Add-on ablation surgery in patients with atrial fibrillation : drivers for intervention

ADD-ON ABLATION SURGERY IN PATIENTS WITH ATRIAL FIBRILLATION

DRIVERS FOR INTERVENTION

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Aan mijn lieve ouders
Voor Frank en de kleine prins

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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).

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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

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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.

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Figure 1: box lesions

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

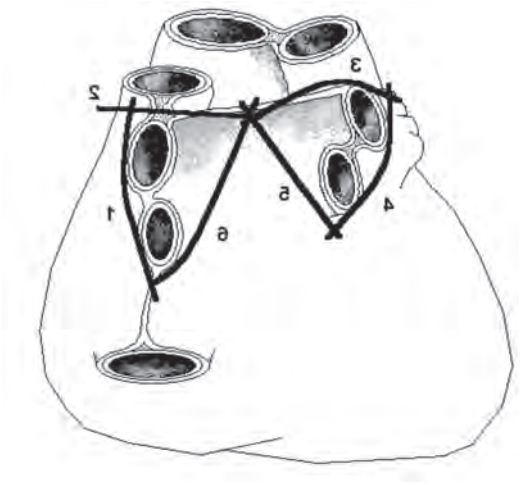

Table 1. Comparison of baseline characteristics and rhythm outcome between control and add-on surgery patients (N=132).

	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?

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Abstract

Objectives: To investigate the relationship between successful sinus rhythm (SR) conversion and 1-year postoperative health-related quality of life (HrQoL) after cardiac surgery

Methods Data of 125 cardiac surgery patients with pre-operative AF from our previous randomized trial (RCT) were used. SR progression/deterioration and HrQoL were measured repeatedly during follow-up. For HrQoL and validated standard questionnaires (SF-36, EuroQol and MFI-20) were used. The 1-year relationship between each of the 19 scales of these instruments and the development of SR-conversion was tested by dummy-regression analysis. Background patient characteristics were also tested as possible confounding variables in this relationship.

Results: Generic HrQoL questionnaires appear to be too insensitive to measure effects from cardiac surgery-induced SR conversion during 12 months of follow-up in patients with pre-operative AF. Specific HrQoL scales, like the General, Physical and Mental Fatigue scales in the MFI-20 measured at six months post-operatively, do show statistically significant beneficial effects from this SR conversion, but only if this conversion takes place from 3 and 6 months after surgery. The Mental Fatigue scale is even significantly and beneficially affected by this same period-bound SR conversion, measured at 12-month follow-up.

Conclusions: The relationship between SR conversion and HrQoL tends to attenuate and wear off with post-operative time. 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.

Introduction

Since 1948, when the World Health Organization defined health as not only the absence of disease but also as the presence of physical, mental and social well-being, quality of life has increasingly become more important in health care practice and research[1]. Enhancing health-related quality of life (HrQoL) has gradually been accepted as one of the most important reasons to treat patients with atrial fibrillation (AF)[2]. Randomized 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 directly related to an enhanced HrQoL[3-5], although this is one of the major reasons to try to restore SR[2]. One of the problems in the above-mentioned studies is the fact that enhancing chronic SR is difficult to obtain. In PIAF, RACE and AFFIRM only 30 to 50% of the patients were in SR at the end of follow-up. Add-on surgery is considered to be more effective in restoring SR than pharmacological treatment, but up till now this has not been studied widely in a randomized way[6]. To the best of our knowledge, only one randomized trial has been published investigating the effect on rhythm outcome and HrQoL[7] of add-on surgery versus isolated cardiac surgery, in patients with documented AF (ASAF trial)[7]. This study showed no statistically significant difference in restoration of SR or in observed improvement in HrQoL between treatment arms at the end of 12-month follow-up. Nonetheless, little is known about the relationship between restoration of SR and HrQoL[2]. Therefore, the aim of the present study was to investigate the association between conversion to SR and 1-year postoperative HrQoL in cardiac surgery patients with pre-operative AF.

Methods

Elective population and patient characteristics

Pre- and post-operative clinical data were used from the patients enrolled in the ASAF study. Demographic and clinical background variables, which may confound or specify this relationship, are included in the data analysis. Patients were, based on their rhythm outcome in the ASAF study, registered as having: SR at 12 months of follow-up (SR12) or AF at 12 months of follow-up (non-SR12). Additional SR

measurements were also used in the analysis: at discharge and after 3 and 6 months follow-up to observe conversion to and from SR.

Quality of life questionnaires

For HrQoL assessment both generic- and disease-specific questionnaires were used. The EuroQoL comprises the VAS (a visual analogue scale, with a range from 0 'the worst imaginable health state' to 100 'the best imaginable health state') and the EQ-5D (five dimensions, which give a description of the patient's own health state, answered on a 3-point scale ranging from no problems at all (level 1), to extreme problems (level 3)[8].

The RAND 36-item Health Survey 1.0 (SF-36) displays eight multi-item scales and has been standardized and translated in the Netherlands. Each domain comprises a 5-point Likert scale ranging from 1 (bad perceived health) to 5 (excellent perceived health)[9].

The Multidimensional Fatigue Inventory (MFI-20) consists of 20 items, organized in the five scales of fatigue, with scores ranging from 'definitely tired' to 'definitely not tired' on a 5-point Likert scale[10]. All questionnaires were self-administered pre-operatively and at 3 months (T1), 6 months (T6) and 12 months (T12) after surgery.

Statistical analysis

To use SR progression or deterioration as a predictor variable, a model of dummy-regression analysis is applied to predict the HrQoL at 6 and 12-month follow-up. For the 6 months follow-up measurement, each questionnaire scale is used as 'dependent' outcome variable, for which variation is expected over the initial SR T0 (at discharge) condition ('0' or '1'), but at the same time also over the change in SR from T0 up till T1 (3 months follow-up) (SR 1→0) and T1 up till T6 (SR 6→1). As a combined duo of dummy predictors in regression analysis the 6-month follow-up period is then neatly divided into two intervals defined as 'T1 changes from a baseline measurement' plus 'T6 changes from T1 upward'. If besides this, in each change variable (improvement vs no-change on the one hand and deterioration vs no-change on the other) equal distances are assumed and variables are labelled as having a score of '+1' and '-1' (improvement and deterioration, respectively), while patients with no change at all are put in the middle category and get the '0' score. The change variables (SR 1→0 and SR 6→1) together with the initial SR baseline measurement are then used as

predictors in regression analysis to test the effects of SR changes on the 6-month questionnaire scales.

The same regression technique is used at 12-month follow-up for all questionnaire sub-scales as a 'dependent' outcome variable. Only this time the post-operative 12-month period is divided into three time intervals during which SR scores may vary compared to the baseline SR T0 score. If used in combination with the baseline SR and the other two change variables, the additional third predictor variable defines the SR change between T6 and T12 (SR 12 →6). Possible confounders such as gender, age, type of operation, type of surgery and type of AF are introduced into all the SR-change regression models to test their significance. If one of the patient' background variables shows a statistically (near) significant effect on the dependent questionnaire-scale, the final results model also contains an extended version of the model. All data analyses awee performed with IBM SPSS Statistics 22 (IBM Corp., Armonk, NY). A *p*-value of less than 0.05 was considered as statistically significant.

Results

Patient characteristics and rhythm follow-up

Seven patients died during 12-month follow-up, consequently a total of 125 patients were included in the analysis. Sixty-two (47%) out of 125 patients had converted to sinus rhythm at 12-month follow-up. At 6-month follow-up this percentage was 60% (69 patients). Baseline patient characteristics were similar for both groups (SR12 and non-SR12) except for 'type of AF' ($p< 0.001$), 'total months of AF' ($p=0.03$) and 'left atrial dimension in mm' ($p<0.01$). See Table 1 for the relationship between demographic data, previous medical and cardiac history and operative data for both groups. Rhythm outcome for each patient changed during total follow-up: 26 patients remained in AF during total follow-up and 27 patients displayed SR the whole time. See Table 2 for a multidimensional cross-tabulation of the four SR measurements during 1-year follow-up.

Morbidity and mortality

Since adverse events can have serious impact on perceived HrQoL, a comparison between groups during total follow-up was made regarding number of rethoracotomies, pulmonary complications, myocardial infarction, renal failure,

stroke, wound infections and other infections, hours of ICU stay and total hospital stay in days. No significant differences between SR-group and non-SR-group were found.

Health-related quality of life measurements at 6 and 12-month follow-up

SF-36

Up to 6-month follow-up (T6), 36 (29%) of the 125 surviving patients had a missing value on at least one of the three SR measurements and/or the 'dependent' variable. None of the HrQoL sub-scales showed any significant association with SR change. Other predictors such as gender, age, type of operation, type of surgery or type of AF showed statistically significant effects on some of the HrQoL sub-scales. 'Age' was statistically negatively correlated with 'Physical Functioning' (p= 0.001) and 'Physical Pain' (p= 0.026). Female gender displayed greater 'Role limitations due to emotional problems' (p= 0.048) and 'Mental Health' was said to be better in case of paroxysmal AF (p= 0.009).

For the HrQoL sub-scales after 12 months follow-up (T12), no statistically significant difference was found with SR conversion, except for the 'Physical pain' scale. When SR conversion within 3-6 months occurred pain was said to be significantly worse (p= 0.041). Testing for patient characteristics, extended models with significant factors were present in predicting two scales. 'Physical functioning' was significantly impaired by advancing age (p= 0.001). Pain was said to be significantly worse with advancing age (p=0.030), or if the patient had received cardiac surgery as usual (p=0.025). All regression results on the HrQoL of the SF-36 outcomes are listed in Table 3.

EuroQoL

At T6, 89 (71%) patients had no missing values on any of the three SR measurements and the 'dependant' variable. None of the EurQoL scales showed statistical significance with changes in SR during the 6-month follow-up. For the subs-cales Mobility, Self Care, Daily activities and Pain confounding variables did show significant associations. Higher age was associated with poorer mobility (p=0.003). Patients with a SR0 baseline showed a significant negative effect on 6-month Self care (p=0.008), while at the same time paroxysmal AF patients

showed more positive effects for Self care than non-paroxysmal ones (p=0.015). It should be noted that the results from regression analysis on Self-care seem to be unstable, because of violations of the normality assumption in the dependant variable.

For the models on T12, 82 (66%) patients showed no missing SR values. Of all EuroQoL sub-scales, only Pain showed a significant association, which was negative (= less pain) with SR0 (p=0.049). Introducing patient characteristics into the models, extended versions for Mobility, Pain and Mood were needed. Mobility was worse in case the patient was older (p<0.001), pain was higher if the patient had received cardiac surgery as usual and depression/anxiety was higher in females and older patients (resp. p=0.009 and p=0.049). No significant associations on the VAS were found. For further details, see Table 4.

MFI-20

Thirty-six (29%) patients had a missing value on at least one of the three SR measurements and/or the 'dependent' variable at T6. For Mental Fatigue, General Fatigue and Physical Fatigue the change between SR T1 and SR T6 did show statistical significance (respectively, p=0.003, p=0.043, p=0.045). SR improvement between 3 and 6 months of follow-up produced lower Fatigue measurements in all three 6-month scales, while SR deterioration within the same period produced higher Fatigue measurements at 6 months. Other patient characteristics played no significant role in predicting Mental fatigue, General fatigue or Reduced activities. Older patients showed a significantly lower score on Physical fatigue (p=0.045). Patients from the ablation group showed more Motivation (p=0.042) than patients who had undergone cardiac surgery as usual.

At T12, 46 (37%) patients showed a missing value on at least one of the four SR measurements and/or 'dependant' variable Mental fatigue, General fatigue, Physical fatigue, Reduced activities or Reduced motivation. For the remaining 79 patients only the change between SR1 and SR6 on Mental fatigue turned out to be statistically significant (p=0.022). SR conversion between 3 and 6 months follow-up again showed lower Mental fatigue at 12 months. Upon testing the possible confounding patient characteristics, no significant effects on Mental fatigue could be demonstrated but for General fatigue an extended version of the model has to be presented. Females showed a significantly negative effect on General fatigue at 12 months, indicating more general fatigue than male patients. See Table 5 for further details.

Discussion

Background

Isolation of the pulmonary veins (box lesion) has a greater impact on the fibrillatory process in paroxysmal AF as compared to permanent AF, suggesting that while the pulmonary veins have a role in maintaining paroxysmal AF, these structures independently contribute less to the maintenance of permanent AF[11]. The higher susceptibility of pAF in conversion to and maintenance of SR after ablation surgery was also clear in this study, in the baseline comparison of the two treatment groups (Table 1). The representation of patients with pre-operative pAF was significantly higher in the SR12-group than in the non-SR12-group as compared to the patients with pre-operative permanent AF. These findings are in accordance with our previous study[7] and indicate that the effect of add-on surgery is largely related to the type of pre-operative AF.

Left atrial (LA) diameter is associated with the persistence of AF[12], which is supported by the significant difference between our two treatment groups in the baseline patient characteristics. The increased atrial dimension in patients with AF (anatomical remodelling) is attributable to the recurrence and maintenance of AF. Because anatomical remodelling of the atria provides the arrhythmogenic substrate for AF in the atria, the success rate for add-on surgery declines with time[12]. This success rate for add-on surgery is higher in patients with limited remodelling.

Thirdly, the number of months of AF plays a crucial role in conversion to and maintenance of SR. AF duration showed a significant difference at baseline between both groups, indicating that the longer AF exists, the more the success rate for SR at 12 months declines. This progressive nature of AF has been demonstrated by numerous experimental and clinical studies[13,15]. Since electro-anatomical remodelling already develops within the first few days of AF, stabilization of the arrhythmia strengthens with time and AF becomes self-perpetuating which complicates treatment.

Atrial arrhythmia during follow-up was treated by the patient's own cardiologist who was, like the patient, blinded to the allocated treatment. Interestingly, our data showed that SR at discharge was a strong predictor for SR during total follow-up (Table 2). On the other hand AF during early follow-up (first 3 months) was a predictor for AF at the end of follow-up. The effect of ablation surgery is generally apparent within the first three months after surgery, and recurrences

of AF are thought to result from recovered pulmonary vein conduction and the pro-arrhythmic effects of ablation itself[16].

Health-related quality of life measurements

This study confirms for add-on ablation surgery what previous randomized trials in pharmacological treatment of AF stated: conversion to SR does not enhance generic HrQoL more than rate control does[3-5]. Some specific HrQoL scales of the questionnaires in our study did however show statistical significance between SR and non-SR patients at 6-month and 12-month follow-up.

If SR was present at discharge, EuroQoL Self Care T6 was significantly impaired and Pain T12 was significantly lower. As for the SF-36, none of the sub-scales were significantly associated with SR change except for Physical pain at T12, which was worse if SR conversion from 3-6 months occurred, irrespective of whether SR was present at discharge or during 6-12 months of follow-up. For the disease-specific HrQoL (MFI-20), Mental fatigue, General fatigue and Physical fatigue at 6 months were significantly improved when SR conversion occurred between 3-and 6-month follow-up. At 12 months of follow-up this effect only remained present for Mental fatigue. The MFI-20 showed a statistically significant association with SR conversion, especially for the direct 'fatigue' scales, but the majority of effects appear to fade out during follow-up. These results on SR conversion and HrQoL suggest that not only the arrhythmia but also the associated pathology and patient characteristics play a role in explaining impairment.

Regarding confounders and patient characteristics, 'Age' was negatively correlated with several sub scales of the SF-36, EuroQoL and MFI-20. In accordance, advancing age has been shown to specifically affect pain, physical mobility and energy in a negative way[17]. Depression reaches its highest level in the elderly >75 years and is highly affected by physical functioning itself and the impact of chronic medical conditions, which coincide with advancing age and have considerable impact on HrQoL in octogenarians[18].

Females displayed significantly worse outcomes on some mental health sub-scales than males even after 12 months follow-up. Females are known to have more impaired mental health after cardiac surgery than males. Sjoland and colleagues reported in a prospective study of 462 patients, that QoL measured by the Nottingham health profile was significantly poorer for women up to two years after cardiac surgery[19].

Paroxysmal AF (pAF) is thought to be more debilitating in daily life as compared to other types of AF but this effect could not demonstrated in this study. Tested for all sub- scales, none displayed a worse outcome if pAF was present as compared to other types of AF. Mental Health T6 (SF-36) and Self care T6 (EuroQoL) even demonstrated a significant improvement in case of pAF, although these effects were no longer present at 12 months of follow-up and the regression model of Self care T6 model may give unstable results.

'Type of surgery' played a significant role in Physical pain T12 (SF-36), Pain T12 (EuroQoL) and Reduced motivation T6 (MFI-20). Fatigue is a common symptom in patients with valve disease and/or coronary artery disease and is highly associated with decreased functional status. On the other hand, fatigue is also a key symptom of AF. As shown in our initial trial the MFI-20 scores revealed an overall population-reduction in perceived dimensions of fatigue during total follow-up[7]. With these new results we can speculate that this reduction in fatigue was not due to treatment of underlying heart disease by cardiac surgery itself nor due to group assignment or SR conversion. Also in case patients were assigned to the 'cardiac surgery as usual' group, Pain was higher and Motivation was significantly enhanced. Pain after cardiac surgery has been reported extensively and the incidence is thought to remain high even after 1-year follow-up[20]. Pain is probably not only due to cardiac surgery itself but also to co-morbidity, since 'age' also played a significant role in the different pain sub-scales as mentioned before.

