sub-groups had comparable cumulative incidences of AF ($p<0.001$). Therefore, our study confirms that the bipolar RF clamp was unable to create a lesion all the way to the mitral annulus probably because of the thickness of the AV groove in that area, although transmurality has been reported by an experimental study achieved with bipolar radiofrequency in this area[85]. In addition, the use of a second unipolar device to complete the mitral line was ineffective and did not improve rhythm outcome.

For these reasons, many surgeons prefer to complete a MI ablation with a cryoprobe because cryoablation should preserve more of the fibrous skeleton of the heart, making it ideal for ablation near valvular tissue[86]. This calls for further studies comparing cryoablation and RF for making mitral isthmus lesions.

Future perspectives: The hybrid ablation. Is it applicable to add-on surgery?

Chapter 8 provides an overview of the hybrid procedure for the treatment of stand-alone AF.

From this overview, the hybrid treatment resulted to be a safe technique. Indeed, either mortality (0.8%) or complications rate (4.1%) were low. In addition, only three patients (0.8%) required a conversion to sternotomy and none experienced thromboembolic events.

Freedom from AF off-AAD at follow-up ranged from 85.7% to 92% in papers employing bipolar RF and from 36.8% to 88.9% in those utilizing monopolar RF. With specific reference to AAD-free success rate by type of AF, it ranged from 60% to 91.6% in paroxysmal AF, from 50% to 77.7% in persistent AF and from 20% to 100% in LSP-AF. However, these figures were very high in papers utilizing bipolar radiofrequency (100%, 100%, 81.8%) and compare favourably with minimally invasive-beating heart surgery[87, 88].

The hybrid approach combines, in one step, a thoracoscopic epicardial ablation with a percutaneous catheter ablation procedure.

There exists a clear rationale for this approach, as some ablation lesions that are incorporated into the well-established Cox-Maze lesions cannot be accomplished using a minimally invasive, off-pump surgical approach. Indeed, while some lesions can be easily performed through the transverse sinus, as seen previously, efficacy and safety of other ablation lesions such as the ablation line to the mitral annulus are the main challenges. In addition, the coronary sinus (CS), which is used as the epicardial landmark for the mitral annulus, is unreliable and may leave a gap[89]. An attempt to address this problem was made by Edgerton et al[90].who developed the 'Dallas lesion' in which a line was made connecting to the anterior annulus at the junction of the left and non-coronary cusps of the aortic root. Nevertheless, this line might not be trans-mural due to the inability of RF energy to effectively penetrate fatty tissue associated with the dome of the left atrium and the superior vena cava. This is an indication for mapping conduction block, which can be checked by using a hybrid approach. In contrast, a mitral isthmus lesion can easily and safely be carried out (or completed) endocardially by the electrophysiologist (EP).

Another potential advantage of the hybrid procedure is that, from the EP's point of view, there is no longer a risk of phrenic nerve and oesophageal injury because these structures can be protected by the surgeon if necessary, as well as no risk of tamponade as the pericardium is open. Furthermore, by reducing the total number of endocardial ablations the risk of emboli during these ablations should be potentially reduced[91].

Also add-on surgery could move towards a multidisciplinary approach involving cardiac surgeons and EPs in order to combine, in one step, a surgical technique with a percutaneous endocardial ablation in order to limit the shortcomings of both techniques and, at the same time, to combine their advantages. Lesions are more likely to be transmural when burning from the inside outwards and from the outside inwards simultaneously and the EP can check the completeness of the lines and add an endocardial 'touch-up' in case of incomplete isolation of one of the pulmonary veins or if the connecting lesions are not transmural. The potential for improved outcomes derives from combining levels of expertise. Surgeons are very good at making linear lesions and EPs at mapping for completeness. Furthermore, as discussed above, a more extensive lesion set beyond the pulmonary veins to include targets along the LA substrate is often necessary in persistent and long-standing persistent AF.

However, the effectiveness and safety of the hybrid procedure as add-on surgery

has not been explored yet and it will be the objective of ongoing clinical research studies.

Conclusions

The main findings of the thesis can be summarized as follows:

- Add-on surgery with bipolar RF ablation showed better results than both unipolar RF and microwave sources.
- Add-on ablation surgery with microwave energy did not affect QoL, which was not influenced by SR conversion.
- Add-on ablation surgery with microwave energy did not prove to be cost effective.
- After unsuccessful add-on surgery electrical cardioversion resulted to be more effective than in patients, undergoing isolated cardiac surgery. Electrical cardioversion should be performed within 88 days from surgery. This might be related to substrate modification induced by ablation surgery.
- Real-life oral anticoagulation prescription after add-on surgery showed a moderate guideline adherence, with high-risk patients being under-treated and low-risk patients being over-treated.
- Completeness of left atrial surgical ablation lines with right atrial ablation is a key point for stable, long-term normal sinus rhythm. The mitral isthmus line still represents an unanswered surgical challenge.
- The hybrid approach is a potentially attractive surgical technique for add-on surgery to be tested.

Further larger randomised studies are necessary to confirm the results of this thesis.

References

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. N Engl JMed. 1982; 306:1018-1022.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998; 98:946-952.
3. Brodell GK, Cosgrove D, Schiavone W, Underwood D, Loop F. Cardiac rhythm and conduction disturbances in patients undergoing mitral valve surgery. Cleve Clin J Med. 1991; 58:397-399.
4. Lim E, Barlow CW, Hosseinpour AR, Wisbey C, Wilson K, Pidgeon W. Influence of atrial fibrillation on outcome following mitral valve repair. Circulation. 2001; 104:159-163.
5. Chua YL, Scaff HV, Orszulak TA, Morris JJ. Outcome of mitral valve repair in patients with preoperative atrial fibrillation: should the maze procedure be combined with mitral valvuloplasty? J Thorac Cardiovasc Surg. 1994; 107:408-415.
6. Obadia JF, El Farra M, Bastien OH, LieÂvre M, Martelloni Y, Chassignolle JF. Outcome of atrial fibrillation after mitral valve repair. J Thorac Cardiovasc Surg 1997; 114:179-185.
7. Ballaux PK, Geuzebroek GS, van Hemel NM, Kelder JC, Dossche KM, Ernst JM et al. Freedom from atrial arrhythmias after classic maze III surgery: a 10-year experience. J Thorac Cardiovasc Surg. 2006; 132(6): 1433-40.
8. Boriani G, Diemberger I, Biffi M, Martignani C, Branzi A.. Pharmacological cardioversion of atrial fibrillation: current management and treatment options. Drugs 2004; 64:2741–62.
9. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012; 14(4): 528-606
10. Phan K, Xie A, La Meir M, Black D, Yan TD. Surgical Ablation for Treatment of Atrial Fibrillation in Cardiac Surgery. A Cumulative Meta-analysis of Randomised Controlled Trials Heart. 2014; 100(9): 722-730.
11. Damiano RJ Jr, Schwartz FH, Bailey MS, Maniar HS, Munfakh NA, Schuessler RB. The Cox-Maze IV procedure: Pedictors of late recurrence. J Thorac Cardiovasc Surg 2011; 1141: 113-21.
12. Gillinov AM, McCarthy PM. Advances in the surgical treatment of atrial fibrillation. Cardiol Clin 2004:147-157.
13. Gillinov AM, McCarthy PM, Marrouche N, Natale A. Contemporary surgical treatment for atrial fibrillation. Pacing Clin Electrophysiol 2003; 26:1-4.
14. Raman J, Ishikawa S, Storer MM, Power JM. Surgical radiofrequency ablation of both atria for atrial fibrillation: results of a multicenter trial. J Thorac Cardiovasc Surg 2003; 126:1357-1366.
15. Sie HT, Beukema WP, Elvan A, Ramdat Misier AR. Long-term results of irrigated radiofrequency modified maze procedure in 200 patients with concomitant cardiac surgery: six years experience. Ann Thorac Surg 2004; 77:512—516; discussion 516-7.
16. Mohr FW, Fabricius AM, Falk V, Doll N, Von Oppell U, Diegeler A. Curative treatment of atrial fibrillation with intraoperative radiofrequency ablation: short-term and midterm results. J Thorac Cardiovasc Surg 2002; 123:919-927.
17. Kress DC, Sra J, Krum D, Goel A, Campbell J, Fox J. Radiofrequency ablation of atrial fibrillation during mitral valve surgery. Semin Thorac Cardiovasc Surg 2002; 14:210-218.
18. Knaut M, Tugtekin SM, Spitzer S, Gulielmos V.. Combined atrial fibrillation and mitral valve surgery using microwave technology. Semin Thorac Cardiovasc Surg 2002; 14:226-231.
19. Venturini A, Polesel E, Cutaia V, Asta A, Mangino D, Moretti R,et al. Intraoperative microwave ablation in patients undergoing valvular surgery: midterm results. Heart Surg Forum 2003; 6:409-411.
20. Benussi S, Nascimbene S, Agricola E, Calori G, Calvi S, Caldarola A,et al. Surgical ablation of atrial fibrillation using the epicardial radiofrequency approach: mid-term results and risk analysis. Ann Thorac Surg 2002; 74:1050-1056.
21. Chilukuri K, Dukes J, Dalal D, Marine JE, Henrikson CA, Scherr D,et al. Outcomes in patients requiring cardioversion following catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2010; 21:27-32.

22. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA et al; Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012; 9:632-696.
23. Damiano RJ Jr. Surgical ablation of lone atrial fibrillation on the beating heart: the chaos continues. Europace 2010; 12:297-298.
24. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010; 3:32-38.
25. Brooks R. Quality of life measures. Crit Care Med 1996; 24:1769.
26. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control inatrial fibrillation-Pharmacological Intervention in Atrial Fibrillation (PIAF): A randomised trial. Lancet 2000; 356:1789-1794
27. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation–executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006; 48:854-906.
28. Beck LB.The role of outcomes data in health-care resource allocation. Ear Hear 2000; 21(4 Suppl): 89S-96S.
29. Kuilman M, Bleeker JK, Hartman JA, Simoons ML.Long-term survival after out-of-hospital cardiac arrest: An 8-year follow-up. Resuscitation 1999; 41:25-31.
30. McHorney CA, Ware JE, Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993; 31:247-263.
31. Jenkins LS, Brodsky M, Schron E, Chung M, Rocco T, Jr, Lader E, et al. Quality of life in atrial fibrillation: The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. Am Heart J 2005; 149:112-120.
32. Smets EM, Garssen B, Bonke B, De Haes JC.The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995; 39:315-325.
33. Gelsomino S, La Meir M, Lucà F, Lorusso R, Crudeli E, Vasquez L et al. Treatment of lone atrial fibrillation: a look at the past, a view of the present and a glance at the future. Eur J Cardiothorac Surg. 2012; 41(6): 1284-94.
34. Brace CL. Microwave Tissue Ablation: Biophysics, Technology and Applications. Crit Rev Biomed Eng. 2010; 38(1): 65–78.
35. MacDonald DR, Marhutappu M, Nagendan M. How effective is microwave ablation for atrial fibrillation during concomitant cardiac surgery? Interact. Cardiovasc Thorac Surg 2011; 1581): 122-7.
36. Kuilman M, Bleeker JK, Hartman JA, Simoons ML. Long-term survival after out-of-hospital cardiac arrest: an 8-year follow-up. Resuscitation 1999; 41:25-31.
37. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Medical care 1993; 31:247-263.
38. Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. J Clin Epidemiol 2000; 53:688–695.
39. Efron B, Tibshirani R. An introduction to the bootstrap. New York: Chapman & Hall, 1993.

40. Fair and sustainable care (in Dutch). The Council for Public Health and Health Care, 2006.
41. Kottkamp H, Hindricks G, Hammel D, Breithardt G, Mohr FW, Scheld HH.et al. Intraoperative radiofrequency ablation of chronic atrial fibrillation: A left atrial curative approach by elimination of anatomic 'anchor' reentrant circuits. J Cardiovasc Electrophysiol 1999; 10:772-780.
42. Magnano AR, Argenziano M, Dizon JM, Vigilance D, Williams M, Yegen H, et al. Mechanisms of atrial tachyarrhythmias following surgical atrial fibrillation ablation. J Cardiovasc Electrophysiol 2006; 17:366–73.
43. Ishii Y, Gleva MJ, Gamache MC, Schuessler RB, Boineau JP, Bailey MS,et al. Atrial tachyarrhythmias after the maze procedure: incidence and prognosis. Circulation 2004; 110: II 164–II168.
44. Cox JL. Intraoperative options for treating atrial fibrillation associated with mitral valve disease. J Thorac Cardiovasc Surg 2001; 122:212-215.
45. Maroto LC, Carnero M, Silva JA, Cobiella J, Pérez-Castellano N, Reguillo F,et al. Early recurrence is a predictor of late failure in surgical ablation of atrial fibrillation. Interact Cardiovasc Thorac Surg 2011;12:681-686.
46. Crijns HJ, Van Gelder IC, Van Gilst WH, Hillege H, Gosselink AM, Lie KL. Serial antiarrhythmic drug treatment to maintain sinus rhythm after electrical cardioversion for chronic atrial fibrillation or atrial flutter. Am J Cardiol 1991; 68: 335-41.
47. Gosselink ATM, Crijns HJGM, Van Gelder IC, Hillige H, Wiesfeld ACP, Lie KI. Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. J Am Med Ass 1992; 267: 3289–93.
48. Podrid PJ. Amiodarone: re-evaluation of an old drug. Ann Intern Med 1995; 122: 689-700.
49. Kim JB, Ju MH, Yun SC, Jung SH, Chung CH, Choo SJ,et al. Mitral valve replacement with or without a concomitant Maze procedure in patients with atrial fibrillation. Heart. 2010; 96:1126-1131.
50. Ad N, Henry R, Hunt S, Holmes SD. Impact of Clinical Presentation and Surgeon Experience on the Decision to Perform Surgical Ablation. Ann Thorac Surg. 2013; 96(3): 763-8.
51. Gage BF. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864-2870.
52. Pisters R, de Vos CB, Nieuwlaat R, Crijns HJ. Use and underuse of oral anticoagulation for stroke prevention in atrial fibrillation: old and new paradigms. Seminars in thrombosis and hemostasis 2009; 35:554-559.
53. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA et al; Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012; 9:632-696.
54. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, et al; Heart Rhythm Society; European Heart Rhythm Association; European Cardiac Arrhythmia Society; American College of Cardiology; American Heart Association; Society of Thoracic Surgeons. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up.A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. Europace 2007; 9: 335–379.