Six-month versus twelve-month follow-up

While numerous studies have revealed significant improvements in HrQoL after ablation, methodological weaknesses including small sample sizes, highly selective patient populations, non-validated questionnaires, lack of control groups, limited follow-up and subjective rhythm evaluation are typical of their design. Because of indications of wearing-down of the effect of add-on surgery within the first 6 months (macro-reentry tachycardias) and earlier experience with post-operative HrQoL in these patients, it was necessary to analyse the relationship between SR and HrQoL not only at the end of follow-up but also up to the first 6 months after operation. Another reason for this additional analysis was that the HrQoL of patients in the long run might be subject to and dependent on many other personal life events and incidents, thus the original hypothesized relationship between SR and HrQoL would gradually become weakened. This assumption

of attenuation seems to be endorsed by our results. Accordingly, several studies have revealed a significant improvement in HrQoL directly following intervention, presumably reflecting immediate symptom relief[21].

Study limitations

First of all, this study was performed retrospectively. Due to the non-significant effect of ablation surgery on rhythm outcome in the ASAF study, we could not demonstrate HrQoL differences between groups[7]. To investigate whether this non-difference in HrQoL was not due to the low success rate of ablation surgery, additional retrospective analysis between SR patients and non-SR patients (defined at the end of follow-up of the ASAF study) was needed.

Furthermore, the most widely employed questionnaires in HrQoL research in AF patients were used. Newly developed questionnaires have been published but not yet tested on a large population of AF-patients[22-23]. As the questionnaires being used in this present trial were not all disease specific, HrQoL outcomes could be weakened by other life events or physical complaints during follow-up. This 'attenuation' effect may become even larger as the follow-up period extends. Sub-scales as ' Physical functioning' (SF-36) are highly dependant on co-morbidity but also on recuperation post-operatively. Not only might physical complaints of AF affect HrQoL, but also the psychological sequelae. A recent study showed that about one-third of patients with AF experience elevated levels of depression and anxiety and that changes in HrQoL were consistently predicted by depression[24]. Thus indicating that restoring SR in AF patients might cure their physical complaints but not immediately their psychological ones and therefore would not enhance HrQoL in general.

Finally, it is thought that the impact of chronic medical conditions, which coincide with advancing age, have considerable impact on HrQoL[25]. Baseline patient characteristics (hypertension, diabetes mellitus and COPD) were compared, but probably other patient factors, e.g. personality traits and co-morbidity may also play an important role in scoring behaviour of respondents, thus impairing HrQoL on specific scales.

Conclusions

Successful conversion to SR after cardiac surgery, with or without additional ablation surgery, in patients with pre-operative AF does not significantly affect generic HrQoL during 1-year follow-up. However, specific HrQoL scales are much more sensitive to SR conversion and do show significant effects. Controlled for additional patient characteristics such as age, type of AF and gender, these effects remain statistically significant. Although these effects are the strongest in disease-specific scales up to 6 months of follow-up and tend to fade out during further follow-up.

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Table 1. Demographic Data (n=125)

	Study Population	SR12-group (N=62)	Non-SR12-group (N=63)	p-value
Age (Years)	67.9 ± 8.9	67.4 (39.0 – 84.0)	68.4 (46.0 – 81.0)	.38
Weight (Kg)	79.2 ± 17.0	78.6 (49 – 170)	79.7 (53 – 111)	.73
Gender (male)	79 (63.2%)	42 (66.7%)	37 (59.7%)	.42
Civil state				
Divorced	8 (6.5%)	7 (11.1%)	1 (1.6%)	
Married	84 (87.7%)	42 (66.7%)	42 (68.9%)	
Unmarried with partner	10 (8.1%)	5 (7.9%)	5 (8.2%)	
Widow(er)	22 (17.7%)	9 (14.3%)	13 (21.3%)	
				.16
Education				
Primary school	27 (22.0%)	11 (17.5%)	16 (26.7%)	
Lower education	30 (24.4%)	15 (23.8%)	15 (25.0%)	
Intermediate education	45 (36.6%)	24 (38.1%)	21 (35.0%)	
High education	21 (17.1%)	13 (20.6%)	8 (13.3%)	
				.52
Previous cardiac history				
Atrial Fibrillation:				<.01
Paroxysmal AF	54(43.2%)	37(58.7%)	17 (27.4%)	
Permanent AF	41 (32.8%)	11 (17.5%)	30 (48.4%)	
Persistent AF	28 (22.4%)	13 (20.6%)	15 (24.2%)	
Atrial flutter	2 (1.6%)	2 (3.2%)	0 (0%)	
Total months of AF	82.0 ± 104.8	67.9 (3 – 403)	96.9 (3 – 617)	.03
Left Atrial Dimension (mm)	50.6 ± 7.4	48.7 (33-65)	53.3 (40-70)	<.01
Left Ventrical Ejection Fraction (%)	52.6 ± 13.5	53.2 (18-80)	51.9 (22-75)	.68
Co-morbidity/Risk factors (N=122)				
Hypertension	51 (41.8%)	25 (40.3%)	26 (43.3%)	.74
Stroke	6 (4.9%)	2 (3.2%)	4 (6.7%)	.38
Smoking				.50
Never	56 (46.3%)	30 (48.4%)	26 (44.1%)	
Current	16 (13.2%)	6 (9.4%)	10 (16.9%)	
Past	49 (40.5%)	26 (41.9%)	23 (39.0%)	
Positive Family History	61 (49.2%)	27 (42.9%)	34 (55.7%)	.15
Diabetes	18 (14.8%)	13 (21.0%)	5 (8.3%)	.05
Renal Disease	7 (5.6%)	3(4.8%)	4 (6.5%)	.68
COPD	20 (16.3%)	8 (12.7%)	12 (20.0%)	.27
Previous myocardial infarction	31 (24.8%)	19 (30.2%)	12 (19.4%)	.16
Cardiomyopathy	21 (17.1%)	10 (16.1%)	11 (18.0%)	.78
Congenital Heart disease	7 (5.7%)	2 (3.2%)	5 (8.3%)	.22
Bllood Pressure mmHg(systolic)	141.9 ± 26.6	144.7 (70-200)	139.3 (80-190)	.28
Blood Pressure mmHg(diastolic)	79.4 ± 17.8	82.3 (40-180)	76.5 (40-110)	.18

Table 1. continued

	Study Population	SR12-group (N=62)	Non-SR12-group (N=63)	p-value
Pre-operative complaints (N=123)				
Palpitations	51 (41.5%)	28 (45.2%)	23 (37.7%)	.40
Dyspnea	98 (79.7%)	48 (77.4%)	50 (82.0%)	.53
Angina	49 (40.2%)	24 (39.3%)	25 (41.0%)	.85
(Pre-) Syncope	7 (5.7%)	3 (4.8%)	4 (6.6%)	.68
Dizziness	32 (26.0%)	17 (27.4%)	15 (24.6%)	.72
Fatigue	62 (50.4%)	31 (50.0%)	31 (50.8%)	.93
Other complaints	12 (9.8%)	5 (8.1%)	7 (11.7%)	.50
Operative data (N=125)				
				.11
Coronary Artery Bypass Grafting (CABG)	39 (31.2%)	23 (36.5%)	16 (25.8%)	
Valve replacement	50 (40.0%)	24 (38.1%)	26 (41.9%)	
CABG and Valve replacement	28 (22.4%)	15 (23.8%)	13 (21.0%)	
Other cardio-surgery	8 (6.4%)	1 (1.6%)	7 (11.3%)	

Comparison of demographic data, previous medical and cardiac history and operative data between SR12-group and non-SR12-group patients (N=125).

Table 2. Multi-dimensional cross tabulation of SR-conversion during follow-up

SR_{T0}	SR_{T1}	SR_{T6}	SR_{T12}	Number of patients
0	0	0	0	26
1	0	0	0	3
0	1	0	0	1
1	1	0	0	1
0	0	1	0	1
1	0	1	0	2
0	1	1	0	4
1	1	1	0	5
0	0	0	1	2
1	0	0	1	1
1	1	0	1	2
0	0	1	1	7
1	0	1	1	2
0	1	1	1	8
1	1	1	1	27

(0=AF, SR=1)

N=92 (23 patients missing rhythm outcome variable on at least 1 time-point during follow-up)

Table 3. Dummy regression results for predicting 6 and 12 months HrQoL sub-scales of SF-36 from SR (change) categories. Listwise deletion of missing values. Extended models are listed if applicable.

SF-36		Dummy regression analysis T6 (N=89)			Extended model of dummy regression analysis T6			Dummy regression analysis T12 (N=82)			Extended model of dummy regression analysis T12		
		B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value
	Const.	6.32	4.46	<.001	126.65	19.35	<.001	63.46	5.21	<.001	133.57	21.15	<.001
Physical functioning	SR0	2.15	6.56	0.744	1.85	6.19	0.776	0.49	7.68	0.949	0.21	7.20	0.977
	SR1→SR0	-6.31	8.17	0.442	-3.86	7.74	0.619	1.66	8.61	0.847	6.19	8.18	0.451
	SR6→SR1	6.08	7.68	0.431	5.19	7.25	0.476	4.60	9.53	0.631	5.42	8.94	0.547
	SR12→SR6	-	-	-	-	-	-	-9.74	8.20	0.239	-11.38	7.70	0.144
	'Áge'				0.95	0.28	0.001				-1.05	0.31	0.001
			R^2 = 0.01			R^2 = 0.130			R^2 =0.22			R^2 = 0.15	
	Const.	41.33	7.68	<.001				47.43	8.30	<.001			
Physical limitations	SR0	7.31	11.31	0.519				8.20	12.23	0.505			
	SR1→SR0	1.33	14.06	0.925		-		-10.03	13.71	0.467		-	
	SR6→SR1	15.73	13.23	0.238				-7.18	15.18	0.638			
	SR12→SR6	-	-	-				11.70	13.05	0.373			
			R^2 = 0.01						R^2 =0.03				
	Const.	59.99	3.53	<.001				51.94	3.86	<.001			
General Health	SR0	2.34	5.20	0.653				6.68	5.68	0.243			
	SR1→SR0	-10.09	6.46	0.122		-		-1.84	6.37	0.773		-	
	SR6→SR1	9.77	6.08	0.122				0.69	7.05	0.923			
	SR12→SR6	-	-	-				0.93	6.06	0.879			
			R^2 = 0.037						R^2 =0.028				
	Const.	74.75	4.54	<.001	119.00	20.02	<.001	71.71	4.79	<.001	109.49	19.99	<.001
Physical Pain	SR0	0.23	6.56	0.972	0.02	6.41	0.997	8.70	7.06	0.222	6.67	6.72	0.324
	SR1→SR0	-0.24	8.16	0.977	1.44	8.00	0.857	7.27	7.92	0.362	10.33	7.58	0.177
	SR6→SR1	-1.69	7.67	0.826	-2.31	7.50	0.759	-17.12	8.76	0.054	-17.20	8.28	0.041
	SR12→SR6	-	-	-	-	-	-	7.20	7.54	0.342	2.99	7.26	0.682
	'Áge'				-0.65	0.29	0.026				-0.63	0.29	0.030
	'Group'										12.52	5.46	0.025
			R^2 = 0.002			R^2 = 0.059			R^2 =0.094			R^2 =0.213	

Table 3. continued

SF-36		Dummy regression analysis T6 (N=89)			Extended model of dummy regression analysis T6			Dummy regression analysis T12 (N=82)			Extended model of dummy regression analysis T12		
		B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value
	Const.	57.12	3.66	<.001				59.37	3.65	<.001	54.91	4.36	<.001
Vitality	SR0	3.49	5.39	0.520				3.03	5.37	0.574	1.46	5.37	0.786
	SR1→SR0	-10.23	6.71	0.131		-		-7.50	6.03	0.217	-7.46	5.94	0.213
	SR6→SR1	11.64	6.31	0.069				2.49	6.67	0.710	3.01	6.58	0.649
	SR12→SR6	-	-	-				-1.85	5.74	0.747	-2.75	5.68	0.630
	'Gender'										7.99	4.43	0.075
			R^2 = 0.043									R^2 =0.089	
	Const.	77.52	4.39	<.001	115.94	19.86	<.001	77.85	4.95	<.001			
Social	SR0	-0.92	6.46	0.888	-1.10	6.36	0.864	0.121	7.29	0.987			
Functioning	SR1→SR0	4.74	8.04	0.557	6.20	7.94	0.437	-0.37	8.18	0.964		-	
	SR6→SR1	2.88	7.56	0.704	2.35	7.44	0.753	-4.50	9.05	0.620			
	SR12→SR6	-	-	-	-	-	-	0.45	7.78	0.954			
	'Age'				-0.57	0.29	0.051						
			R^2 = 0.022			R^2 = 0.066			R^2 = 0.009				
	Const.	76.56	2.91	<.001	75.76	2.82	<.001	75,85	3.32	<.001	71.41	3.95	<.001
Mental Health	SR0	0.03	4.28	0.995	-7.74	5.05	0.129	0.99	4.89	0.840	-0.58	4.86	0.906
	SR1→SR0	-1.07	5.32	0.841	-2.63	5.17	0.612	-3.02	5.48	0.583	-2.98	5.38	0.581
	SR6→SR1	1.64	5.00	0.744	-3.06	5.14	0.553	-5.60	6.06	0.359	-5.08	5.96	0.397
	SR12→SR6	-	-	-	-	-	-	8.36	5.22	0.113	7.47	5.14	0.150
	'Gender'				-	-	-				7.96	4.01	0.050
	'pAF'				11.38	4.26	0.009						
			R^2 = 0.001			R^2 = 0.080			R^2 = 0.037			R^2 = 0.085	
	Const.	64.00	7.06	<.001	54.15	8.50	<.001	62.59	7.89	<.001			
Role limit.	SR0	16.12	10.39	0.124	13.29	10.31	0.201	14.04	11.62	0.231			
Emotional	SR1→SR0	17.04	12.92	0.191	16.16	12.71	0.207	-1.46	13.03	0.911		-	
problems	SR6→SR1	-4.91	12.15	0.687	-4.69	11.94	0.695	-9.06	14.42	0.532			
	SR12→SR6	-	-	-	-	-	-	17.48	12.40	0.163			
	'Gender'				17.78	8.87	0.048						
			R^2 = 0.042						R^2 = 0.038				

Table 4. Dummy regression results for predicting 6 and 12 months HrQoL sub-scales of EuroQoL from SR (change) categories. Listwise deletion of missing values. Extended models are listed if applicable.

EuroQoL		**Dummy regression analysis T6 (N=89)**			**Extended model of dummy regression analysis T6**			**Dummy regression analysis T12 (N=82)**			**Extended model of dummy regression analysis T12**		
		B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value
Mobility	Const.	1.38	0.09	<.001	0.16	0.40	0.690	1.48	0.10	<.001	-0.19	0.39	0.635
	SR0	0.17	0.13	0.210	0.18	0.13	0.174	0.06	0.15	0.679	0.24	0.16	0.143
	SR1→SR0	0.17	0.17	0.328	0.12	0.16	0.461	0.02	0.17	0.900	-0.03	0.15	0.854
	SR6→SR1	0.04	0.16	0.802	0.06	0.15	0.708	0.08	0.19	0.650	0.17	0.18	0.326
	SR12→SR6	-	-	-	-	-	-	0.11	0.16	0.492	0.15	0.14	0.310
	'Age'				0.02	0.01	0.003				0.03	0.01	<.001
	'pAF'										-0.24	0.13	0.072
			R^2 = 0.029			R^2 =0.129			R^2 =0.030			R^2 =0.254	
Self Care	Const.	1.05	0.06	<.001	1.06	0.05	<.001	1.08	0.08	<.001			
	SR0	0.13	0.08	0.128	0.26	0.10	0.008	0.10	0.11	0.362			
	SR1→SR0	0.12	0.10	0.258	0.14	0.10	0.151	0.15	0.12	0.224		-	
	SR6→SR1	0.02	0.10	0.840	0.10	0.10	0.299	-0.03	0.14	0.815			
	SR12→SR6	-	-	-	-	-	-	0.05	0.12	0.680			
	'pAF'				-0.20	0.08	0.015						
			R^2 =0.038			R^2 =0.104			R^2 =0.030				
Usual activities	Const.	1.55	0.11	<.001	1.68	0.13	<.001	1.55	0.12	<.001			
	SR0	0.05	0.17	0.780	0.06	0.16	0.700	-0.06	0.17	0.72			
	SR1→SR0	0.08	0.21	0.674	0.09	0.20	0.646	-0.19	0.20	0.34		-	
	SR6→SR1	-0.30	0.20	0.134	-0.25	0.19	0.193	0.22	0.22	0.32			
	SR12→SR6	-	-	-	-	-	-	0.01	0.19	0.97			
	'Group'				-0.29	0.14	0.035						
			R^2 =0.048			R^2 =0.097			R^2 =0.029				

Table 4. continued

EuroQoL		Dummy regression analysis T6 (N=89)			Extended model of dummy regression analysis T6			Dummy regression analysis T12 (N=82)			Extended model of dummy regression analysis T12		
		B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value
	Const.	1.61	0.11	<.001	1.76	0.12	<.001	1.67	0.12	<.001	1.83	0.12	<.001
Pain/	SR0	-0.20	0.16	0.227	-0.18	0.16	0.261	-0.34	0.17	0.049	-0.28	0.16	0.089
Discomfort	SR1→SR0	0.10	0.20	0.621	0.11	0.19	0.581	-0.07	0.19	0.718	-0.08	0.18	0.660
	SR6→SR1	-0.12	0.19	0.512	-0.07	0.18	0.695	0.13	0.21	0.558	0.15	0.20	0.474
	SR12→SR6	-	-	-	-	-	-	-0.19	0.18	0.297	-0.08	0.18	0.634
	'Group'				-0.35	0.13	0.008				-0.42	0.13	0.002
		R^2=0.024			R^2=0.103			R^2=0.064			R^2=0.174		
	Const.	1.23	0.07	<.001				1.24	0.09	<.001	2.11	0.37	<.001
Anxiety/	SR0	-0.06	0.10	0.538				-0.09	0.13	0.490	-0.04	0.13	0.757
Depression	SR1→SR0	-0.24	0.13	0.055		-		-0.06	0.15	0.701	-0.01	0.14	0.930
(mood)	SR6→SR1	0.07	0.12	0.572				0.26	0.17	0.118	0.25	0.16	0.112
	SR12→SR6	-	-	-				-0.26	0.14	0.076	-0.24	0.14	0.078
	'Age'										-0.01	0.01	0.049
	'Gender'										-0.28	0.11	0.009
		R^2=0.049						R^2=0.052			R^2=0.175		
	Const.	68.92	3.23	<.001				64.59	3.49	<.001			
VAS	SR0	0.85	4.76	0.859		-		9.97	5.93	0.056		-	
	SR1→SR0	-6.63	5.92	0.266				-3.54	5.76	0.541			
	SR6→SR1	5.00	5.57	0.372				2.55	6.37	0.691			
	SR12→SR6	-	-	-				2.39	5.48	0.663			
		R^2=0.016						R^2=0.064					

Table 5. Dummy regression results for predicting 6 and 12 months HrQoL sub-scales of MFI-20 from SR (change) categories. Listwise deletion of missing values. Extended models are listed if applicable.