55. Comparison of 12-risk stratification schemes to predict stroke in patients with non-valvular atrial fibrillation. Stroke Risk in Atrial Fibrillation Working Group. Stroke 2008, 39:1901-1910.
56. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE, Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. Journal of the American College of Cardiology 2008; 51:810-815.
57. Dagres N, Hindricks G, Kottkamp H, Sommer P, Gaspar T, Bode K et al: Real-life anticoagulation treatment of atrial fibrillation after catheter ablation. Possible overtreatment of low-risk patients. Thromb Haemost 2009; 102:754-758.
58. Nieuwlaat R, Olsson SB, Lip GY, Camm AJ, Breithardt G, Capucci A et al; Euro Heart Survey Investigators. Guideline adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. Am Heart J 2007; 153: 1006–1012.
59. Tay KH, Lip GY, Lane DA. Atrial fibrillation and stroke risk prevention in real-life clinical practice. Thromb Haemost 2009; 101: 415–416.
60. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Stroke risk in atrial fibrillation patients on warfarin. Predictive ability of risk stratification schemes for primary and secondary prevention. Thromb Haemost 2009; 101: 367–372.
61. Lane DA, Lip GY. Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients. Thromb Haemost 2009; 101: 802–805.
62. Mant JW. Pro: Warfarin should be the drug of choice for thromboprophylaxis in elderly patients with atrial fibrillation. Why warfarin should really be the drug of choice for stroke prevention in elderly patients with atrial fibrillation. Thromb Haemost 2008; 100:14–15.
63. Hylek EM. Contra: 'Warfarin should be the drug of choice for thromboprophylaxis in elderly patients with atrial fibrillation. Caveats regarding use of oral anticoagulant therapy among elderly patients with atrial fibrillation. Thromb Haemost 2008; 100: 16-17.
64. Peterson GM, Boom K, Jackson SL, Vial JH. Doctors' beliefs on the use of antithrombotic therapy in atrial fibrillation: identifying barriers to stroke prevention. Internal medicine journal 2002; 32:15-23.
65. Jaïs P, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R et alTechnique and results of linear ablation at the mitral isthmus. Circulation 2004; 110(19): 2996-3002.
66. Pappone C, Manguso F, Vicedomini G, Gugliotta F, Santinelli O, Ferro A et al. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation: a prospective randomized study comparing circumferential pulmonary vein ablation with a modified approach. Circulation 2004; 110(19): 3036-42.
67. Gillinov AM, Bhavani S, Blackstone EH, Rajeswaran J, Svensson LG, Navia JL et al. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. Ann Thorac Surg. 2006; 82(2): 502-13.
68. Prasad SM, Maniar HS, Diodato MD, Schuessler RB, Damiano RJ Jr. Physiological consequences of bipolar radiofrequency energy on the atria and pulmonary veins: a chronic animal study. Ann Thorac Surg. 2003; 76(3): 836-41;
69. Miyagi Y, Ishii Y, Nitta T, Ochi M, Shimizu K. Electrophysiological and histological assessment of transmurality after epicardial ablation using unipolar radiofrequency energy. J Card Surg 2009; 24(1): 34-40.
70. Garcia-Villarreal OA. eComment. "Electric" Cox-maze IV with bipolar radiofrequency: toward full transmurality Interact Cardiovasc Thorac Surg. 2012; 14(6): 847.
71. Gaita F, Riccardi R, Caponi D, Shah D, Garberoglio L, Vivalda L et al. Linear cryoablation of the left atrium versus pulmonary vein cryoisolation in patients with permanent atrial fibrillation and valvular heart disease: correlation of electroanatomic mapping and long-term clinical results. Circulation 2005; 111:136-42.
72. Sueda T., Nagata H., Orihashi K.; Efficacy of a simple left atrial procedure for chronic atrial fibrillation in mitral valve operations. Ann Thorac Surg. 63 1997:1070-1075.
73. Chauvin M, Shah DC, Haïssaguerre M, Marcellin L, Brechenmacher C. The anatomic basis of connections between the coronary sinus musculature and the left atrium in humans. Circulation. 2000; 101(6): 647-52.

74. Lin YJ, Tai CT, Kao T, Tso HW, Huang JL, Higa S et al. Electrophysiological characteristics and catheter ablation in patients with paroxysmal right atrial fibrillation. Circulation. 2005; 112(12): 1692-700.

75. Cox JL, Schuessler RB, D'Agostino HJ, Stone CM, Chang BJ, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation, III: development of a definitive surgical procedure. J Thorac Cardiovasc Surg. 1991; 101:569-583.

76. Wang J, Meng X, Li H, Cui Y, Han J and Xu C. Prospective randomized comparison of left atrial and biatrial radiofrequency ablation in the treatment of atrial fibrillation. Eur J Cardiothorac Surg 2009; 35: 116-122.

77. Albrecht A, Kalil RA, Schuch L, Abrahão R, Sant'Anna JR, de Lima G et al Randomized study of surgical isolation of the pulmonary veins for correction of permanent atrial fibrillation associated with mitral valve disease. J Thorac CardiovascSurg 2009; 138:454-9.

78. Melo J, Santiago T, Aguiar C, Berglin E, Knaut M, Alfieri O. et al Surgery for atrial fibrillation in patients with mitral valve disease: results at five years from the International Registry of Atrial Fibrillation Surgery. J Thorac Cardiovasc Surg. 2008; 135(4): 863-9.

79. Lammers WJ1, Schalij MJ, Kirchhof CJ, Allessie MA. Quantification of spatial inhomogeneity in conduction and initiation of reentrant atrial arrhythmias. Am J Physiol. 1990; 259(4 Pt 2): H1254-63.

80. Onorati F, Mariscalco G, Rubino AS, Serraino F, Santini F, Musazzi A et alImpact of lesion sets on mid-term results of surgical ablation procedure for atrial fibrillation. J Am Coll Cardiol. 2011; 57(8): 931-40.

81. Gillinov AM, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF et al. Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality. J Thorac Cardiovasc Surg. 2005; 129(6): 1322-9.

82. Benussi S, Nascimbene S, Calori G, Denti P, Ziskind Z, Kassem S. et al Surgical ablation of atrial fibrillation with a novel bipolar radiofrequency device. J Thorac Cardiovasc Surg 2005; 130(2): 491-7.

83. Gelsomino S, Corradi D, Lorusso R, Parise O, Callegari S, Macchi E et al. Anatomical basis of minimally invasive epicardial ablation of atrial fibrillation. Eur J Cardiothorac Surg. 2013; 43(4): 673-82.

84. Corradi D, Callegari S, Gelsomino S, Lorusso R, Macchi E. Morphology and pathophysiology of target anatomical sites for ablation procedures in patients with atrial fibrillation. Part I: atrial structures (atrial myocardium and coronary sinus). Int J Cardiol. 2013; 168(3): 1758-68

85. Aupperle H, Doll N, Walther T, Ullmann C, Schoon HA, Wilhelm Mohr F. Histological findings induced by different energy sources in experimental atrial ablation in sheep. Interact Cardiovasc Thorac Surg 2005;4(5):450-5.

86. Robertson JO, Saint LL, Leidenfrost JE, Damiano RJ Jr Illustrated techniques for performing the Cox-Maze IV procedure through a right mini-thoracotomy. Ann Cardiothorac Surg. 2014; 3(1):105-16.

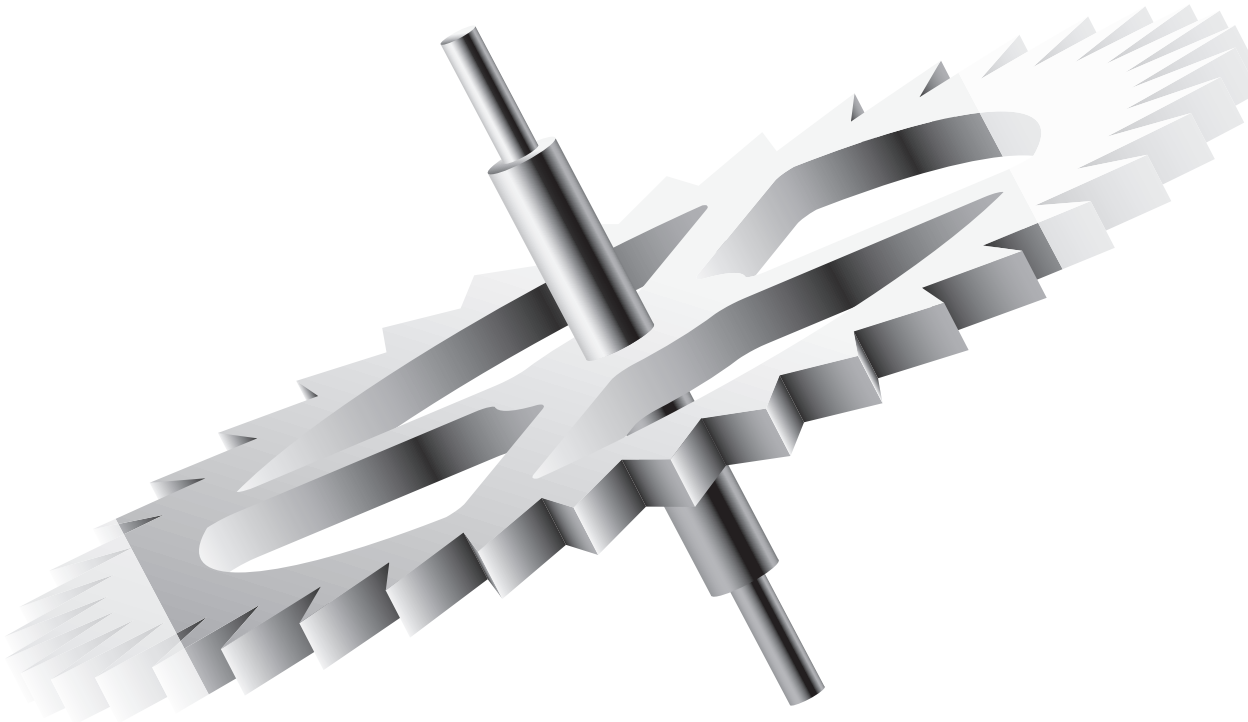
87. La Meir M, Gelsomino S, Lucà F, Pison L, Colella A, Lorusso R, et al. Minimal invasive surgery for atrial fibrillation: an updated review. Europace. 2013; 15:170-182.

88. Gelsomino S, La Meir M, Lucà F, Lorusso R, Crudeli E, Vasquez L, et al. Treatment of lone atrial fibrillation: a look at the past, a view of the present and a glance at the future. Eur J Cardiothorac Surg. 2012; 41:1284-1294.

89. Shinbane JS, Lesh MD, Stevenson WG, Klitzner TS, Natterson PD, Wiener I,et al. Anatomic and electrophysiologic relation between the coronary sinus and mitral annulus: implications for ablation of left-sided accessory pathways. Am Heart J 1998; 135:93-8.

90. Edgerton RJ, Jackman WM, Mahoney C, Mack MJ. Totally thoracoscopic surgical ablation of persistent atrial fibrillation and long-standing persistent atrial fibrillation using the 'Dallas' lesion set. Heart Rhythm 2009; 6:S64-70.

91. Sauren LD, La Meir M, De Roy L, Pison L, van der Veen FH, Mess WH, et al. Increased number of cerebral emboli during percutaneous endocardial pulmonary vein isolation versus a thoracoscopic epicardial approach. Eur J Cardiothorac Surg 2009; 36:833-7.



Addendum

Summary
Samenvatting
Dankwoord
Curriculum Vitae
Publications
Valorisatie addendum

Summary

In the present thesis, drivers for add-on ablation surgery in atrial fibrillation (AF) are investigated.
AF is the most prevalent cardiac arrhythmia in the Western world and is characterized by uncoordinated and rapid activation of the atria. Its prevalence increases with advancing age and has been projected to increase to 1 million in The Netherlands in 2050, thus increasingly placing a burden on our (financial) health care resources.
AF may occur in self-limiting episodes lasting from minutes to days (paroxysmal AF) or may be permanent in nature (persistent or permanent AF). It coincides with significant clinical morbidity and is also an independent risk factor for mortality. Ischaemic heart disease, cardiac failure, valvular heart disease, hypertension, diabetes, alcohol abuse, thyroid disorders, anxiety and depression and pulmonary disease are often found in AF patients. Due to the uncoordinated and rapid activation of the atria in AF patients, atrial blood flow diminishes and can cause thromboembolisms. Thromboembolic stroke is the most serious and debilitating of all the complications of AF.
AF is common in patients who undergo valvular and/or coronary bypass surgery, dependant on underlying heart disease and age. Nonetheless, in a percentage of non-eligible people presenting with AF, there is no identifiable aetiology and this subset of patients is often referred to as 'lone AF' (LAF).

Because of its multiple manifestations and concomitant diseases, AF management can be quite complicated. Historically, long-term treatment for AF consists of rate versus rhythm control. Randomised trials have shown an almost significant trend towards reduced morbidity, mortality and stroke by rate control, but this may have been due to inadequate anticoagulation among patients in whom AF seemed to be controlled with antiarrhythmic drugs. Two drawbacks for treatment with antiarrhythmic drugs in the maintenance of sinus rhythm (SR) are inconsistent efficacy and severe side effects. Furthermore, SR is difficult to obtain. As a large group of patients show severe and frequent symptoms of AF (despite the use of many antiarrhythmic and rate control drugs) while being at great risk for systemic embolization, non-pharmacological approaches in the treatment of AF have gained increased interest in the last few years.

Multiple surgical approaches in the treatment of AF have been developed, all aimed at eliminating mechanisms in the initiation and maintenance of AF. In add-on ablation surgery, a procedure performed to treat AF during cardiac surgery where a number of incisions or ablations are made, the gold standard is still the Cox-Maze III technique, although a lot of variations have been developed over the last years. Also, new techniques such as minimally invasive catheter ablation approaches and the 'hybrid' procedure have gained a lot of interest over time. However, the efficacy of these procedures as well as their potential superiority over standard add-on surgical techniques has to be confirmed by large comparative studies.