MFI-20		Dummy regression analysis T6 (N=89)			Extended model of dummy regression analysis T6			Dummy regression analysis T12 (N=82)			Extended model of dummy regression analysis T12		
		B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value
General Fatigue	Const.	2.86	0.21	<.001				2.90	0.22	<.001	3.25	0.26	<.001
	SR0	-0.14	0.30	0.65				-0.18	0.32	0.587	-0.02	0.32	0.941
	SR1→SR0	0.59	0.38	0.12		-		0.31	0.38	0.418	0.27	0.37	0.462
	SR6→SR1	-0.73	0.36	0.043				0.13	0.40	0.748	0.11	0.39	0.784
	SR12→SR6	-	-	-				0.16	0.34	0.645	0.23	0.33	0.483
	'Gender'										-0.64	0.26	0.018
			R^2 = 0.049						R^2 =0.082			R^2 =0.150	
Mental Fatigue	Const.	2.31	0.17	<.001				2.26	0.21	<.001			
	SR0	-0.31	0.25	0.212				-0.10	0.31	0.755			
	SR1→SR0	0.19	0.31	0.530		-		0.20	0.36	0.588		-	
	SR6→SR1	-0.88	0.29	0.003				-0.90	0.38	0.022			
	SR12→SR6	-	-	-				0.28	0.33	0.389			
			R^2 =0.123						R^2 =0.085				
Physical Fatigue	Const.	3.01	0.22	<.001	1.08	0.97	0.270	2.89	0.23	<.001			
	SR0	-0.27	0.32	0.391	-0.27	0.31	0.398	-0.06	0.34	0.863			
	SR1→SR0	0.38	0.40	0.338	0.31	0.39	0.433	0.26	0.40	0.521		-	
	SR6→SR1	-0.76	0.37	0.045	-0.73	0.37	0.049	-0.23	0.42	0.584			
	SR12→SR6	-	-	-	-	-	-	0.47	0.36	0.193			
	'Age'				0.28	0.14	0.045						
			R^2 =0.048			R^2 =0.092			R^2 =0.054				

Table 5. continued

MFI-20		Dummy regression analysis T6 (N=89)			Extended model of dummy regression analysis T6			Dummy regression analysis T12 (N=82)			Extended model of dummy regression analysis T12		
		B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value	B	S.E.	p-value
Reduced Activities	Const.	2.83	0.22	<.001				2.77	0.24	<.001			
	SR0	-0.12	0.33	0.728				-0.04	0.36	0.911			
	SR1→SR0	0.24	0.44	0.558		-		-0.21	0.42	0.624		-	
	SR6→SR1	-0.35	0.39	0.367				0.27	0.44	0.540			
	SR12→SR6	-	-	-				-0.21	0.38	0.583			
			R^2 =0.010						R^2 =0.008				
Reduced Motivation	Const.	2.42	0.19	<.001	2.63	0.21	<.001	2.30	0.21	<.001	2.48	0.22	<.001
	SR0	0.03	0.28	0.922	0.05	0.28	0.844	0.08	0.30	0.802	0.15	0.30	0.629
	SR1→SR0	0.38	0.35	0.274	0.39	0.34	0.253	0.12	0.36	0.746	0.09	0.35	0.807
	SR6→SR1	-0.62	0.33	0.060	-0.55	0.32	0.090	-0.06	0.38	0.884	-0.03	0.37	0.932
	SR12→SR6	-	-	-	-	-	-	0.13	0.32	0.697	0.25	0.32	0.445
	'Group'				-0.48	0.23	0.042				-0.47	0.24	0.056
			R^2 =0.050						R^2 =0.005			R^2 =0.054	

Chapter 4

Cost-effectiveness of ablation surgery in patients with atrial fibrillation undergoing cardiac surgery

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Abstract

This study was performed to assess the cost-effectiveness of concomitant ablation surgery compared to regular cardiac surgery in atrial fibrillation (AF) patients during 1-year follow-up.

Cost analysis was performed from a societal perspective alongside a prospective, randomised, double-blinded, multicentre trial. One hundred and fifty patients with documented AF were randomly assigned to undergo cardiac surgery with ablation surgery or without. One hundred and thirty-two patients were included in the cost-effectiveness study. All costs (medical and non-medical) were measured during follow-up. Cost data were combined with Quality Adjusted Life Years (QALY) to obtain the incremental costs per QALY. Total costs of the ablation surgery group were significantly higher compared to the regular cardiac surgery group (cost difference bootstrap: €4,724; 95% UI, €2,770 to €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 (ICER) mounted to €73,359 per QALY. The acceptability curve showed that, even in the case of a maximum threshold value of 80,000 euro per QALY gained, the probability of ablation surgery being more cost-effective than regular cardiac surgery did not reach beyond 50%.

In conclusion, concomitant ablation surgery in AF is not cost-effective after 1-year follow-up compared to regular cardiac surgery.

Introduction

The impact of atrial fibrillation (AF) on health care costs 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. Recently, Ringborg et al.[1] performed a sub-study of the Euroheart Survey in which the annual costs of AF in the Netherlands was estimated at €554 million but studies on the cost-effectiveness of surgical treatment of AF are limited.

Surgical catheter ablation is an increasingly effective and potentially curative but expensive therapy for AF. Although associated costs of additional ablative surgery are high, the potential enhanced health-related quality of life (HrQoL) through long-term absence of arrhythmia and associated prognostic benefits may outweigh these costs.

Since to our knowledge no prospective randomised studies on cost effectiveness of add-on ablation surgery (AS) have been performed, we performed a cost-effectiveness study alongside a prospective randomised trial in which ablation surgery (AS) was compared to cardiac surgery as usual during 1-year follow-up[2].

Methods

Study design

This economic evaluation was embedded in a prospective, randomised, clinical, multicentre trial, comprising one hundred and fifty AF patients in two treatment strategies undergoing cardiac surgery (ASAF study). Patients were randomly assigned to 'surgery as usual' or 'add-on ablation surgery'. Informed consent was obtained and the trial was approved by the Local Ethics Committee. Maintenance of sinus rhythm (SR) at 1-year follow-up after surgery and HrQoL were considered as primary end points, morbidity, mortality and cost-effectiveness as secondary outcomes[2].

One hundred and thirty-two of the initial one hundred and fifty patients were willing to complete a minimum of one out of five cost diaries during 1-year follow-up.

Surgical procedure

The surgical microwave ablation procedure is described elsewhere[2].

Quality of life measurements

HrQoL was assessed by means of the EuroQoL, RAND 36-item Health Survey 1.0 and Multidimensional Fatigue Inventory at baseline and at 3, 6 and 12 months after surgery[3-5]. For the economic evaluation the effectiveness was expressed as quality adjusted life years (QALYs). A QALY is a measure of disease burden in which time spent in a health state is combined with the HrQoL experienced during that time. In order to calculate a QALY, participants' responses to the EuroQoL were converted to utility scores by using the Dolan algorithm. The maximum number of QALY's within this study was 1 (1-year follow-up in perfect health (=1) multiplied by 1).

Volumes or resources used

The costs and effects of AF were collected during one year, at baseline and at 2-6 weeks, 3-4 months, 6-7 months and 11-12 months post-operatively, by means of the cost diary method in which participants continuously recorded volumes of healthcare utilization[6]. The diary contained questions regarding three categories of costs 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 effectiveness ratio (ICER), the difference in costs between two treatment options is divided by the gain in HrQoL. The result of this calculation was defined as the incremental costs per quality-adjusted-life year (QALY).

Unit prices

Unit costs for surgery and hospitalisation days were derived from hospital information systems, empirical time registrations and financial departments of both hospitals. Total operative costs were calculated by using time registrations of the patient being in the operating theatre as well as the actual operation time. Costs for additional prosthetic material were not added to the total surgery costs. Catheter costs for add-on surgery were added for the interventional group. Costs regarding total hospital stay consisted of days in the ICU, medium care unit and regular nursing department with additional patient transportation costs. For

cost valuation of specialist consultation, E.R. visits and formal care, standardized cost prices from the Dutch manual for cost analysis in healthcare research was used[7]. Medication costs were derived from the Dutch Pharmacotherapeutic Compass[8]. Absence of paid work was calculated according to the friction costs method and absence of voluntary work was valued by the shadow costs method[7]. All costs are presented in Euro and were indexed for annual inflation to the year of 2004. Hospital prices include overhead costs. Table 1 provides an overview of costs per unit.

Statistical analysis

For statistical analysis SPSS for Windows version 15.0 (SPSS Inc. Chicago IL) was used. Data were analyzed by the intention-to-treat principle in which mean substitution for missing cases was applied. For the cost diary, mean imputation was performed at variable levels before computing cost prices.

To test the robustness of the cost analysis and to obtain uncertainty intervals around the mean difference of the costs and the QALY's, 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[9]. To account for the uncertainty surrounding the ICER's, a bootstrap analysis was also performed. Results are presented in a cost-effectiveness plane, which is a graphical presentation in which additional costs and health outcome effects of a new therapy are compared with standard therapy. Furthermore, an acceptability curve is calculated which shows the probability of a new therapy being more cost-effective than regular treatment for various thresholds: these represent the maximum amount society would be willing to pay for a gain in effectiveness or a QALY.

Results

Patient characteristics and quality of life

One hundred and thirty-two patients completed at least one cost-diary during follow-up and were analysed in this study. In total, 65 patients underwent additional AS and 67 patients underwent normal cardiac surgery. At baseline, HrQoL and background characteristics in terms of demographic data, previous cardiac history, co-morbidity and risk factors were comparable for both groups[2].

Cost analysis

Table 2 shows the results for the various cost categories for both groups during 1-year follow-up. Mean total direct health care costs for the intervention group were significantly higher (p<0.001). This was mainly caused by longer surgery time and costs of the ablation catheter. Other subcategories were comparable without significant differences. Total societal costs were significantly higher for the ablation group, due to the significantly higher operation costs.

Cost-effectiveness analysis

After one year the total QALYs for AS were 0.75 and 0.69 for the control group, resulting in a difference of 0.06 (Table 3). Since the difference in total costs between both groups was €4,425, the incremental cost-effectiveness ratio mounted to €73,359 per QALY gained.

The cost-effectiveness plane shows that 92% of all ICER's are located in the northeastern quadrant: AS is more effective with regard to enhancing HrQoL but also more expensive (Figure 1). The acceptability curve (Figure 2) shows that for the ICER of 73,359, the probability of AS being more-cost-effective than regular cardiac surgery is 47%.

Discussion

This study shows that additional AS is not cost-effective compared to cardiac surgery as usual in the Netherlands. Societal costs during follow-up were comparable in both groups, except for surgery costs, which were significantly higher in the intervention group, mainly as a result of longer surgery time and additional costs for the ablation catheter. When costs for both treatment strategies were compared for their effectiveness, the result was an ICER of €73,359 per QALY gained. Although the cost-effectiveness plane showed most ratios in the northeast quadrant, offering additional AS depends on the threshold value (how much society is willing to pay extra to gain a QALY) and whether the estimated ICER lies beneath this threshold. However, a threshold for the surgical treatment of AF has not yet been determined.

The Dutch Council for Public Health and Health Care argues that thresholds can vary from €16,000 to a maximum of €80,000 Euro for a condition with a high disease burden[10]. Based on this information, assuming a threshold value of

€60,000 Euro for the treatment of AF seems acceptable. Since the estimated ICER is higher than this threshold, AS is not likely to be considered a cost-effective treatment. Even if we assume that society would be willing to pay a maximum amount of €80,000 per QALY gained, the acceptability curve shows that for this value the probability of AS being more cost-effective than cardiac surgery as usual does not go beyond 50%. Hence, based on the data of 1-year follow-up, AS is not considered a cost-effective treatment.

Comparison with previous studies

As most studies on ablation surgery for AF concern an endocardial approach instead of an epicardial surgical approach, it is difficult to compare cost-effectiveness with the current study . Furthermore, rhythm restoration success is largely related to pre-operative type of AF and whether AS was performed as an concomitant procedure. One of the few studies on cost-effectiveness of AS as a concomitant procedure was published by Quenneville et al[11]. This study systematically reviewed AS and the long-term cost-effectiveness at the time of scheduled mitral valve surgery. This in itself is a drawback for comparison with the present study, as mitral valve disease is in itself a major risk factor for developing and perpetuating AF. Furthermore, a Markov decision model was used. Most research assessing the cost-effectiveness of catheter ablation for AF is based on decision-analytic techniques: decision trees and Markov (state transition) models[12-14], instead of prospective randomised trials. Decision-analytic methodologies may suffer from limitations: they may not reflect clinical practice, assumptions are simplified in order to avoid complex structures, rates and probabilities derived from the literature may not reflect the hypothetical patient cohort and HrQoL estimates can vary widely. To our knowledge, this present study is the first prospective, blinded, randomised trial investigating the cost-effectiveness of concomitant AS from a societal perspective.

Strengths and limitations

This study has several strengths. Firstly, patients were consecutively and prospectively evaluated, baseline characteristics were comparable and all subtypes of AF were equally represented in the patient population. Group assignment was blinded to patients and all medical personnel (except the operating team) during follow-up, thereby reducing confounding factors in health care consumption. Secondly, we did not use decision-analytic methodologies, which require simplified assumptions

and might not reflect clinical practice. Thirdly, the duration of follow-up was one year, which is also a limitation. Although most studies on AS have a 6- or 12-month follow-up period, it seems reasonable to suppose that longer follow-up would more accurately define differences in health care consumption. On the other hand HrQoL outcomes may become confounded by additional co-morbidity as follow-up extends and therefore affect the QALY calculation and coinciding ICER. During the trial there was no statistical difference in co-morbidity between treatment groups[2]. Furthermore, longer follow-up might result in a higher drop-out 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. But again, 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-morbidities 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, economic healthcare evaluations are always influenced by co-morbidity and in the present study both patient groups were comparable regarding baseline characteristics and co-morbidity and a large group was evaluated[2].

Conclusions

This prospective, blinded, randomised trial shows that AS as a concomitant procedure in patients with AF is not cost-effective after 1-year follow-up as compared to cardiac surgery as usual. As this is the first prospective randomised study to investigate the actual costs of concomitant AS, further research is needed. Given that most new therapies are initially not cost-effective, these economic benchmarks underpin the conclusions of most cost-effectiveness studies. This important distinction and other limitations lead to the conclusion that cost-effectiveness studies offer useful insights into the economics of medical care, rather than definitive conclusions on optimal practice.

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Table 1. Unit costs used to value resource use within the clinical trial

	Unit	*Cost per unit in euros* €	*Source*
Direct healthcare costs			Dutch Guidelines (Oostenbrink)[7]
- General Practitioner			
- Home visit	Visit	13,50	
- Practice visit	Visit	9,00	
- Telephonic consultation	Visit	4,0	
- Out of office hours: home consultation	Visit	49,10	
- Out of office hours: practice consultation	Visit	32,70	
- Cardiologist consultation	Visit	98,00	
- Cardio-surgeon consultation	Visit	110,00	
- Other specialist consultation	Visit	98,00	
- E.R. visit	Visit	139,00	
- Additional exams			
- Blood work	Basic set	2,20	
- Defining INR range	Procedure	10,00	
- EKG	Procedure	15,00	
- X-ray	Test	21,60	
- Echocardiographic heart exam	Test	41,23	
- Physiotherapist	Visit	22,75	
- Basic domestic care help	Hour	12,70	
- Family care help	Hour	26,70	
- Domestic care help	Hour	8,30	
Direct non-healthcare costs			Dutch Guidelines (Oostenbrink)[7]
- Informal care (family, friends)	Hour	8,30	
Indirect healthcare costs			Dutch Guidelines (Oostenbrink)[7]
- Paid work loss	Hour	34,98* x 0.8^	
- Domestic work loss	Hour	8,30	
- Voluntary work loss	Hour	8,30	

* Productivity costs per hour, ^ elasticity of working hours: according to the Dutch manual for costs analysis [7]

Table 2. Mean annual costs in Euros per resource category for the intervention group versus control group from a societal perspective

Cost category	**Intervention** (N=65)		**Control** (N=67)		**Bootstrap 95% Uncertainty Interval**			
	Mean	SD[a]	Mean	SD[a]	Mean difference	SEM	2.5th percentile	97.5th percentile
Direct healthcare costs	18.390	5.189	14.091	4.389	4.299	804	2.781	5.928
- Operative costs	11.061	2.085	7.257	2.316	3.796	380	3.112	4.553
- Hospital stay	5.875	4.299	5.486	3.284	368	671	-868	1.642
- Visits general practitioner *	45	38	50	47	-5	8	-20	10
- Specialist consultation *	490	273	416	308	75	52	-30	176
- Additional exams *	163	100	163	132	0	20	-42	38
- Visits E.R *	52	118	59	127	-8	22	-51	35
- Physiotherapist *	132	178	87	117	47	27	-3	103
- Formal care *	389	926	377	523	9	134	-225	294
- Medication *	182	128	196	196	-13	29	-70	39
Direct non-healthcare costs	844	2.338	530	894	316	315	-230	1.027
- Informal care	839	2.339	516	897	313	308	-198	1.017
- Self medication	6	22	13	51	-8	7	-22	3
Indirect healthcare costs	1.609	3.014	1.497	2.598	112	496	-817	1.061
- Friction costs	1.099	2.988	864	2.455	269	473	-585	1.258
- Domestic work loss	500	829	609	1.184	-110	175	-467	221
- Loss voluntary work	10	32	24	99	-14	13	-41	5
Total costs	20.843	6.477	16.117	5.210	4.724	992	2.770	6.678

* After discharge, [a] Standard deviation

Table 3. Incremental cost-effectiveness ratio of additional ablation surgery versus regular cardiac surgery

Procedure	**Costs €**	**QALY**	**ICER* Costs per QALY**
Intervention group (n=65)	20,38	0,75	
Control group (n=67)	16.312	0,69	
Increment	4.426	0,06	73.359

* ICER: incremental cost-effectiveness ratio

Figure 1. Cost-effectiveness plane for costs (Euros) versus quality adjusted life years (QALY's)

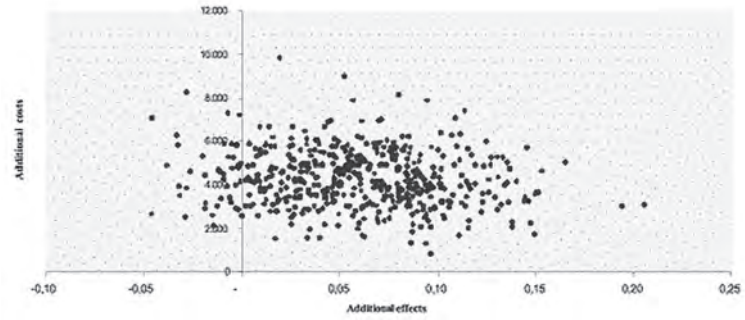
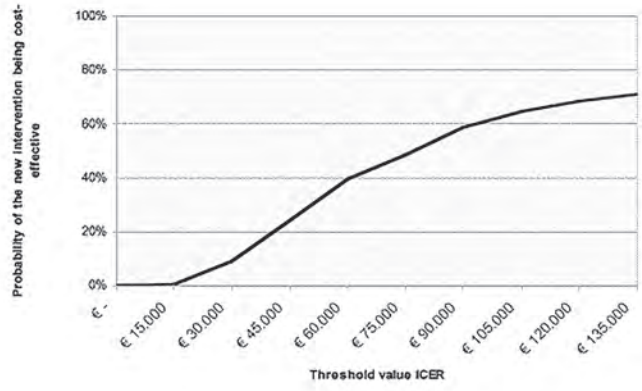


Figure 2. Acceptability curve of costs (Euros) per quality adjusted life years (QALY's)



Chapter 5

Maintenance of sinus rhythm after electrical cardioversion for recurrent atrial fibrillation following mitral valve surgery with or without associated radiofrequency ablation

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Abstract

Background: This study reports the outcomes of patients who underwent electrical cardioversion for atrial fibrillation (AF) recurrence following mitral valve surgery and associated radiofrequency ablation compared to those who did not undergo concomitant AF ablation.

Methods: The population consisted of 116 patients with persistent/ long-standing persistent AF who underwent mitral valve surgery with (Group A, n=54) or without (Group B, n=62) associated radiofrequency ablation between January 2007 and January 2011 at three Institutions and who subsequently underwent cardioversion for persistent AF within 12 months of their initial procedure.

Results: The mean follow-up duration was 30.7± 9.4 months. Of the 104 patients with acute restoration of SR, 42 (40.3%) had AF recurrence. The average time to recurrence after cardioversion was 7.3 ± 4.2 days. Recurrence was significantly lower in patients undergoing ablation surgery (21.4%) than in those who with no ablation surgery (78.6 %, $p<0.001$). Non-performed ablation procedure ($p<0.001$), time from surgery ≥ 88 days and left atrial dimensions ≥ 45.5 mm before cardioversion (both, $p=0.005$) were multivariable predictors of atrial fibrillation recurrence. In group B the use of amiodarone was inversely correlated with recurrence of AF ($p<0.001$). This correlation was not significant ($r=-0.02$, $p=0.85$) in group A.

Conclusions: Electrical cardioversion for recurrent AF showed better results and stable recovery of sinus rhythm in patients undergoing concomitant surgical ablation during mitral valve surgery. This might be attributable to substrate modification caused by surgical lesions. Amiodarone improved the ECV-success rate only in patients with no associate ablation. Further larger randomised studies are necessary to confirm our findings.

Introduction

Since its introduction in 1989 by Cox and colleagues[1], the surgical treatment of atrial fibrillation (AF) has experienced a new dawn during the past few years[2]. Technological innovations have helped to simplify the original Maze technique replacing the surgical incisions with transmural ablation lines created by various energy sources[3].

In patients with mitral valve disease, preoperative AF is present in 30-50% and it is associated with less favourable short- and long-term outcomes. It has been demonstrated that surgical correction of the underlying cardiac abnormality usually will not abolish AF that has been present for six months or more[4,5]. In contrast, the Maze procedure associated with mitral valve surgery is reported to have several clinical benefits[6-8] and to restore stable sinus rhythm (SR) with a success rate ranging from 74% to 83%[9-10].

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[11] and little is known about the benefit of ECV, with or without additional pharmacological pre-treatment, after unsuccessful ablation surgery.

Therefore, the purpose of this study is to report early and mid-term outcomes of patients who underwent ECV for AF recurrence following mitral valve surgery and associated radiofrequency (RF) 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.

Methods

Patient population

Ethical Committee approval was waived due to the retrospective analysis of the study according to National laws regulating observational retrospective studies (Italian law no.11960, released on 13/07/2004; Dutch law). However, written informed consent was obtained from all the patients prior to the surgical procedure.

The patient population consisted of one hundred and sixteen patients with persistent and long-standing persistent AF who survived mitral valve surgery with (Group A, n=54) or without (Group B, n=62) associated radiofrequency AF ablation between January 2007 and January 2011 at three Institutions (Careggi Hospital, Florence, Italy, University Hospital, Catanzaro, Italy, University Hospital, Maastricht, the Netherlands) and who subsequently underwent ECV for persistent AF within 12 months of their initial procedure. During this interval a total of 317 patients with mitral disease and AF underwent cardiac surgery at these Institutions and among them, 115 (36.2%) had concomitant ablation surgery.

Sixteen patients refused ECV or did not undergo cardioversion because of a contraindication. Patients with paroxysmal AF, those who underwent prior cardiac surgery or catheter ablation and those with postoperative residual/recurrent moderate mitral or tricuspid regurgitation were excluded from the study. AF was defined according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society[12]. Clinical characteristics are shown in Table 1. Baseline data were comparable between the two groups.

Surgical technique

Indication to surgical ablation was given following the recent European Society of Cardiology Guidelines[13]. However, the final decision to perform or not perform a surgical ablation was at the attending surgeon`s discretion. All operations were carried out on cardiopulmonary bypass with cardiac arrest being achieved with antegrade blood cardiopelgia. The mitral valve surgery was performed through a standard left atriotomy and different techniques of mitral repair were accomplished according to the underlying valve disease (Table 1). With regards to arrhythmia surgery, pulmonary vein isolation was carried out with a bipolar RF clamp (Medtronic Cardioablate, Medtronic, Minneapolis, MN). The left isthmus lesion was always performed with a unipolar RF pen (Cardioablate, Medtronic, Minneapolis, MN). The left lesion set was completed by bipolar RF lesion connecting the left superior pulmonary vein to the left atrial appendage. A bipolar RF cavo-troscuspid isthmus line was carried out in three (5.5%) whereas ganglia ablation was performed in 11 patients (20.4%). Finally, the left appendage was excluded in 52 patients (96.2 %) either by external ligation or by an internal stitch, according to the surgeon's choice. More details about surgical technique have been previously reported[14].

Follow-up after surgery

Patients were seen in the outpatient clinic 3 months, 6 months and 12 months after the surgical procedure and annually thereafter. Between visits, patients were followed by their referring physician on a regular basis and routine ECGs were obtained at each clinic visit regardless of symptoms. Event monitors were prescribed for patients who complained of palpitations or symptoms compatible with AF during follow-up. The follow-up evaluation consisted of a detailed history, physical examination and 7-day Holter monitoring. Patients with persistent AF at the time of follow-up or between scheduled visits were advised to undergo electrical cardioversion.

Antiarrhythmic therapy and anticoagulation protocol

Postoperatively, unless contraindicated, patients in the ablation group received amiodarone or another antiarrhythmic drug, while patients who had no ablation had amiodarone only if internal DC cardioversion restored SR intraoperatively. For purposes of reporting long-term outcomes of surgical ablation and following the Heart Rhythm Society Consensus document on AF[12], the initial 90 days after the ablation were considered as the blanking period. Patients who were free of AF at their 3-month post-surgery clinic visit had their antiarrhythmics discontinued. However, the final decision of discontinuing antiarrhythmic drugs was at the discretion of referring cardiologists.

In addition, all patients were put on anticoagulation therapy (warfarin) for at least three months. The effectiveness of anticoagulation was assessed by international normalized ratio level and anticoagulation was considered adequate when its value was > 2.0 (optimal range 2.0–3.0). Patients who were in stable SR for three months had their warfarin discontinued unless otherwise indicated.

Electrical cardioversion.

Cardioversion was defined as early cardioversion if performed within 90 days of the surgical procedure and late cardioversion if it was performed > 90 days following surgery. Anticoagulation ECV-protocol was strictly adhered to current guidelines[15]. A transoesophageal echocardiography was performed to rule out intra-atrial thrombi before ECV in patients who were not fully anticoagulated[16].

All patients gave written informed consent to the procedure. All cardioversions were carried out in day-hospital regimens, with continuous electrocardiographic monitoring and full equipment for cardiopulmonary resuscitation. Blood pressure

was measured before and after the procedure, while pulse oximetry and cardiac rhythm were continuously monitored throughout. Oxygen supplementation and ventilation support were given if necessary. Twelve-lead EKGs were recorded before and after the procedure to verify restoration of SR. Pacing pads were placed anteriorly over the chest and posteriorly in the interscapular area. After intravenous sedation (propofol 1.5 mg/kg) performed by an anaesthesiologist, an R-wave synchronized direct-current biphasic shock was delivered, with an initial energy of 200 J and then, if the first shock was ineffective, of 300 J up to 360 J according to the body weight and transthoracic impedance. After the procedure, patients were monitored by telemetry for at least six hours and then discharged. Cardioversion was considered successful if patients were discharged in SR. After ECV, patients continued the prescribed antiarrhythmic drug therapy for three months unless side effects, complications, or referring physicians' decision dictated otherwise.

Post-ECV follow-up and outcomes

Follow-up appointments were systematically scheduled at 1, 3, 6 and 12 months after ECV and then every year. During such visit patients underwent physical examination, ECG and 7-day Holter monitoring. Between visits, all patients were encouraged to seek 12-lead ECG documentation for any symptom suggestive of AF/atrial flutter recurrence and a physician routinely performed trans-telephonic monitoring of any symptoms and complications.

Any episode of symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial tachycardia, atrial flutter) after the initial 90-day blanking period (for patients who underwent early cardioversion) or after the final cardioversion (for patients who underwent late cardioversion) that lasted 30 seconds or longer was considered as AF recurrence. Complete success was defined as the absence of AF recurrence off-AAD, as recommended by the Heart Rhythm Society Consensus Document[12].

Statistical analysis

Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data were expressed as mean ± standard deviation whereas non-normally-distributed data were presented as median and interquartile range and frequencies as proportions. Between-group differences were assessed by the unpaired t test, Mann-Whitney U test, or Pearson χ^2 test. Pearson's correlation was used to test linear relationships between variables.

Furthermore, we performed univariate analysis on the entire population with post-ECV AF recurrence as a dependent variable and demographic and clinical parameters (Table 2) as independent variables. Significant and borderline (≤ 0.1) variables were introduced into multivariate logistic regression analysis, which was performed by means of a backward stepwise algorithm (cut-off for entry 0.05, for removal 0.10) to select independent predictors of post-ECV AF recurrence. Internal validation of predictors generated by multivariate logistic regression was performed by means of bootstrapping techniques[17], with 1000 cycles and generation of OR and bias corrected 95% CI. Model fit for logistic regression was assessed with the Hosmer-Lemeshow statistic and predictive accuracy was assessed by the concordance index[18].

Optimal cut-off values of left atrial (LA) dimensions just before ECV and time from surgery to ECV were determined by receiver operating characteristic curve analysis as the optimal threshold for predicting recurrence of AF. We validated the results using the bootstrap method (1,000 iterations).

Finally, to assess whether the predictive value of surgical ablation was secondary to other factors such as left atrial dimensions before ECV and time from surgery to ECV, we estimated the effect of surgical ablation in sub-groups that included these two factors using logistic regression analysis. Then we tested for interaction between surgical ablation and sub-group variables using a multivariate general linear model.

SPSS 12.0 (SPSS, Chicago, IL, USA) and Stats Direct 2.5.7 (Stats Direct, UK) software packages were used for calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

Results

Cardioversion timing

The mean time from surgery to cardioversion procedure was 82.6 ± 33.2 days in the ablation group and 85.5 ± 44 days in patients who did not undergo surgical ablation (p=0.86). In group A, this time was < 90 days in 21 patients (38.8%) and ≥ 90 days in 33 (61.2%). In group B, 22 patients underwent early ECV and 40 patients late ECV (p=0.7). At the time of cardioversion, 32 patients in group A (59.2%) and 37 in group B (59.6%) were in treatment with amiodarone (0.9). In addition, 9 patients in group A (16.7%) and 10 in group B (16.1%, p> 0.9) received

another antiarrhythmic drug whereas 28 patients (13 in group A [24.1%] and 15 in group B [24.2%], $p > 0.9$) did not have any antiarrhythmic drugs at the time of ECV. Finally, the atrial dimension at the time of ECV was not significantly different in the two groups (45.3 ± 9.8 mm vs. 49.0 ± 10.6 mm in group A and B, respectively, $p=0.08$).

Acute restoration of sinus rhythm

One hundred and four patients (89.6%) had a successful cardioversion and were discharged from the procedure recovery area in SR In the remaining 12 patients (10.4%, 8 with persistent AF and 4 with atrial flutter) ECV failed: 2 underwent trancatheter ablation while 10 had rate-control therapy. We did not observe significant differences in terms of acute success between groups (group A, 90.7% [n=49] vs group B, 88.7%, [n=55], $p= 0.76$).

In addition, among patients with successful ECV, 29/49 (59.1%) patients in group A and 34/55 in group B (61.8%, $p= 0.78$) were treated with amiodarone. Finally, no difference was observed in the acute efficacy of ECV depending on whether the cardioversion was performed early or late (86.0 % [37/43] vs 91.0% [67/73], $p= 0.34$).

Follow-up and AF recurrence

The mean patient follow-up duration after ECV was 30.7 ± 9.4 months (range 16.4-47.8 month, $p= 0.9$ between groups). Of the 104 patients with acute restoration of SR, 42 (40.3%) had AF recurrence. Recurrences were treated as follows: 29 (69.1%) patients were candidates for rhythm control, 13 [30.9%] underwent transcatheter ablation and 16 [38.2%] a second ECV, whereas 13 (30.9%) underwent rate-control therapy. Recurrence of AF (Figure 1A) was significantly lower in patients undergoing ablation surgery (n=9, 21.4%) compared to patients with no ablation surgery (n=33, 78.6 %, $p< 0.001$). Furthermore, in group A, among patients with post-ECV AF recurrence there was no significant statistical difference between those taking amiodarone or not (5/9, 55.5% vs 4/9, 44.4%, $p=0.58$). In contrast, in group B, the number of patients showing AF recurrence at follow-up and who were not treated with amiodarone was significantly higher (20/33 [60.6%] vs 13/33 [39.3%], $p< 0.001$). In addition in this group we found a significant inverse correlation between amiodarone and recurrence of AF ($r= -0.51$, $p< 0.001$). This correlation was not significant ($r=-0.02$, $p= 0.85$) in patients undergoing concomitant ablation surgery.

The mean time from ECV to AF recurrence was 7.3 ± 4.2 days. There was an increased incidence of relapse of AF during the first six days immediately after cardioversion (Figure 1B). Finally, the time to AF recurrence was significantly shorter in group B (6.0 ± 4.4 days vs 11.8 ± 5.5 days, p= 0.006).