In addition to purely clinical criteria such as morbidity and mortality as reasons to treat patients with AF, enhancing health-related quality of life (HrQoL) has gradually been accepted as another driver for AF treatment. Since 1948, when the World Health Organisation defined 'health' as being not only the absence of disease, but also as the presence of physical, mental and social well-being, HrQoL has become more important in health care practice and research. HrQoL in AF patients is diminished due to palpitations, dyspnoea, dizziness, syncope, fatigue and decreased exercise tolerance. In this respect the benefit of chronic SR has to outweigh the risks of a prolonged operation. In addition, cardiovascular complaints unrelated to AF may persist even after successful surgery, thus offsetting the benefit of maintaining chronic SR. At the present time we do not know whether surgical techniques indeed affect quality of life, since randomised trials are lacking. Besides enhancing HrQoL, preventing the use of oral anticoagulation (OAC) is a key-point issue in finding a definite treatment strategy for AF. About 1 out of 6 ischaemic strokes is associated with AF and a worse outcome is seen than for those without AF: portraying higher mortality and morbidity, greater disability, longer hospital stay, increased costs and higher recurrence rate. Long-term treatment with OAC can reduce stroke risk in AF patients. Although this mainstream therapy in reduction of stroke risk has been confirmed by multiple trials, it is distressing to note that OAC therapy still remains widely under-utilized in high-risk patients, insufficiently protecting them against (recurrent) stroke. On the other hand, OAC use in itself can cause serious bleeding complications: therefore OAC should only be prescribed if justified by the patient's individual stroke risk profile. As ceasing OAC therapy and therefore reducing its risk of complications might be one of the reasons for the definite treatment of AF, it has

never been investigated if additional indications for OAC are present within the AF patient population. In other words, should OAC be continued even after AF (and its indication for OAC) is cured by ablation surgery for additional individual reasons, therefore discarding OAC-freedom as a reason for curing AF.
As mentioned before, the burden of AF on our (financial) health care resources is high and will become even higher in the next decades due to the general aging and growing of our Dutch population. Today, costs are an important issue in health care and may even direct options in treatment strategy. Although associated costs of (add-on ablation) surgery are high, restoration of SR through ablation surgery might still turn out to be cost-effective in the long run. The potential enhanced HrQoL, reduction in health care consumption due to decreased risk in stroke, lower pharmacological drug use and fewer complications due to AF, might outweigh additional surgery costs during long-term follow-up. Therefore add-on ablation surgery could well be cost saving.
Nonetheless, there are still also many aspects of add-on ablation surgery that have been poorly investigated. Controversy exists as to whether the considerable proportion of health care resources spent on add-on surgery in AF represents a cost-effective approach in an attempt to maintain a meaningful QoL and if QoL is affected by the restoration of SR.
Furthermore, electrical cardioversion (ECV) is commonly recommended for patients with recurrent AF following an initial ablation procedure. Nonetheless, although the long-term effect of ECV might be promising under these circumstances, it has been reported that a large number of patients who undergo ECV for persistent AF or atrial flutter after ablation surgery have AF recurrences. However, little is known about the benefit of ECV, with or without additional pharmacological pre-treatment, after unsuccessful add-on ablation surgery.
Moreover, the current management of OAC therapy following add-on ablation surgery is unknown and no guidelines were put in place until recently. Moreover little work has been done to investigate the best anticoagulation treatment strategies after surgical ablation. In addition, the long-term efficacy of add-on surgical ablation has not yet been fully determined and the role of lesion sets on long-term outcome has been poorly defined.

Chapter 2 describes the effect of add-on ablation surgery on HrQoL in AF patients. During 1-year follow-up HrQOL showed an overall linear enhancement after cardiac surgery, this was irrespective of whether add-on ablation surgery

was performed or not. Thus the HrQoL improvement was probably more affected by treating the underlying heart disease during surgery than by restoring sinus rhythm. But since there was no significant difference in SR restoration between the add-on surgery patient group and the regular cardiac surgery group, additional analysis was performed to investigate the effect of SR restoration on HrQoL.

Chapter 3 presents a retrospective analysis demonstrating that generic HrQoL was not influenced by SR conversion nor by possible confounders such as age, gender and type of AF. However, specific HrQoL scales are much more sensitive to SR conversion and do show significant effects and remain statistically significant after being controlled for additional confounders. In addition, the relationship between SR conversion and HrQoL (both generic and specific) tended to attenuate and wear off with postoperative time. In conclusion, the results of these two chapters with respect to HrQoL indicate that overall HrQoL in AF patients does not improve in case SR is achieved, regardless of whether this restoration was brought about by ablation surgery or the corrective effect of cardiac surgery on underlying heart disease. However, more disease-specific HrQoL questionnaires have to be used, developed and tested in clinical research to properly gauge and evaluate the effects of operation-induced SR conversion in AF patients.

Chapter 4 depicts the cost-effectiveness of add-on ablation surgery compared to isolated cardiac surgery procedures in AF patients after 1-year follow-up. To calculate the incremental cost-effectiveness ratio (ICER), the difference in costs between the two treatment options was divided by the gain in HrQoL. When the costs for both treatment modalities were compared for their effectiveness, the result was an ICER above the assumed threshold for the surgical treatment of AF. Additional ablation surgery could not be considered a cost-effective treatment in AF patients.

Chapter 5 reports the early and mid-term outcomes in patients undergoing electrical cardioversion (ECV) for persistent AF after add-on ablation surgery (radiofrequency) in mitral valve surgery compared to patients undergoing ECV after mitral valve surgery without concomitant AF ablation. After successful ECV, statistically more patients in the add-on ablation group were in stable SR off-antiarrhythmic drugs, than in the no-ablation group. We can postulate that some kind of substrate modification occurred after surgical ablation which made the patients more susceptible to the treatment of ECV. Also the timing of the

cardioversion procedure proved to be of utmost importance. Ideally the ECV should be performed within 88 days post-surgery. Left atrial (LA) dimensions were significantly more reduced in patients with associated ablation surgery than in those with isolated mitral valve surgery, probably because of scarring along the ablation lines or because of reverse remodelling of the atria. Amiodarone improved the ECV success rate only in patients without add-on ablation surgery.
Chapter 6 explores the real-life OAC treatment after ablation surgery and examines whether this treatment is adherent to the current guidelines. The main finding was that OAC prescription before and after surgical ablation in AF patients was hardly guided by the patient's individual stroke risk. Contrary to current recommendations, the rate of OAC remains high even in patients with a low stroke risk. The most important factors that influence the use of anticoagulants seem to be older age, type of AF, preoperative OAC use and other indications for OAC use than AF. This results in possible over-treatment of low-risk patients and under-treatment of high-risk patients. Over-treatment and under-treatment did not show significant differences in stroke or bleeding risk.
Chapter 7 discusses a multicentre trial analysing the long-term outcomes of patients undergoing add-on radiofrequency (RF) ablation. The findings confirm the superiority of a bipolar source for rhythm outcome and transmurality of the lesions. Furthermore, right-sided atrial ablations in addition to left-sided lines lead to better long-term rhythm outcome. LA connecting lesions and mitral isthmus lines do not show to be significant predictors for AF recurrence. Further studies are necessary to confirm these findings.
Chapter 8 provides a review of the 'hybrid procedure' for the treatment of LAF. In this technique percutaneous epicardial catheter ablation (PECA) and endocardial ablation are combined. Papers selected for this review were identified on PUBMED and the final selection included nine studies. The hybrid approach achieved satisfactory results, with atrial fibrillation-antiarrhythmic drug-free success rates higher than in isolated procedures. In particular, the bilateral approach with a bipolar device had a high success rate and seems to be the better choice for the hybrid procedure. Despite good preliminary results, large, multicentre trials on hybrid atrial fibrillation ablation, that target a population of patients with long-standing-persistent disease, are necessary to establish whether this approach may in the future represent the gold-standard treatment for atrial fibrillation.