Predictors of AF recurrence

Table 2 presents the univariate correlation between clinical and procedural parameters and AF recurrence after ECV at follow-up. In the group that remained in SR a significantly higher number of patients underwent ablation surgery (p< 0.001). Furthermore, the proportion of patients who were taking amiodarone before ECV was significantly higher in patients in SR (p= 0.002). Moreover, in patients with AF recurrence, left atrial dimensions before ECV were significantly larger (p< 0.001) and the time from surgery to ECV was longer (p< 0.001).

Multivariate analysis revealed that omission of ablation procedure (p< 0.001), time from surgery to ECV (p= 0.005) and left atrial dimensions before ECV (p= 0.005) were independent predictors for AF recurrence. The model proved to be reliable (Hosmer–Lemeshow test, p= 0.67) and accurate (c-index = 0.8). On receiver operating characteristic curves (Figure 2 A-B), the left atrial size just before ECV was a predictor for AF recurrence with a cutoff of ≥ 45.5 mm (sensitivity 90%, specificity 81%, area under the curve 0.91, 95% confidence interval 0.86 to 0.96). The time from surgery to ECV had 81% sensitivity and 83% specificity with an optimal cutoff of ≥ 88 days (area under the curve 0.85, 95% confidence interval 0.78 to 0.93).

When we allowed for an interaction between surgical ablation and other risk factors (Figure 3) the predictive value of non-performed ablation procedure was significant across a wide spectrum of patients and the odds ratios were always greater in low-risk sub-groups and attenuated in higher risk patients. No significant interaction was found between surgical ablation and any of the covariates (all, p> 0.05).

Discussion

In this study we reported early and mid-term outcomes in patients who underwent cardioversion for persistent AF occurring after RF ablation associated with mitral valve surgery (Group A) and we compared these outcomes to patients

undergoing ECV after mitral surgery without concomitant AF ablation (Group B). The main findings of our study can be summarized as follows: 1) Recurrence of AF following ECV was significantly lower in patients undergoing ablation surgery compared to patients with no associated ablation surgery; 2) Non-performed ablation procedures, time from surgery to ECV and left atrial dimensions before ECV were multivariate predictors of AF recurrence; 3) The use of amiodarone did not significantly reduce the AF recurrence after ECV.

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. This might suggest that some kind of substrate modification occurred after surgical ablation and it made patients more susceptible to the treatment of ECV. Indeed, intra-operative RF ablation methods limited to the left atrium have proven to be efficacious for modification of the AF substrate[19]. 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[20] to alter the arrhythmia substrate sufficiently to be responsive to ECV.

In addition, left atrial LA dimensions < 45 mm ($p= 0.005$) before ECV predict 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 with over-stretched myocardium and residual high wall stress might not achieve significant reverse remodeling 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 the Maze procedure is explained by changes induced in atrial electrophysiology by myocardial edema and inflammatory response to cardiac surgery[21]. There is evidence that this condition tends to resolve within the first post-operative month when the myocardial edema tends to disappear[22]. In contrast, the genesis of late recurrence might be attributed to lesion incompleteness[23] Since early recurrence is 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.

However, since patients with post-ECV AF recurrence had a significantly larger left atrium and longer time to surgery, the predictive value of ablation surgery could be secondary to these factors, which could be primary predictors. Nonetheless, when we allowed for an interaction between surgical ablation and these two risk factors, omission of an ablation procedure was associated with increased AF recurrence in patients with left atrium < 45 mm and time to ECV < 88 days whereas this effect was attenuated in higher risk patients. Also, we failed to find any interaction between surgical ablation and two other variables, 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.

Notably, the use of amiodarone and other antiarrhythmics at the time of cardioversion did not influence AF recurrence in group A whereas in group B, among patients showing AF recurrence at follow-up, the number of those who were not treated with amiodarone was significantly higher (60.6% vs 39.3%, p< 0.001). In addition, in this group, there was a significant inverse correlation between amiodarone and recurrence of AF (r= -0.51, p< 0.001). This correlation was not significant (r=-0.02, p= 0.85) in patients undergoing ablation surgery. Therefore, from our experience, 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[24-26] 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 is not important in patients undergoing an associated ablation procedure since the epicardial RF ablation itself leads to attenuated shortening of atrial refractoriness[27].

In addition the use of amiodarone might also have affected the time from ECV to AF recurrences, since the number of patients with recurrence who were not

treated with amiodarone was significantly higher in group B which showed a shorter time to AF recurrence (p= 0.006). Nonetheless, this finding must be read in light of lack of randomisation for surgical ablation that might have led to unbalanced use of amiodarone in the two groups. However, amiodarone reduces early AF recurrences and it is comparable to diltiazem whereas calcium channel blocker therapy has no significant effect on long-term SR maintenance[28]. This observation, together with the experimental data showing that atrial electric remodeling is completely reversible within one week after SR restoration[29], confirms that mechanisms involved in long-term AF recurrences are different from those involved in the short-term recurrences and that several actions of amiodarone on cellular mechanisms such as its effect on sarcoplasmic reticulum calcium content in ventricular myocytes[30,31], may be responsible for its positive effect on early recurrence.

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 also important to 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 any 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 low surgeons' experience and the little knowledge of the surgical lesion sets. Nonetheless, this drawback is shared by most of the published studies on this topic[32]. Also, it must be taken into account that the type of surgery in relation to left appendage exclusion was not randomised. This might have biased our results because of the potential pro-arrhythmic role of atrial appendage. In addition, ligation/amputation of the left atrial appendage in combination with mitral valve surgery might have been effective in relieving AF after cardioversion through a more pronounced LA size reduction, which in our experience had a predictive value in determining mid-term success of sinus conversion after ECV.

Finally, several studies have reported better efficacy when the right atrial ablation pattern is added to the left when treating persistent and permanent AF[33], indicating that connecting lines to the tricuspid valve annulus may be important

in this clinical setting[34]. Indeed, continuous AF needs two components to exist: the triggers generating AF located in the pulmonary veins and the drivers or macro re-entrant circuits sustaining AF found in both atria. The Maze lesions work isolating the triggers in the pulmonary veins and breaking the macro re-entrant circuits in the atria[22]. In our series, bi-atrial ablation was carried out in only 5.5% of patients and this might explain the macro-re-entry and thus the recurrence of AF during follow-up.

Study limitations

The present paper has certain limitations that need to be addressed. First of all, the retrospective design of the study and its multicentric nature do not provide a definitive causative link between surgical ablation and improved outcome after ECV. Furthermore, the follow-up was limited to a mean of 2.5 years and the demonstration of long-term maintenance of SR would have been more desirable. Moreover, different ablation techniques and different protocols were employed and this might have affected our results. Furthermore, the etiology of mitral valve disease might have influenced the persistence of AF after surgery. This aspect deserves further investigation. Finally, the absence of rigorous ECG monitoring for asymptomatic AF between scheduled follow-up appointments. We acknowledge that we may have missed some patients with asymptomatic AF and this is an important limitation of our study.

However, besides these limitations, the study presented a relatively large patient population and, to the best of our knowledge, it is the first of its kind published in the scientific literature.

Conclusions

Based on the results of this study, patients who require ECV after mitral surgery without concomitant ablation have a high chance of developing AF recurrence. The better results in patients undergoing concomitant ablation might be attributable to substrate modification caused by surgical lesions. However, further larger randomised studies are necessary to confirm our findings.

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Table 1. Baseline characteristics and surgical data (n =116).

	Group A Ablation Group (n=54)	Group B No Ablation Group (n=62)	*p*
Age	69.9 ± 8.6	68.2 ± 8.9	NS
Sex (Male/Female)	28/26 (51.8/48.2)	31/31 (50/50)	NS
Body Mass Index (Kg/m^2)	26.0 ± 3.1	26.7 ± 2.8	NS
Co-morbidities			
Hypertension	20 (37.1)	21 (33.9)	NS
Diabetes	14 (25.9)	15 (24.1)	NS
Cerebrovascular Disease	6 (11.1)	6 (9.6)	NS
Chronic Obstructive Pulmonary Disease	4 (7.4)	3 (4.8)	NS
Congestive Heart Failure	3 (5.5)	5 (8.0)	NS
Renal Failure	1 (1.9)	2 (3.2)	NS
Atrial Fibrillation type			
Persistent	32 (59.3)	36 (58.1)	NS
Long-standing persistent	22 (40.7)	26 (41.9)	
Atrial Fibrillation duration before surgery (months)	33 (27-44)	28 (21-37)	NS
New York Heart Association Functional Class	3 (2-3)	3 (2-3)	
II	12 (22.2)	21 (33.9)	
III	30 (55.6)	27 (43.6)	NS
IV	12 (22.2)	14 (22.5)	
EuroScore	5.3 (4.0-6.2)	6.0 (5.0-7.0)	NS
Mitral Valve Pathology			
Rheumatic	9 (16.7)	11 (17.7)	
Degenerative	26 (48.2)	31 (50.1)	
Ischemic	14 (25.9)	14 (22.5)	NS
Functional	4 (7.4)	5 (8.1)	
Other	1 (1.9)	1(1.6)	
Mitral Lesion			
Stenosis	1 (1.9)	2 (3.2)	
Insufficiency	49 (90.7)	58 (93.6)	NS
Mixed	4 (7.4)	2 (3.2)	
Coronary Artery Disease	16 (29.6)	16 (25.8)	NS
Aortic Valve Disease	7 (12.9)	12 (19.3)	NS
Tricuspid Valve Disease	16 (29.6)	18 (29.0)	NS
Left Atrial Size (mm)	52.3 ± 9.0	55.1±11.5	NS
Left Ventricular Ejection Fraction (%)	56.0±11.6	58.5±11.9	NS
End systolic diameter (mm)	31.4±3.3	30.5±2.2	NS
End diastolic diameter (mm)	52.3±4.3	51.8±4.0	NS
Mitral Valve Surgery			
Repair	42 (77.8)	46 (74.2)	
Replacement			NS
Bioprosthesis	8 (14.8)	11 (17.7)	
Mechanical	4 (7.4)	5 (8.1)	
Coronary Artery Bypass Grafting	16 (29.6)	14 (22.5)	NS
Anastomoses (n)	2.0 (2-3)	2.5 (2-3)	
Aortic Valve Replacement			
Bioprosthesis	6 (11.1)	6 (9.6)	NS
Mechanical	1 (1.9)	4 (6.4)	
Tricuspid Valve Repair	14 (25.9)	16 (25.8)	NS
Right Atrial lesions	3 (5.5)	-	NS
Left Atrial Appendage exclusion/ligation	52 (96.2)	-	NS

Table 1. continued.

	Group A Ablation Group (n=54)	Group B No Ablation Group (n=62)	*p*
Ganglia Ablation	11 (20.4)	-	NS
Cardiopulmonary bypass time (min)	170 ± 40	160 ± 34	NS
Aortic cross clamp time (min).	144 ± 29	129 ± 20	NS

Values are expressed as mean ± standard deviation (normally distributed data), median (Interquartile range) non-normally distributed data or n (%). Abbreviations: NS: Not significant.

Table 2. Predictors of atrial fibrillation recurrence after electrical cardioversion: Univariate analysis

	Sinus Rhythm (n=62)	AF Recurrence (n=42)	*p*
Age	69.8 ± 8.4	68.0 ± 9.2	NS
Sex (Male/Female)	28 (45.2)	23 (45.3)	NS
Body Mass Index (Kg/m^2)	26.6 ± 3.3	26.2 ±2.5	NS
Co-morbidities			
Hypertension	20 (32.2)	16 (38.1)	NS
Diabetes	14 (22.5)	16 (38.1)	NS
Cerebrovascular Disease	5 (8.1)	5 (11.9)	NS
Chronic Obstructive Pulmonary Disease	3 (4.8)	2 (4.8)	NS
Congestive Heart Failure	4 (6.4)	3 (7.1)	NS
Renal Failure	2 (3.2)	1 (2.4)	NS
Persistent Atrial Fibrillation	40 (64.5)	23 (54.8)	NS
Long-standing persistent Atrial Fibrillation	22 (35.5)	19 (45.2)	NS
Atrial Fibrillation duration before surgery (months)	30 [25-38]	32 [20-40]	NS
New York Heart Association Functional Class	2[2-3]	2 [2-3]	NS
EuroScore	6.2 [5.2-7.5]	5.9 [4.9-7.0]	NS
Mitral Valve Pathology			
Rheumatic	10 (16.2)	5 (11.9)	
Degenerative	28 (45.2)	25 (59.5)	NS
Ischemic	19 (30.6)	8 (19.1)	
Functional	3 (4.8)	4 (9.5)	
Other	2 (3.2)	0 (0)	
Mitral Lesion			
Stenosis	1 (1.7)	1 (2.4)	
Insufficiency	58 (93.5)	39 (92.8)	NS
Mixed	3 (4.8)	2 (4.8)	
Coronary Artery Disease	21 (33.8)	10 (23.8)	NS
Aortic Valve Disease	8 (12.8)	6 (14.2)	NS
Tricuspid Valve Disease	19 (30.6)	10 (23.8)	NS
Left Atrial Size (mm)	52.2 ± 9.5	55.7 ± 11.4	NS
Left Ventricular Ejection Fraction (%)	55.0 ±10.0	59.0 ± 11.1	NS
End systolic diameter (mm)	30.5 ±2.9	31.4 ± 2.6	NS
End diastolic diameter (mm)	52.2 ± 4.1	51.8 ± 4.3	NS
Mitral Valve Repair	48 (77.4)	34 (80.9)	NS
Mitral Valve Replacement	14 (22.5)	8 (19.1)	NS
Coronary Artery Bypass Grafting	20 (32.2)	12 (28.5)	NS
Associated Aortic Valve Replacement	10 (16.2)	6 (14.2)	NS

Table 2. continued

	Sinus Rhythm (n=62)	AF Recurrence (n=42)	*p*
Tricuspid Valve Repair	17 (27.4)	9 (21.4)	NS
Ablation Surgery	40 (64.5)	9 (21.4)	<0.001
Right Atrial lesions	1 (1.7)	1(2.4)	NS
Time Surgery to Cardioversion	62.6 ± 26.6	110.2 ± 35.4	<0.001
Left Atrial Appendage exclusion/ligation	40 (64.5)	27 (64.2)	NS
Ganglia Ablation	4 (6.4)	3 (7.1)	NS
LA dimensions before Cardioversion	40.7 ± 7.8	55.4 ± 6.8	<0.001
Amiodarone at time of Cardioversion	45 (72.5)	18 (42.8)	0.002
Other Antiarrhythmics at time of Cardioversion	7 (11.3)	10 (23.8)	NS
Cardiopulmonary bypass time (min)	166 ± 39	164 ± 35	NS
Aortic cross clamp time (min).	138 ± 27	135 ± 22	NS

Values are expressed as mean ± deviation standard (normally distributed data), median (Interquartile range) non-normally distributed data or n (%). Abbreviations: NS: Not significant.

Table 3. Multivariate predictors of atrial fibrillation recurrence after electrical cardioversion

Variable	Odds Ratio	*p*	95% Bias-corrected CI	
			Low Limit	Upper Limit
No Ablation Surgery	4.2	<0.001	2.3	7.5
Time Surgery to Cardioversion	2.7	0.005	1.1	3.4
Left Atrial dimensions before Cardioversion	2.7	0.005	1.2	3.2
Amiodarone before Cardioversion	2.0	0.07	0.9	2.7

Figure 1.

A. Recurrence of atrial fibrillation following electrical cardioversion in patients undergoing mitral valve surgery with (ablation group) or without (no ablation group) associated surgical ablation.
B. The daily incidence of relapse of atrial fibrillation during 1-month follow-up. There was an increased incidence during the first 6 days immediately after cardioversion compared with the rest of the follow-up period. Abbreviations: ECV: Electric Cardioversion. Pts: Patients.

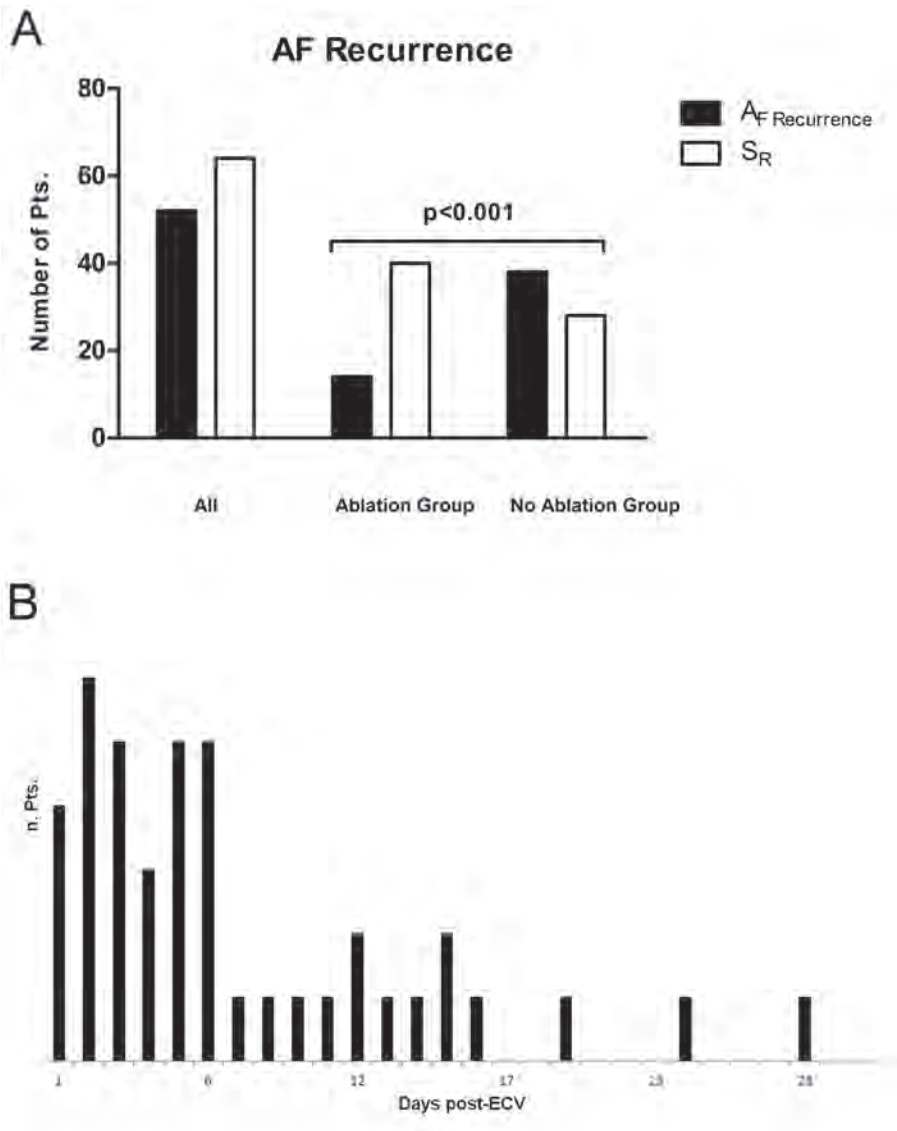


Figure 2.

A. The figure shows a receiver operating characteristics (ROC) curve from time to surgery to electrical cardioversion (ECV) in predicting recurrence of AF after the procedure.
B. ROC curve of left atrial (LA) size in predicting recurrence of AF after ECV.

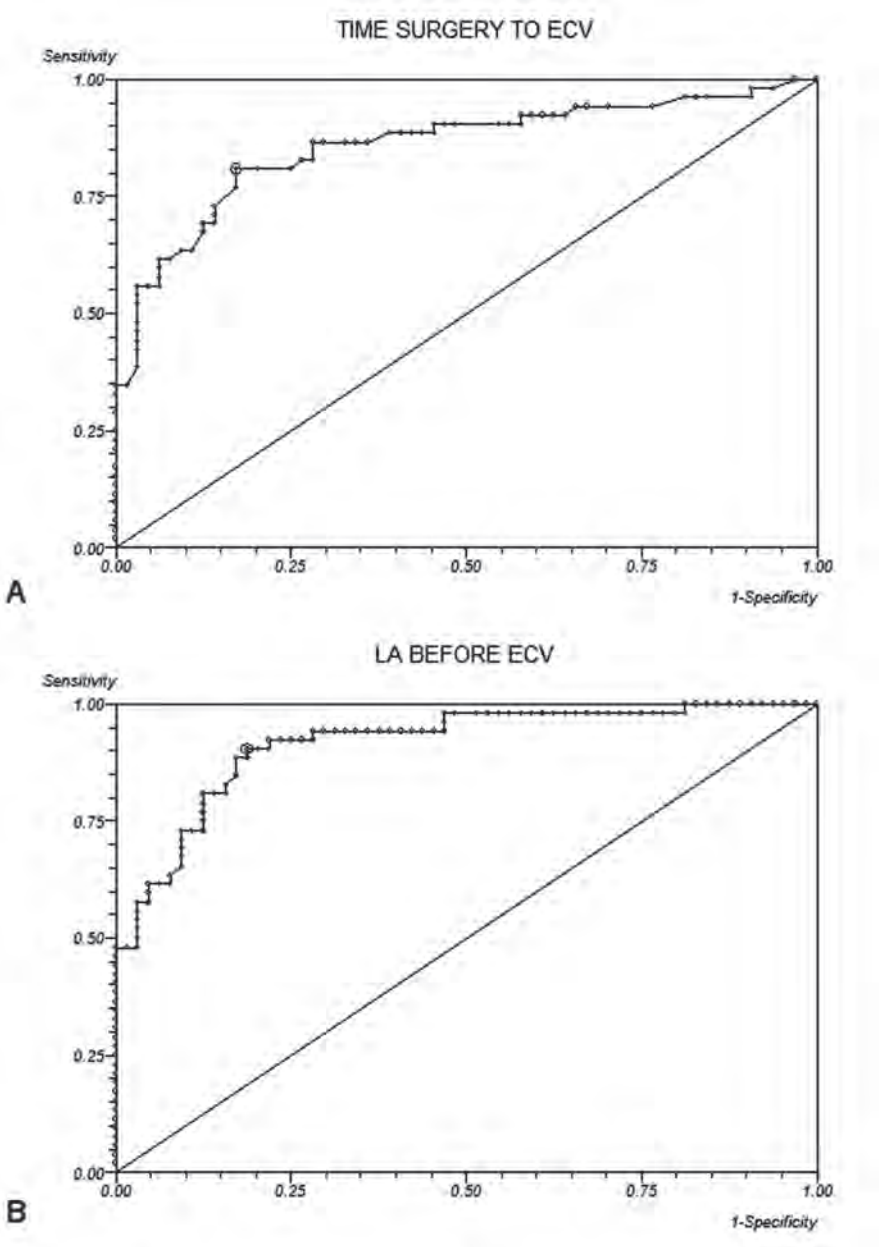
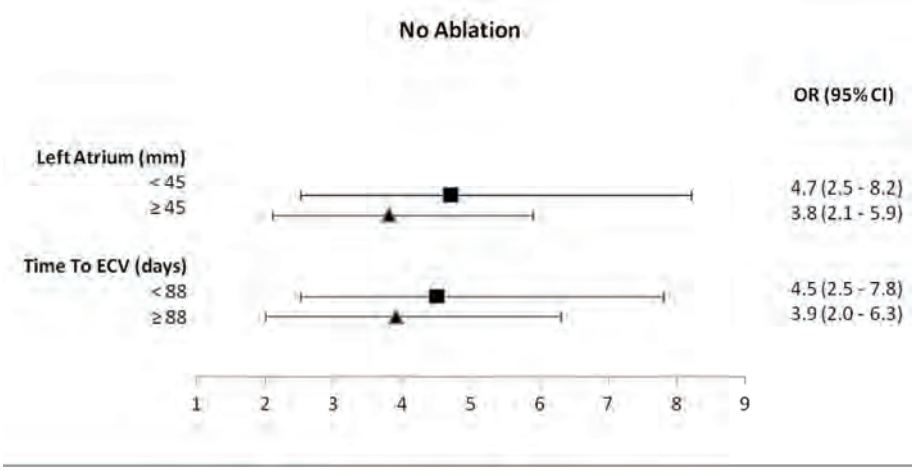
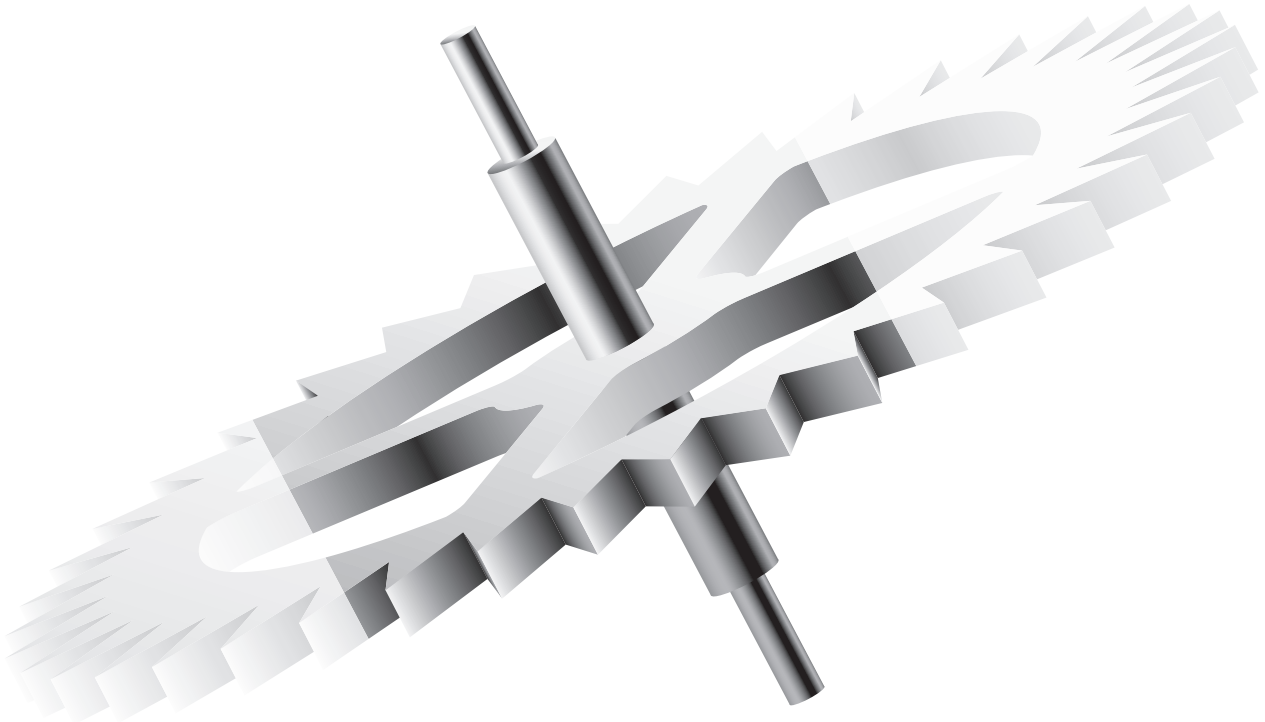


Figure 3.

Subgroup analysis: Odds Ratio (OR) and 95% CI of surgical ablation versus left atrial dimensions before ECV and time from surgery to ECV. Odds ratios were greater in low-risk sub-groups and attenuated in higher risk patients.





Chapter 6

Guideline adherence in antithrombotic treatment after concomitant ablation surgery in atrial fibrillation patients.

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Abstract

Objective. We investigated real-life oral anticoagulation (OAC) treatment after surgical ablation and examined its adherence to current recommendations. We also explored factors related to OAC use pre-operatively and at follow-up.

Methods. One hundred fifteen patients with atrial fibrillation (AF) were evaluated during 12 months of follow-up after surgery. Patients were divided into two categories according to the $CHADS_2$ score: sixty patients were assigned to the high-risk group ($CHADS_2$ score ≥ 2) and 55 to the low-risk group ($CHADS_2$ score ≤1). OAC use was defined as guideline adherent, under-treatment or over-treatment.

Results. Baseline overall guideline adherence was 62%. OAC was under prescribed in high-risk and over prescribed in low-risk patients (both, $p< .001$). The only factor associated with OAC use after logistic regression analysis were age >75 years ($p= .01$) and preoperative AF > paroxysmal ($p=. 013$). Overall guideline adherence at 12-month follow-up showed a trend towards a better adherence in the sinus rhythm (SR) subgroup (74.4% vs.55.2%, $p= .02$). OAC was under prescribed in high-risk and over prescribed in low-risk patients (both $p< .001$). After logistic regression analysis preoperative OAC use ($p= .007$) and other indications for OAC ($p= .01$) were predictors of anticoagulation treatment.

Conclusions. Real-life OAC prescription in AF patients showed a moderate guideline adherence, with high-risk patients being under treated and low-risk patients being over treated. These findings stress the importance that antithrombotic treatment in patients undergoing AF surgery needs to be critically re-evaluated.

Introduction

Stroke and thromboembolism are recognised as one of the most serious complications of atrial fibrillation (AF) because they are associated with a substantial risk of morbidity and mortality[1]. The number of patients being treated surgically for AF is increasing and there is also a well-recognised rise in the number of patients having ablation surgery as a stand-alone procedure[2]. One of the biggest theoretical advantages of surgical ablation over catheter ablation is the higher success rate and the management of the left atrial appendage[3]. This may in turn lead to higher rates of patients' off-warfarin after the intervention. Nonetheless, the current management of anticoagulation is inconsistent and challenging and no guidelines were put in place until recently[4]. Furthermore, 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[4] and what factors drive the decision to anticoagulate or not these patients in the daily clinical practice.

Therefore, the aim of this study was to investigate real-life anticoagulation treatment after ablation surgery and to examine whether this treatment adheres to current guidelines. Additionally, we explored factors related to OAC use preoperatively and at follow-up.

Methods

Study design, patient population and clinical follow-up

Patients were recruited from the ASAF study, an ongoing multicentre, prospective, randomised controlled trial aimed at determining the effect of add-on arrhythmia surgery on health related quality of life (HrQoL) in cardiac surgery patients with AF[5]. A total of 115 consecutive subjects undergoing cardiac surgery and associated ablation were selected. Inclusion and exclusion criteria and surgical details have been previously reported[5]. At baseline all patients had documented AF and all were without contraindications for OAC.

Patients were divided into two categories according to the $CHADS_2$ score (congestive heart failure [CHF], hypertension, age ≥ 75 years, diabetes [1 point each], and prior stroke or transient ischaemic attack [TIA] [2 points]), which is a validated clinical prediction tool commonly, used to estimate the risk of stroke in AF[6,7]. Sixty patients were assigned to the high-risk group ($CHADS_2$ score of ≥ 2) and 55 to the low-risk group ($CHADS_2$ score of ≤ 1). Table 1 shows patient characteristics at inclusion: apart from the $CHADS_2$ score and female gender, less frequent in low-risk patients, baseline demographic variables were comparable between groups.

Data were collected from medical information systems at baseline and at 3, 6 and 12 months postoperatively. All patients were followed-up according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) expert consensus statement on catheter and surgical ablation of AF[4] and updated European Society of Cardiology (ESC) Guidelines were followed to distinguish the type of AF and to score the AF-related symptoms (European Heart Rhythm Association [EHRA] score)[8].

Rhythm status was evaluated using serial electrocardiograms and 24-hour Holter recordings after the procedure and at follow-up appointments and any arrhythmia which had the ECG characteristics of AF, atrial flutter or atrial tachycardia and lasted longer than 30 seconds was reported as recurrence. Surgical ablation success was defined as freedom from AF off-antiarrhythmic drugs (AAD). Ninety-seven patients reached 1-year follow-up whereas 18 were lost at the 12-month follow-up appointment: three moved out of the country, one became unwilling to participate in the study and 14 died because of non-related-OAC-use reasons. Median follow-up was 15 months (IQR 13-17 months).

We conducted the study in compliance with the principles of the Declaration of Helsinki. Institutional Ethical Committees approved the protocol and all patients signed an informed consent prior to surgery and gave their written consent to treat their data for clinical purposes.

Definition of appropriate antithrombotic treatment

Indications for antithrombotic drug prescription pre-operative and during follow-up were analysed with reference to the 2004 American College of Chest Physicians (ACCP) Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis and the 2007 HRS/EHRA/ECAS Expert Consensus Statement[4,9]. According to these guidelines the real-life OAC use was evaluated as guideline adherent, over-treatment or under-treatment.

Statistical analysis

Normal values were expressed as mean ± 1 standard deviation (SD), non-normal values as median and interquartile range (IQR), and categorical variables as percentages. Group comparison between continuous variables was performed, using 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. To test the association between OAC use at inclusion and end of follow-up with different patient factors, univariate logistic regression was performed. Based on our previous experience[5, 7], the following covariates were included in the model: age >75, sex, 'high-risk, 'low-risk', $CHADS_2$ score, type of pre-operative AF > paroxysmal, type of cardiac surgery, left ventricular ejection fraction, left atrial dimensions, rhythm outcome, other indications for OAC than AF, pre-operative OAC use and OAC-related complications. Multivariate stepwise logistic regression was then carried out including covariates, which were found to have a significant/borderline association in the univariate analysis ($p \leq .10$). The Pearson correlation was employed to test the correlation between OAC-related complications at 12-month follow-up and guideline adherence, over-treatment and under-treatment.

P values of less than .05 were considered as statistically significant. All data analysis were performed with SPSS for Windows version 15.0 (SPSS Inc. Chicago, IL).

Results

Oral anticoagulant therapy and guideline adherence at inclusion

Figure 1A shows that among the AF patients at inclusion, a total of 26 (23%) patients had an additional reason for OAC besides their $CHADS_2$ risk score with an even distribution among groups (high-risk, 28% [n=17] vs. low-risk, 16% [n=9], p=. 13). Overall guideline adherence (Figure 1B) was 62 % (n=71): 68% (n=41) for the high-risk group and 54% (n=30) for the low-risk group (p=. 13). On the other hand, 20% of patients (n=23) were over treated, with predominance in the low-risk group (41% [n=23] vs. 0% [0], p<. 001) whereas 18% (n=21) were under treated with predominance in the high-risk group (31% [n=19] vs. 3% [n=2], p<. 001).

Oral anticoagulant therapy and guideline adherence at 12-month follow-up

At 1-year follow-up 39 patients (40%) were in sinus rhythm off-AAD: therefore 58 patients were in AF, 30 in the high-risk group (62%) and 28 in the low-risk group (57%, *p*=. 75). The number of patients with additional reasons for OAC use other than the $CHADS_2$ risk scheme rose to 42 (43%) without significant differences between groups (high-risk, 43% [N=13] vs. low-risk, 46% [n=13], *p*=. 91). Figure 2A displays the appropriateness of OAC prescription in AF patients at 12 months. Overall guideline adherence for the AF group was 55 % (n=32): 60% (n=18) for the high-risk group and 50% (n=14) for low-risk patients (*p*=. 12). On the other hand, 20 % of patients (n=12) were over treated (Figure 2B), with predominance in the low-risk group (42% [n=12] vs. 0% [n=0], *p*<. 001) and 24% of patients (n=14) were under treated with predominance in the high-risk group (40% [n=12] vs. 7% [n=2], *p*<. 001).