In **Chapter 9** the results of this thesis, including the drivers for add-on surgery such as rhythm outcome, HrQoL, cost-effectiveness, substrate modification, OAC prescription and recommendations on ablation set administration and its future directions, are defined. Many aspects of add-on microwave ablation surgery have been poorly investigated and are the main aims of this thesis. It is concluded that add-on ablation surgery with microwave energy did not affect HrQoL, which was not influenced by SR conversion. Furthermore, it is also not considered as being cost-effective. These unsatisfactory results may be explained by the use of microwave energy to make lesions. Add-on ablation surgery with bipolar RF shows better results in SR restoration than both unipolar RF and microwave sources. But after unsuccessful add-on microwave ablation surgery, ECV results were more effective than in patients undergoing isolated cardiac surgery. This might be related to substrate modification induced by ablation surgery, although the initial SR conversion effect was not satisfactory.

Real-life oral anticoagulation prescription after add-on surgery shows a moderate guideline adherence, with high-risk patients being under-treated and low-risk patients being over-treated.

In assessing the importance of lesion set and surgical technique, completeness of left atrial surgical ablation lines with right atrial ablation is a key point for stable, long-term normal sinus rhythm. The mitral isthmus line still represents an unanswered surgical challenge.

The findings of this thesis suggest that add-on microwave ablation surgery is currently not recommended as an intervention for the treatment and/or management of AF. The hybrid approach is a potentially attractive surgical technique for add-on surgery in AF patients to be tested.

Samenvatting

Bij boezemfibrilleren oftewel atriumfibrilleren (AF) is de hartslag onregelmatig. Bij een normaal hartritme ontstaat de prikkel voor elektrische geleiding in de sinusknoop, van waaruit deze zich geleidelijk verspreidt over beide boezems. Bij boezemfibrilleren ontstaat de elektrische prikkel niet op één plek, maar op verschillende plekken in de boezems, kriskras en snel door elkaar. Hierdoor trekken ook de kamers onregelmatig en vaak te snel samen, waardoor er geen effectieve samentrekking (contractie) van het hart tot stand komt. Het gevolg enerzijds is dat het bloed trager stroomt en er 'stasis' optreedt waardoor er stolsels (bloedpropjes) kunnen ontstaan. Deze kunnen vervolgens leiden tot een van de meeste gevreesde complicaties van AF: een beroerte. En anderzijds is het gevolg dat door AF er een verminderde pompfunctie van het hart ontstaat (hartfalen).

AF is de meest voorkomende ritmestoornis in de Westerse wereld. Het vóórkomen van AF neemt toe met de leeftijd en verwacht wordt dat tegen 2050 ongeveer 1 miljoen mensen in Nederland lijden aan deze ritmestoornis. AF kan optreden in aanvallen die vanzelf stoppen, variërend in duur van een paar minuten tot dagen (paroysmaal AF) of kan optreden in een meer chronische vorm (persisterend of persistent AF). De klachten bij AF variëren van duizeligheid, hartkloppingen, vermoeidheid en transpireren tot helemaal geen klachten.
Om de vorming van stolsels (wat kan leiden tot een beroerte) en andere bijwerkingen van de snelle, onregelmatige hartfrequentie te voorkomen, worden AF patiënten behandeld met antistollingsmiddelen en medicamenten die de frequentie beïnvloeden (de zogenaamde 'rate control' therapie). Een andere behandelingsstrategie is het proberen herstellen van het normale sinus ritme (de zogenaamde 'rhythm control' therapie). Dit kan bereikt worden door een elektrische shock (een cardioversie) of door het toedienen van medicijnen welke de elektrische activiteit van het hart beïnvloeden. Maar medicijnen hebben over het algemeen allerlei bijwerkingen en men moet ze blijven gebruiken. Het liefste zou men AF op een meer permanente manier willen behandelen.
Een deel van de patiënten die een open hartoperatie ondergaan hebben ook AF. Juist bij deze groep patiënten is het mogelijk om tijdens de hartoperatie een additionele ingreep uit te voeren om te proberen het AF te verhelpen. Dit kan door het hart aan de buitenkant en/of binnenkant te beschadigen door middel van insnijdingen (incisies) of verbrandingen (ablaties). Hiermee kunnen de elektrische prikkels en

geleidingsstromen onderbroken worden, waardoor AF niet (meer) kan ontstaan. Maar helaas werkt deze behandeling niet bij alle patiënten. Met name patiënten die al langere tijd AF hebben zijn minder gevoelig voor deze therapie. Bovendien komt bij een groot aantal patiënten het AF weer terug nadat de behandeling initieel succesvol is uitgevoerd. In de loop der jaren zijn er daarom ook vele verschillende chirurgische ablatie technieken ontwikkeld, voor verschillende subtypen AF patiënten.
Het adequaat behandelen en/of genezen van AF is belangrijk omdat AF vaak gepaard gaat met significante klinische morbiditeit en mortaliteit. Coronaire hartziekten, hartfalen, klep afwijkingen, hoge bloeddruk, diabetes, alcoholmisbruik, schildklier aandoeningen, longziekten, angst en depressie komen vaak voor bij AF patiënten. Maar naast mortaliteit en morbiditeit als redenen om AF te behandelen, zijn er ook andere redenen te bedenken zoals het verbeteren van de kwaliteit van leven bij de patiënt, het verlagen van de zorgkosten, het reduceren van het aantal beroertes en het kunnen stoppen van antistollingsmedicatie.

Dit proefschrift beschrijft het effect van de additionele 'microwave' chirurgische ablatie techniek op de verschillende voorgenoemde redenen ('drivers') om AF te behandelen. Tenslotte worden de resultaten van de veelbelovende hybride procedure ter behandeling van AF bediscussieerd.

Hoofdstuk 2 beschrijft het effect van de additionele chirurgische 'microwave' ablatie techniek op de kwaliteit van leven gedurende 1 jaar follow-up na een open hartoperatie. Er worden 2 groepen vergeleken: AF patiënten met een open hartoperatie en AF patiënten met een open hartoperatie én een additionele ablatie behandeling ten behoeve van AF. De overall kwaliteit van leven na een hartoperatie verbetert aanzienlijk bij beide groepen patiënten maar dit is onafhankelijk van het feit of er een additionele ablatie procedure heeft plaatsgevonden voor de behandeling van AF. Dit impliceert dat de hartoperatie zelf meer invloed heeft gehad op de verbeterde kwaliteit van leven dan het herstel van sinus ritme (SR). Omdat het effect van de operatie de ware betekenis van het herstel van sinus ritme zou kunnen maskeren werd er een additionele analyse uitgevoerd waarbij speciaal het effect van SR herstel op kwaliteit van leven wordt onderzocht.
Hoofdstuk 3 geeft de resultaten van deze retrospectieve analyse weer. Herstel van SR heeft geen invloed op de algemene kwaliteit van leven. Maar de meer specifieke sub-schalen (zoals 'vermoeidheid') van de kwaliteit van leven meetinstrumenten

tonen wel degelijk significante verbeteringen wanneer SR is hersteld. Overigens bleken deze effecten uiteindelijk te verminderen en te verdwijnen met het verstrijken van de tijd. Aangezien er geen ziekte-specifieke (dus AF-specifieke) kwaliteit van leven meetinstrumenten bestaan, zijn er algemene meetinstrumenten gebruikt. Meer ziekte-specifieke meetinstrumenten zullen moeten worden ontwikkeld om het daadwerkelijke effect van SR herstel op kwaliteit van leven te kunnen bepalen.

Hoofdstuk 4 rapporteert de resultaten van de kosteneffectiviteitsanalyse van additionele chirurgische 'microwave' ablatie techniek. De 'incrementele kosteneffectiviteitsratio (IKER)' is het verschil in kosten tussen de twee behandelgroepen (hartchirurgie mét en zonder additionele ablatie) gedeeld door de toename in kwaliteit van leven. De gemeten gezondheidswinst (QALY) is niet voldoende om te kunnen spreken van een kosteneffectieve ingreep in het geval van de additionele chirurgische 'microwave' ablatie techniek.

Hoofdstuk 5 beschrijft de vroege en tussentijdse uitkomsten van een elektrische cardioversie (ECV) bij patiënten met persisterend of recidief AF, na mitraalklep chirurgie mét en zonder additionele ablatie chirurgie (radiofrequentie). Na een succesvolle cardioversie zonder additionele anti-arrhythmica blijven significant meer patiënten uit de additionele ablatie groep in SR dan de patiënten zonder additionele ablatie chirurgie. Dit suggereert een substraatmodificatie door de ablatie chirurgie, waardoor deze patiënten meer gevoelig zijn voor SR conversie door ECV. Daarnaast blijkt dat de kans op een succesvolle ECV ook wordt bepaald door de tijd tussen de chirurgie en de ECV: de ECV zou binnen 88 dagen post-chirurgie moeten plaatsvinden. Tenslotte blijken linker atrium afmetingen significant meer gereduceerd te zijn bij patiënten die additionele ablatie chirurgie hebben ondergaan dan bij patiënten die enkel mitraalklep chirurgie hebben ondergaan: dit kan verklaard worden door de littekenvorming langs de ablatie lijnen, welke op het hart gemaakt zijn of door 'reverse remodelling' van de boezems. Het medicijn Amiodarone verbeterde het succespercentage van een ECV enkel bij patiënten zonder additionele ablatie chirurgie.

In **Hoofdstuk 6** is het gebruik van antistollingsmiddelen (OAC) na additionele ablatie chirurgie onderzocht en of dit gebruik voldoet aan de huidige richtlijnen. De belangrijkste bevinding in dit onderzoek is dat het voorschrijven van antistollingsmiddelen, zowel voor de chirurgie als na de chirurgie, nauwelijks bepaald wordt door het individuele risicoprofiel van de patiënt. In tegenstelling tot de huidige richtlijnen, werd bij patiënten waarbij OAC niet aanbevolen wordt, toch OAC voorgeschreven. Laag-risico patiënten worden overgedoseerd en hoog-risico

patiënten worden ondergedoseerd. Factoren die dit voorschrijfgedrag beïnvloeden zijn hoge leeftijd, type AF, pre-operatief gebruik van OAC en andere indicaties voor OAC gebruik behalve AF. Er werd echter geen verschil in bloedingsrisico of risico op een beroerte gezien tussen de overgedoseerde groep en de ondergedoseerde groep.

Hoofdstuk 7 bespreekt een multicenter onderzoek, waarbij de lange termijn resultaten van additionele ablatie chirurgie (radiofrequentie) zijn geanalyseerd. De bevindingen bevestigen dat een bipolaire energiebron betere resultaten levert t.a.v. het gewensteritme herstelen penetratie van de ablatie laesie door de hele wand van de boezem (transmuraliteit). Daarnaast blijken additionele rechtszijdige ablatie laesies van de boezem, naast de reguliere linkszijdige laesies, te leiden tot betere lange termijn ritme uitkomsten. Connecterende ablatie laesies van de linker boezem en mitraal isthmus blijken geen voorspellers te zijn voor recidief AF. Verder onderzoek is noodzakelijk om deze bevindingen te staven.

Hoofdstuk 8 geeft een literatuurstudie weer naar de resultaten van de relatief nieuwe 'hybride' procedure in de behandeling van 'lone AF' (AF waarbij geen sprake is van een hart- en/of longziekte). Bij deze procedure wordt een percutane epicardiale catheter ablatie gecombineerd met een endocardiale ablatie. Hierbij wordt de wand van het hart dus zowel van binnen als van buiten uit geableerd. Via Pubmed werden negen wetenschappelijke publicaties betreffende dit onderwerp geselecteerd. De hybride procedure laat betere resultaten zien in medicatie vrij SR herstel dan geïsoleerde procedures. Met name de bilaterale benadering met een bipolaire energie toepassing laat hoge succes percentages zien en lijkt de beste techniek. Maar ondanks deze hoopvolle resultaten, dienen er eerst grote gerandomiseerde onderzoeken te worden opgezet met een patiëntenpopulatie waarbij sprake is van langdurig persistent AF, om te kunnen bewijzen of de hybride procedure in de toekomst als de gouden standaard voor de behandeling van 'lone AF' kan worden betiteld.

In **hoofdstuk 9** wordt geconcludeerd dat additionele 'microwave' ablatie chirurgie de kwaliteit van leven bij AF patiënten niet beïnvloedt, maar ook conversie naar SR niet. Daarnaast blijkt de procedure ook niet kosteneffectief. Deze resultaten zouden kunnen verklaard worden door het gebruik van 'microwave' als energiebron: additionele ablatie chirurgie op basis van bipolaire radiofrequentie toont betere resultaten in SR restoratie. Hoewel additionele 'microwave' ablatie chirurgie niet meer succesvol bleek te zijn in SR restoratie dan reguliere hartchirurgie, leek er wel sprake te zijn van substraatmodificatie bij ECV.

In het onderzoek naar het voorschrijven van antistollingsmiddelen, blijkt dat het voorschrijfgedrag nauwelijks beïnvloedt wordt door het individuele patiënt risicoprofiel. Zowel voor als na de chirurgische ingreep blijken laag-risico patiënten overgedoseerd te worden en hoog-risico patiënten ondergedoseerd. Het al dan niet uitvoeren van een additionele ablatie procedure heeft hier geen invloed op.
Bij nadere bestudering van laesie sets en chirurgische technieken, blijkt de combinatie van chirurgische ablatie lijnen op het linker en rechter atrium een cruciale factor te zijn voor stabiele, lange termijn SR restoratie. De mitrale isthmus blijft hierbij nog de uitdaging.
De resultaten van dit proefschrift tonen aan dat additionele 'microwave' ablatie chirurgie momenteel niet gezien kan worden als de aangewezen techniek voor het behandelen en managen van AF. De hybride procedure is een potentiële attractieve techniek voor de additionele chirurgische behandeling van AF en vraagt om verder onderzoek.

Dankwoord

Dankbetuigingen zijn inflationair: met elke extra naam wordt het gebaar betekenislozer.

Voor sommigen zal het een teleurstelling zijn; in dit meestgelezen deel van een proefschrift hoort een lange opsomming van namen en anekdotes van iedereen die mij heeft gesteund, gemotiveerd en geïnspireerd gedurende mijn promotietraject. Bij gebrek aan inspiratie hou ik het kort.