Figure 3A shows the distribution of patients in sinus rhythm (SR) off-AAD at the end of follow-up in the high-risk and low-risk groups. The majority of patients in SR displayed guideline adherence (n=29, 74%, *p*=. 02 vs. AF patients) whereas the proportions of over- and under-treatment (Figure 3B) were much lower (15% [n=6] and 10% [n=4], in high-risk and low-risk patients, respectively) with no difference between groups (over treatment, *p*=. 61; under treatment, *p*=. 60)

Factors associated with oral anticoagulant use

At univariate logistic regression (Table 2), age >75 years (*p*=. 06), preoperative AF> paroxysmal (*p*=. 04), type of cardiac surgery (*p*=. 04) and left atrial dimensions (*p*=. 01) were significant predictors of OAC use at baseline. Preoperative $CHADS_2$ score was not significant (*p*=. 34). At multivariate logistic regression age >75 years (*p*=. 01) and preoperative AF> paroxysmal (*p*=. 01) were significant predictors of OAC use at inclusion.

Univariate predictors of OAC use at 12-month followup (Table 3) were preoperative AF>paroxysmal (*p*=. 02), type of cardiac surgery (*p*=. 03), preoperative OAC use (*p*=. 02) and other indications for OAC use than AF (*p*=. 09). Preoperative $CHADS_2$ score was not significant (*p*=. 39). Preoperative OAC use (*p*=. 007) and other indications for OAC use than AF (*p*=. 01) were multivariate predictors of anticoagulation treatment at follow-up (Table 3).

OAC-related complications during follow-up

Among the 97 patients reaching the 12-month follow-up, six patients (6%) suffered from gastrointestinal bleeding and two (2%) had a stroke secondary to OAC use, without significant differences between the two study groups (p=0.10). There was no significant association between OAC-related postoperative complications at 12-month follow-up and guideline adherence (p=. 45), over-treatment (p=. 73) and undert-reatment (p=. 06).

Discussion

The main finding of the study is that oral anticoagulation before and after AF surgical ablation is hardly guided by the patient's individual stroke risk. Contrary to current recommendations, the rate of oral anticoagulation 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", "type of AF " (> paroxysmal at inclusion), "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.

This is in contrast with the current guidelines, which advocate basing decisions regarding anticoagulation treatment after surgical and catheter ablation on the patient's risk factors, and not on the presence or type of AF[4,11], and to continue anticoagulation treatment in patients with a high stroke risk as expressed by a $CHADS_2$ score ≥2.

Therefore, 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, 1-year after the procedure, 96 % of patients (47/49) with a low stroke risk ($CHADS_2$ score ≤1) were still receiving oral anticoagulation. This might be explained by an increasing percentage (43%) of patients with additional reasons (e.g. mechanical valve implantation) for OAC use other than the $CHADS_2$ risk scheme at 12-month follow-up.

Our study showed 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 at 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[12,13]. Similarly, Dagres et al.[14] 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 the OAC appropriateness following surgical ablation and our findings may have important clinical consequences since the guideline-deviant management has been shown to be associated to worse outcome in daily practice[15]. Interestingly, the adherence was slightly higher in patients in SR at one year (74%) indicating that a positive rhythm outcome did not trigger inappropriate cessation of OAC.

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 must be emphasised that for the patients in 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, the 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[16-17]. 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[18]. Finally, the lack of large randomised trials regarding the necessity and efficacy of anticoagulation after a presumably successful surgical procedure might be also responsible for a poor guideline-adherence of antithrombotic treatment following ablation surgery.

As a result, the choice of the appropriate antithrombotic therapy for the individual AF patient is still debated[19, 20] 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.
In our study it is striking that in the multivariate analysis, 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. Although the literature suggests that elderly patients with AF benefits most from OAC[21], advanced age might also be a barrier for many clinicians to the prescription of OAC: the possibility of poor anticoagulant control, increased risk of bleeding complications and fall risk were mentioned as reasons for not prescribing OAC[22]. However, considering the results of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study[23], older age can no longer be seen as a contraindication for OAC use, since this trial showed fewer strokes in the elderly AF patients treated with OAC as compared to those using aspirin. Furthermore the protective effect of antiplatelet therapy decreased with age, whereas the protective effect of OAC remained constant.
Factors influencing the decision for OAC prescription at the end of follow-up were "OAC use at inclusion' (p=0.007) and "other indications for OAC use than AF" (p=0.01). The first factor indicates that the patient's risk profile or rhythm outcome did not contribute in any way to the decision for prescribing OAC at follow-up and that there is a great reluctance to abandon OAC prescription after ablation surgery, also when SR is restored.
Suboptimal application rates of OAC prescription are associated with poor outcome in clinical practice in the treatment of AF patients. Although application rates of OAC have been improved according to the Euro Heart Survey[24], AF patients have a realistic chance of suffering from stroke or bleeding as a consequence of guideline deviance. 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[22]. In this study over-treatment or under-treatment did not show 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 under-treatment. This finding is in contrast with Nieuwlaat et al[15] 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.

Study limitations

Our study presents some limitations, which must be pointed out. First of all, the number of patients might be not large enough to draw an absolute conclusion. Second, asymptomatic recurrences after AF surgical ablation are frequent and represent a significant hurdle in the correct assessment of procedural success. Although in our study rhythm outcome was evaluated several times by serial electrocardiograms and 24-h Holter monitor recording, undetected asymptomatic episodes of AF might have occurred. With more extensive monitoring, a higher number of recurrences might have been identified although, in daily practice, the use of complex follow-up methods poses a significant workload and reduces patient compliance.

Third, reasons for prescribing OAC or not were unknown since patients were treated by their own cardiologists and general practitioners during follow-up. Thus, although the recommendation of our centre followed the HRS/EHRA/ECAS recommendations, it might not have been adopted by the physicians who made the final decisions. For instance, if the patient complains of symptoms of transient palpitations, some physicians give them OAC to prevent TIA regardless of the $CHAD_2$ score since they are concerned about AF complications, especially in cases with warfarin after mechanical valve replacement with $CHAD_2$ score <2. Finally, our patients were classified only on the basis of their $CHADS_2$, which has been shown to have a limited efficacy for the prediction of peripheral thromboembolism in AF[25] and to lead to misclassification of individual patient risk[16-17]. Consequently, its appropriateness and accurateness are still uncertain and this should be taken into account when examining our findings.

Conclusions

Real life prescription of oral anticoagulation before and after concomitant ablation surgery is marginally guided by the patient's stroke risk profile. This leads to over-treatment of low-risk patients and under-treatmentment of high-risk subjects. These findings stress the importance that antithrombotic treatment in patients undergoing AF surgery needs to be critically re-evaluated. However, our results must be confirmed by larger randomised studies.

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Table 1. Patient characteristics and demographics at inclusion

	All (n=115)	High-risk (n= 60)	Low-risk (n=55)	*p*
Age (years)	69.7± 8.0	71.9 ± 7.4	67.4 ± 8.7	.09
Male sex	68 (59%)	28 (47 %)	40 (73 %)	.01
Pre-operative atrial fibrillation:				.33
Paroxysmal AF	51 (44 %)	26 (43 %)	25 (45 %)	
> Permanent AF	62 (56 %)	32 (57%)	30 (55 %)	
Atrial flutter	2 (2 %)	2 (3 %)	-	
EHRA Score	4[3-4]	4[3-4]	4[3-4]	>.9
Total months of AF prior to surgery	83.9 ± 72.3	97.1 ± 105.7	69.7 ± 72.3	.33
LA diameter (mm)	49.9 ± 7.1	50.0 ± 7.1	49.8 ± 6.9	.87
LVEF (%)	52.3 ± 14.7	52.0 ± 15.0	52.7 ± 14.3	.78
Associated Procedures				.30
CABG	40 (35 %)	20 (33 %)	20 (36 %)	
Valve replacement	49 (43 %)	23 (38 %)	26 (47 %)	
CABG and valve replacement	26 (23 %)	17 (28 %)	9 (16 %)	

Data are presented as mean ± Standard Deviation and number (percentage). Abbreviations: AF: Atrial Fibrillation; EHRA: European Hear Rhythm Association; LA: Left Atrium; LVEF: Left Ventricular Ejection Fraction; CABG: Coronary Artery Bypass Grafting.

Table 2. Univariate and multivariate logistic regression analysis of factors associated with oral anticoagulant (OAC) use at inclusion.

Univariate Logistic Regression			
Covariates	***p***	**OR**	**95% CI**
Age >75 yrs. (Y/N)	.04	.9	.8-1.0
Sex (M/F)	.65	.8	.3-1.8
Type of AF>paroxysmal (Y/N)	.04	.9	.8-1.0
LA diameter (mm)	.01	1.1	1.0-1.2
LVEF (%)	.59	1.0	.9-1.0
Type of surgery*	.004	1.3	1.1-1.4
Additional ablation surgery (mm)	.11	.5	.2-1.1
Other indications for OAC than AF (Y/N)	.27	.5	.1-1.6
High-risk patient (Y/N)	.20	1.6	.7-3.4
Pre-operative $CHADS_2$ score	.34	1.1	.8-1.6
Duration of AF (months)	.86	1.0	.9-1.1
Multivariate Logistic Regression			
Covariates	***p***	**OR**	**95% CI**
Age >75 yrs. (Y/N)	.01	.9	.8-1.0
Type of AF>paroxysmal (Y/N)	.01	.9	.8-1.0
LA diameter (mm)	.30	1.0	.9-1.1
Type of surgery*	.14	.7	.6-.8

Abbreviations: OR: Odds Ratio; CI: Confidence Interval. AF: Atrial Fibrillation; LA: Left atrium; LVEF: Left Ventricular Ejection Fraction; $CHADS_2$: congestive heart failure, hypertension, age ≥75 years, diabetes, and prior stroke [or TIA or thromboembolism] score; Y/N: Yes/Not; M/F: Male Female; *Isolated CABG/Isolated Valve procedure/Combined

Table 3. Univariate and multivariate logistic regression analysis of factors associated with oral anticoagulant (OAC) use at 12-month follow-up.

Univariate Logistic Regression			
Covariates	***p***	**OR**	**95% CI**
Age >75 yrs. (Y/N)	.13	.9	.8 – 1.0
Sex (M/F)	.74	1.1	.4 – 3.3
Type of AF>paroxysmal (Y/N)	.02	.1	.9-1.0
LA diameter (mm)	.34	1.0	.9 – 1.1
LVEF (%)	.20	.9	.8– 1.0
Type of surgery*	.003	1.2	1.0-1.4
Rhythm outcome (NSR/AF)	.28	.8	.6-.9
High-risk patient (Y/N)	.34	1.3	1.2-1.6
Pre-operative $CHADS_2$ score	.39	.9	.6 – 1.0
Pre-operative OAC use (Y/N)	.002	.1	.04 – .5
Complications due to OAC use(Y/N)	.99	.03	.02-.06
Other indications for OAC use than AF (Y/N)	.009	.06	.01-.05
Multivariate Logistic Regression			
Covariates	***p***	**OR**	**95% CI**
Type of AF>paroxysmal (Y/N)	.12	.3	.1 – 1.3
Type of surgery*	.47	1.0	.9-1.1
Pre-operative OAC use (Y/N)	.007	.1	.03 - .5
Other indications for OAC use than AF (Y/N)	.01	.05	.01 - .06

Abbreviations: OR: Odds Ratio; CI: Confidence Interval. AF: Atrial Fibrillation; LA: Left atrium; LVEF: Left Ventricular Ejection Fraction; $CHADS_2$: congestive heart failure, hypertension, age ≥75 years, diabetes, and prior stroke [or TIA or thromboembolism] score. Y/N: Yes/Not; M/F: Male Female; NSR/AF: Normal Sinus Rhythm/Atrial Fibrillation; *Isolated CABG/Isolated Valve procedure/Combined

Figure 1A. Appropriateness of oral anticoagulation (OAC) prescription in atrial fibrillation patients at inclusion according to the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) Expert Consensus Statement and 2004 American College of Chest Physicians (ACCP) Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis.

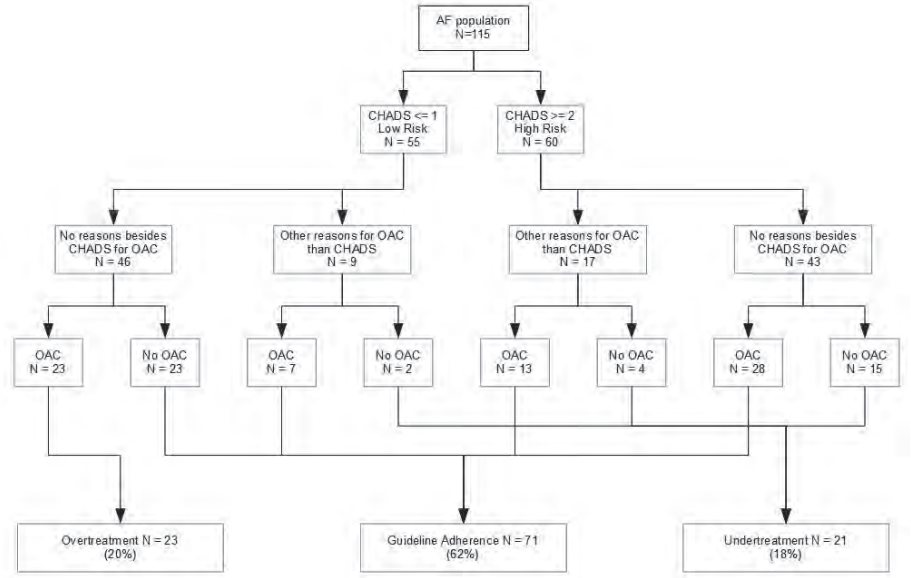


Figure 1B. Guideline adherence, over-treatment and under-treatment in the two groups at inclusion.
* $p<0.05$

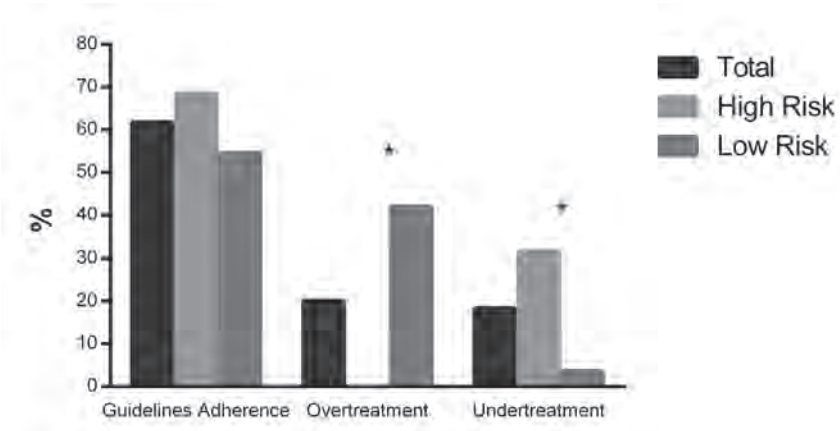


Figure 2A. Appropriateness of oral anticoagulation (OAC) prescription in atrial fibrillation patients at inclusion according to the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) Expert Consensus Statement and 2004 American College of Chest Physicians (ACCP) Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis.

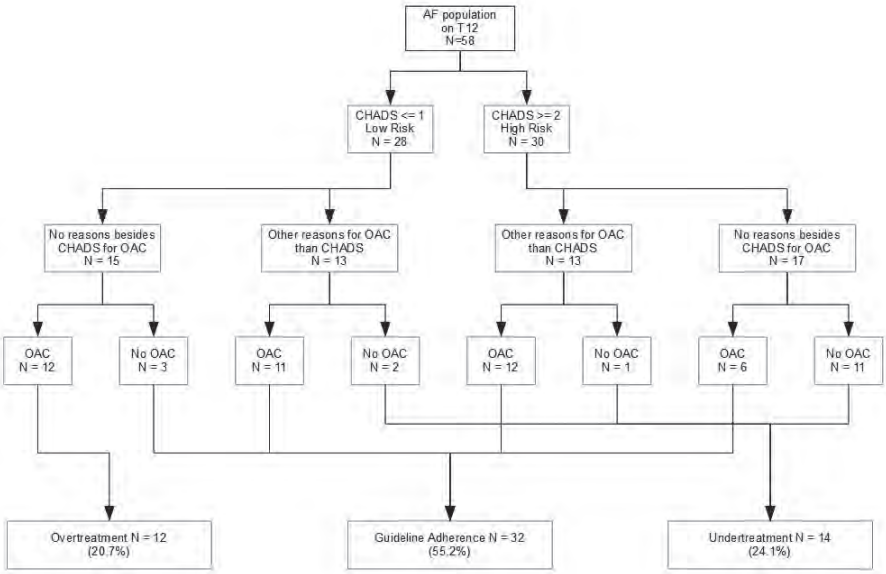


Figure 2B. Guideline adherence, over-treatment and under-treatment in the two groups of patients in atrial fibrillation at 12-month follow-up. *p <0.05

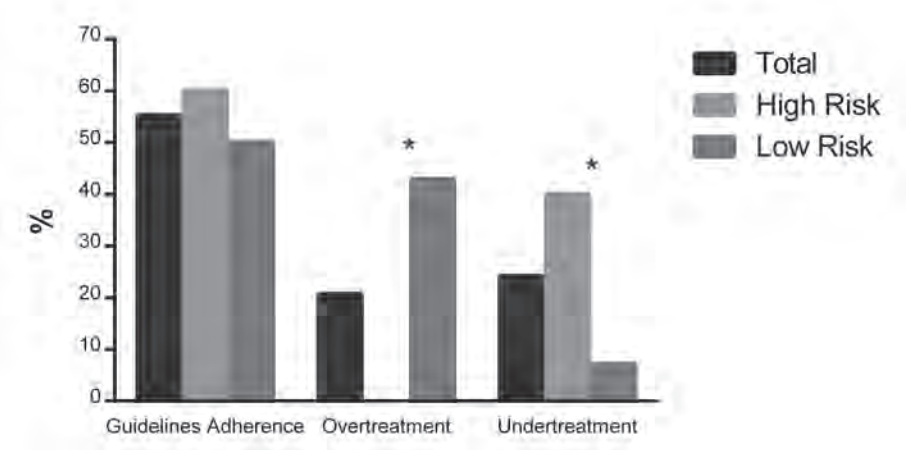


Figure 3A. Appropriateness of oral anticoagulation (OAC) prescription in atrial fibrillation patients at inclusion according to the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) Expert Consensus Statement and 2004 American College of Chest Physicians (ACCP) Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis.