Prof. Dr. J.G. Maessen, beste Jos, je stille vertrouwen heeft me gevormd in mijn carrière. Jij was degene die het zaadje plantte om vertrouwen te hebben in mijn kwaliteiten buiten het conventionele pad als arts en me altijd stimuleerde en ruimte gaf om 'uitvinder' te spelen. Ik zal je begrip en lovende woorden, tijdens het moeilijkste gesprek uit mijn leven, nooit vergeten.

Prof. Dr. Sandro Gelsomino, dear Sandro, thanks to your endless motivation, input and efforts in these last few months, I could finally conclude my thesis. Where would I have been without you!

De leden van de beoordelingscommissie, Prof. Dr. Roekaerts, Prof. Dr. Hoorntje, Dr. Kietselaer, Prof. Dr. La Meir, hartelijk dank voor het zorgvuldig doorlezen van mijn proefschrift.

'Circle of trust', een pact voor het leven.

Lieve pap en mam, alles wat ik ben, ben ik dankzij jullie.

Frank en mijn kleine prins Maurits: jullie zijn mijn drijvende kracht.

Curriculum vitae

Nathalie van Breugel is geboren op 6 Februari 1976 te Boxtel. Na het afronden van het Gymnasium B aan het Jacob Roelands Lyceum te Boxtel, is zij in 1994 gestart met de opleiding Gezondheidswetenschappen aan de Universiteit van Maastricht.
In 1997 startte zij, na diverse malen uitgeloot te zijn, aan haar studie Geneeskunde aan de Universiteit van Maastricht en behaalde in 2001 haar doctoraalexamen en vervolgens in 2003 haar artsexamen. Aansluitend was zij werkzaam als arts-assistent Cardio-thoracale Chirurgie (AGNIO en AGIO) in het Maastricht Universitair Medisch Centrum, waar zij ook in 2007 startte met haar promotietraject. In 2010 besloot zij haar carrière een andere richting te geven en verliet zij de Cardiochirurgie voor een toekomst in zorgmanagement. Na de afronding van haar opleiding aan Harvard Business School in 2012 is zij werkzaam als manager voor de zorggroep Huisartsen OZL te Heerlen.

Publications

Henrica N.A.M. van Breugel, Fred H.M. Nieman, Ryan. E. Accord, Sandro Gelsomino, Fabiana Lucà, Pieter Lozekoot, Orlando Parise, Ghislaine. A.P.G. van Mastrigt, Jan.F.M.A. Nijs, Ries Vrakking, Jos.G. Maessen. Sinus rhythm coversion after cardiac surgery: does it affect postoperative health related quality of life? Under review: Eur J Cardiothoracic Surg

Henrica N.A.M. van Breugel, Sandro Gelsomino, Pieter Lozekoot, Idserd D. G. Klop, Roberto Lorusso, Carlo Rostagno, Fabiana Lucà, Attilio Renzulli, Filiberto Serraino, Orlando Parise, Francesco Matteucci, Harry J.G.M. Crijns, Gian Franco Gensini, Mark La Meir, Jos G. Maessen. Ten-year results of surgical radiofrequency ablation for atrial fibrillation in patients undergoing mitral valve surgery: impact of lesion set and surgical techniques on long-term arrhythmia recurrence. Under review: J Am Coll Cardiol.

Van Breugel HN, Gelsomino S, de Vos CB, Accord RE, Tieleman RG, Lucà F, Rostagno C, Renzulli A, Parise O, Lorusso R, Crijns HJ, Maessen JG. Maintenance of sinus rhythm after electrical cardioversion for recurrent atrial fibrillation following mitral valve surgery with or without associated radiofrequency ablation. Int J Cardiol. 2014 Aug 1; 175 (2): 290-6

Van Breugel HN, Gelsomino S, Lozekoot PW, Accord RE, Lucà F, Parise O, Crijns HJ, Maessen JG. Guideline adherence in antithrombotic treatment after concomitant ablation surgery in atrial fibrillation patients. Interact Cardiovasc Thorac Surg. 2014 Mar; 18(3): 313-20

S. Gelsonimo, **H. van Breugel**, L. Pison, H. Crijns, F. Wellens, J. Maessen, M. La Meir. Hybrid thoracoscopic and transvenous catheter ablation of atrial fibrillation. Eur J Cardiothoracic Surg. 2014 Mar; 45(3): 401-7.

H.N.A.M. van Breugel, E. Bidar, B.A.B. Essers, F.H. Nieman, R.E. Accord, J.L. Severens, J.G. Maessen Cost-effectiveness of ablation surgery in patients with atrial fibrillation undergoing cardiac surgery. Interact Cardiovasc Thorac Surg. 2011 Mar; 12(3): 394-8.

H.N.A.M. van Breugel, F.H. Nieman, R.E. Accord, G.A. van Mastrigt, J.F. Nijs, J.L. Severens, R. Vrakking, J.G. Maessen A prospective randomized multicenter comparison on Health related Quality of Life: the value of add-on arrhythmia surgery in patients with paroxysmal, permanent or persistent atrial fibrillation undergoing valvular and/or coronary bypass surgery. Journal of cardiovascular electrophysiology. 2010 May; 21(5): 511-20.

M. Palmen, **H.N.A.M. van Breugel**, G.G. Geskes, A. van Belle, J.M. Swennen, A.H. Drijkoningen, R.R. van der Hulst, J.G. Maessen. Open window thoracostomy treatment of empyema is accelerated by vacuum-assisted closure. Annals of thoracic surgery 2009; 88 (4); 1131-6

H.N.A.M. van Breugel, T.H.A. Ekhart, R. Aardenburg, M.E.A. Spaanderman, L.L.H. Peeters (2002) Vascular complicated pregnancies are associated with de-novo hypertension and migraine on long term basis. Journal of Society for Gynaecological Investigation 2002; 9(1); 178.

Valorisatie addendum

Atriumfibrilleren (AF) is de meest voorkomende cardiale aritmie (ritmestoornis) in de Westerse wereld en wordt gekarakteriseerd door een ongecoördineerde en snelle activatie van de boezems van het hart. Het voorkomen van AF neemt toe met de leeftijd en de verwachting is dat tegen 2050, 1 miljoen mensen lijden aan deze ritmestoornis. Dit zal dus grote financiële en maatschappelijke consequenties gaan hebben voor ons zorgstelsel. Des te meer reden om dus niet alleen voor de individuele patiënt te onderzoeken hoe AF behandeld/ voorkomen dient te worden en wat hiervan de consequenties zijn, maar ook voor het maatschappelijke belang.

In toenemende mate wordt er binnen de gezondheidszorg gekeken naar kosten en kosteneffectiviteit van behandelingen. Uit dit proefschrift blijkt dat de kosten van een additionele AF ablatie (met microgolven) bij een cardiochirurgische ingreep hoog zijn. Daarnaast weegt de toegevoegde waarde op het gebied van ritme conversie, de bevordering van kwaliteit van leven en reductie van complicaties, niet op tegen de additionele kosten. Tenslotte zijn er andere chirurgische technieken beschikbaar (gekomen) welke meer positieve resultaten lijken te boeken bij de behandeling van AF. Momenteel zijn er dan ook geen concrete plannen om de chirurgische behandeling van AF door middel van de additionele microgolven ablatie techniek om te zetten in een commerciële activiteit.

Hoewel de nieuwere, meer innovatieve chirurgische technieken positievere resultaten laten zien, dienen deze eerst verder wetenschappelijk gevalideerd te worden, alvorens er nagedacht kan worden over een valorisatietraject.