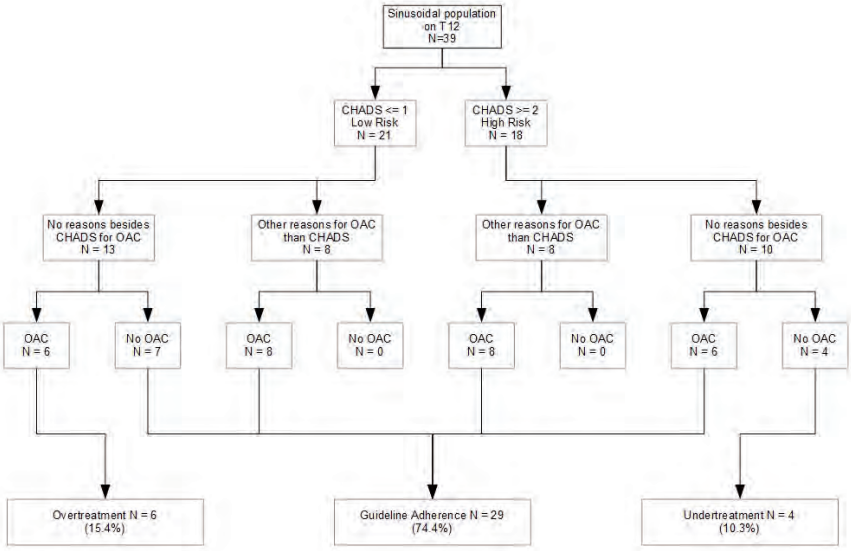
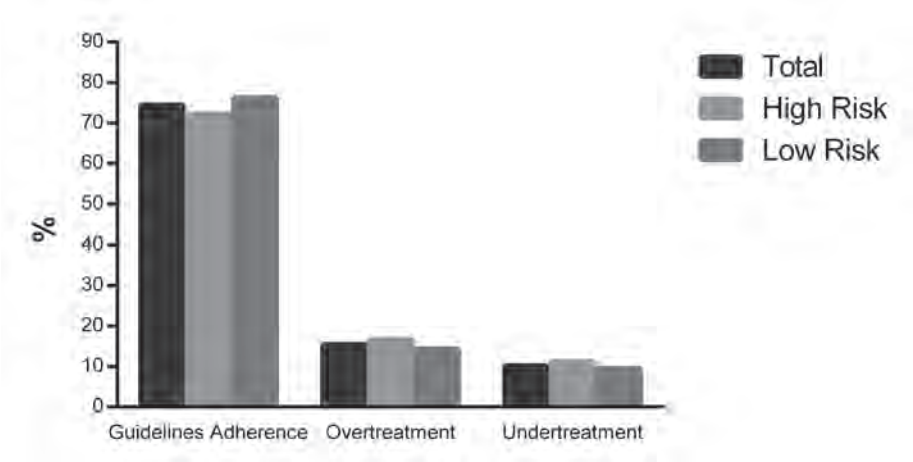


Figure 3B. Guideline adherence, over-treatment and under-treatment in the two groups of patients in sinus rhythm at 12-month follow-up.



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.

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Abstract

Objectives: To assess the impact of lesion set and surgical technique on late recurrence of atrial fibrillation (AF).

Background: The role of lesion sets on long-term outcome is poorly defined.

Methods: The patient population consisted of 685 subjects undergoing cardiac surgery for mitral valve disease as the primary indication and concomitant radiofrequency AF ablation between January 2003 and March 2014 at three Institutions (Careggi Hospital, Florence, Italy, University Hospital, Catanzaro, Italy, University Hospital, Maastricht, the Netherlands). One hundred and sixty-six patients underwent unipolar (24.2%), 371 (54.2%) bipolar and 371 (54.2%) combined the two energy sources. Median follow-up was 49.8 months (IQR27.0-86.5). A competing risk model was used to appropriately estimate the incidence of AF in patients remaining alive and surgical techniques were analysed for their association with AF recurrence employing a competing risk regression,

Results: The percentage of patients in normal sinus rhythm (NSR) and off antiarrhythmic drugs (AAD) was 62.3% (n=361). The cumulative incidence of AF recurrence was 39.7% (95% CI 33.3-46.8). Bipolar radiofrequency resulted to be the technique with the highest number of patients in NSR-off AAD at follow-up (p=0.001 vs. unipolar; p=0.001 vs. combined). A lower number of patients undergoing RA ablation showed a higher number of patients in NSR-off AAD (71.9 vs. 63.2, p=0.03). Competing risk regression revealed that use of unipolar RF (sub-hazard ratio [SHR] 7.41[5.22-12.43], p<0.001), combined unipolar/bipolar ablation (SHR 3.93 [2.89-5.87], p=0.003) and absence of right atrial ablation (SHR 2.79[1.27-6.48], p=0.011) were independently associated with high incidence of AF recurrence. Left atrial (LA) connecting lesions and mitral isthmus (MI) line were not significant

Conclusions: This study shows the favourable long-term results following surgical AF ablation during mitral surgery. Our experience suggests that a right-sided ablation should be routinely added. In addition, the use of a bipolar clamp improves electrophysiological long-term results. LA connecting lesions and MI lines resulted as nonsignificant. Further studies are necessary to confirm our findings.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting 1-2% of the general population[1, 2]. Although it may occur in the absence of structural cardiac disease, it is often associated with other heart disorders and is observed in approximately 40%-60% of patients undergoing mitral valve surgery influencing negatively short- and long-term outcomes[3-5]. In addition, it has been demonstrated that, whereas AF markedly reduces survival and increases the risk of stroke if left untreated, successful concomitant AF ablation improves outcomes in these patients[6]. The cut-and-sew Cox-Maze III procedure produced excellent results and was considered the gold standard for curing AF[7]. However, despite its clinical success, the procedure was rarely performed due to its complexity and technical challenges.

Technological innovations as well as a better understanding of pathological and electrophysiological mechanisms underlying AF have helped to simplify the original technique replacing the surgical incisions with transmural ablation lines created using various energy sources[8]. Nonetheless, the long-term efficacy of surgical ablation in a patient population undergoing mitral valve surgery has not yet been fully determined and the role of lesion sets on long-term outcome has been poorly defined[9].

This multicentre study analyses the long-term follow-up outcomes of patients undergoing concomitant radiofrequency (RF) ablation of AF during mitral valve surgery. Our main objective was to assess the impact of lesion set and surgical technique on late recurrence of AF.

Methods

Patient population

Ethical Committee approval was waived due to the retrospective analysis of the study according to National laws regulating observational retrospective studies (Italian law nr. 11960, released on 13/07/2004; Dutch law). However, written informed consent was obtained from all the patients prior to the surgical procedure.

The patient population consisted of 685 subjects undergoing cardiac surgery for mitral valve disease as the primary indication and concomitant radiofrequency

AF ablation between January 2003 and March 2014 at three Institutions (Careggi Hospital, Florence, Italy, University Hospital, Catanzaro, Italy, University Hospital, Maastricht, the Netherlands). Patients undergoing isolated or associated cryothermy (n=296), or ablation with other energy sources (n=156) were excluded from this study. Atrial fibrillation was defined according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society[10]. Clinical characteristics are shown in Table 1.

Surgical Technique

Indication to surgical ablation was given following the recent European Society of Cardiology Guidelines[11]. Surgical procedures were performed as previously described[12, 13]. Briefly, all patients underwent median sternotomy and cardiopulmonary bypass with bicaval cannulation. The heart was arrested and access to the left atrium (LA) was through a left atriotomy. The mitral valve procedure and associated surgery are shown in Table 2.

Ablation was performed before the principal surgical procedure. Choice of lesion set was at the surgeon's discretion. One hundred and sixty-six patients (24.2%) underwent irrigated unipolar RF ablation with the Cardioablate surgical pen (Medtronic, Minneapolis MN). Isolation of right pulmonary veins (RPVs) was carried out by a circular ablation line followed by encircling of left pulmonary veins (LPVs). An ablation line from the left atrial appendage (LAA) to the left superior pulmonary vein was created. Three further linear lesions were performed endocardially. The first two connected the two encircling lines to prevent any damage to the oesophagus: these lesions on the postero-superior atrial wal were kept cranial, opposite to the transverse sinus. The third line connected the LAA to the posterior mitral annulus and care was taken not to damage the circumflex artery.

Five hundred and nineteen patients (75.8%) underwent bipolar pulmonary veins (PV) RF ablation with the Cardioablate (n=371) clamp (Medtronic, Minneapolis, MN) or with the Atricure (n=148) clamp (Atricure, West Chester, OH). PV isolation was carried out by placing the jaws of the bipolar clamp around the LA cuff, adjacent to the pulmonary veins, to widely include both pulmonary vein antra[14]. LA connecting lesions were carried out with a bipolar clamp (1172 lines) and a unipolar pen (972 lines).

Care was taken not to injure the coronary arteries when the mitral annulus lesion was performed using a bipolar clamp: the coronary-free area of the AV groove

was marked epicardially by sticking a needle into the left atrial wall, behind the coronary sinus or marking this area with methylene blue. The projection of the needle marker on the mitral annulus was then identified through the atriotomy and an endo-epicardial ablation was performed with the bipolar device involving the atrial wall, the coronary sinus, up to the annulus[15]. A second ablation line was always made by slightly slipping the clamp backward, off the ventricular part of the groove, which, being thicker, might prevent proper contact of the jaws with the thin atrial wall[15].

Three hundred and eighteen patients (46.4%) underwent right atrial lesions and 279 (40.7%) ganglia ablation was performed as previously described[12].

The LAA was always excluded by external ligation (n=534, 77.9%) or internal stitching (n=151, 22.1%). Finally, 212 patients (30.9%) underwent electrical isolation of the LAA.

Postoperative management

An intravenous amiodarone bolus (150 mg), followed by continuous intravenous infusion at 1 mg/kg/h for 12 hours and then 0.5 mg/kg/h until patients tolerated oral intake, was routinely administered intraoperatively. Patients then received oral amiodarone (200 mg twice daily for 1 week, then 200 mg daily) until six months post surgery. Patients still in AF despite optimal medical therapy had at least one attempt of external cardioversion by biphasic direct current (DC)-shock.

Oral anticoagulation was given to maintain the international normalized ratio between 2.5 and 3.5 for the first six months in all patients and life-long in patients who received mechanical valves or who had AF persistence, or both.

Twelve-lead ECG recordings were performed on admission to the intensive therapy unit and daily thereafter until hospital discharge or whenever necessary. All patients underwent continuous ECG monitoring for the first 72 hours post-operatively.

Follow-up

Patients were seen in the outpatient clinic 3, 6 and 12 months after the surgical procedure and annually thereafter. Between visits, the referring physician followed patients on a regular basis and routine ECGs were obtained at each clinic visit regardless of symptoms. Event monitors were prescribed for patients who complained of palpitations or symptoms compatible with AF during follow-up.

Between visits, all patients were encouraged to seek 12-lead ECG documentation for any symptom suggestive of AF/atrial flutter recurrence and a physician routinely performed trans-telephonic monitoring of any symptoms and complications.
The follow-up evaluation consisted of a detailed history, physical examination and 24-h Holter monitoring. Any episode of symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial tachycardia, atrial flutter) after the initial 30-day blanking period that lasted 30 seconds or longer was considered as AF recurrence. Complete success was defined as the absence of AF recurrence off antiarrhythmic drugs (off-AAD), as recommended by the Heart Rhythm Society/ European Heart Rhythm Association / European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) Expert Consensus Document[16]. Median follow-up was 49.8 months (IQR27.0. -86.5) with 1,865 patient-years available for analysis.
Echocardiographic examinations were carried out pre-operatively, at discharge and during follow-up appointments following the American Society of Echocardiography recommendations[17].

Statistical analysis

Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data wae expressed as mean ± standard deviation whereas non-normally-distributed data were presented as median and interquartile range (IQR) and frequencies as proportions. Between-group differences were assessed by the unpaired t test, Mann-Whitney test, or Pearson χ^2 test.
The competing risk of death is important to take into account when examining the incidence of AF. Simple Kaplan-Meier curves essentially assume that the risk of AF is similar in patients remaining alive and those censored at the time of death. Therefore, we used a competing risk model to appropriately estimate the incidence of AF in patients remaining alive. The Cumulative Incidence was reported with the 95% confidence interval (CI) and the standard error (SE). Gray's test[18] was employed to compare the cumulative incidence functions.
Surgical techniques were analysed for their association with AF recurrence employing competing risk regression based on Fine and Gray's proportional hazards model[19] using sub-hazard ratios (SHRs) as measures of association. The model was adjusted for age, gender, pre-operative duration of AF, type of pre-operative AF, preoperative LA diameter and area. The assumption of proportional sub-distribution hazards was checked graphically using Schoenfeld-type residuals. A sub-group analysis was carried out on patients having LA linear ablation lines

either with an unipolar pen or bipolar clamp to test whether the type of sources affected AF recurrence.
IBM SPSS Statistics 22 (IBM Corp., Armonk, NY) and R version 3 (R Foundation for Statistical Computing, Vienna, Austria) software packages were used for calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

Results

Early results

There were no ablation-related complications. Six patients (0.8%) died during hospitalization. Causes of death were low cardiac output (n=2), septic shock (n=2), myocardial infarction (n=1) and cerebral haemorrhage (n=1). Hospital morbidity included reoperation for bleeding in twelve patients (1.7%), respiratory failure in nine patients (1.4%), renal failure in eight (1.1%), acute myocardial infarction in six patients (0.8%), low cardiac output in two patients (0.4%), deep sternal wound infection in two patients (0.4%) and transient ischemic attack in two patients (0.4%). Overall in-hospital morbidity was 5.9% (n=41). Median ICU and hospital length of stay were two (IQR 1-3) and six days (IQR 5-8), respectively.

Acute restoration of sinus rhythm

On aortic declamping 472 (68.9%) patients recovered normal sinus rhythm (NSR), 137 (20%) were in junctional rhythm, thus requiring temporary pacemaker stimulation, and 76 patients (11.1%) displayed AF. Twenty-four patients (5.0% of survivors) underwent successful direct-current (DC) cardioversion.
At hospital discharge 602 (88.6% of survivors) patients were in NSR, 65 (9.5% of survivors) were in AF and 12 (2.5% of survivors) required definitive pacemaker implantation. Indications for pacemaker implantation included sinus node dysfunction (7 patients), complete heart block (4 patients) and bradycardia with second-degree heart block.

Follow-up

Six hundred and two (87.8%) patients survived whereas 77 (11.2%) died during the follow-up: 47 (61.1%) because of cardiac causes (four arrhythmia-related deaths) and 30 (38.9%) because of non-cardiac cause or unknown. Ten-year

freedom from death (Figure 1) was 75.5 % (SE 3.5%). One hundred and twenty-one patients experienced 168 (27.9%) hospital readmissions: 54 (32.2%) for non-cardiac-related events and 114 (67.8%) for cardiac-related events. Among the latter 44 (38.5%) readmissions were rhythm-related. Cerebrovascular events were reported in six patients (0.9%) during follow-up: four of them had complete resolution of neurological deficits, one remained with a slight right paresis and one died.

Rhythm at follow-up and predictors of AF recurrence

During follow-up 11 patients (1.8%) underwent permanent pacemaker implantation, all for sinus node dysfunction. Excluding deaths and patients remaining paced at late follow-up, 579 were available for rhythm evaluation (See appendix 1).

At the last control 458 patients (79.2 %) were in NSR after a single procedure whereas 121 (20.8%) were not in NSR (71 AF, 6 atrial tachycardia, 10 atrial flutter). Patients who were not in NSR were treated as followed: 27 underwent transcatheter ablations, which were successful in 17 (62.9%), 17 had DC cardioversion (10 successful, 58.8%) and 77 underwent pharmacological cardioversion (success, 59.7 %, n=46). In all patients who were still not in NSR, pharmacological rate control therapy was instituted. The percentage of patients in NSR and off-AAD was 62.3% (n=361). The cumulative incidence of AF recurrence at follow-up was estimated to be 39.7% (95% CI 33.3-46.8; SE 3.3%). Table 3 shows the rhythm at follow-up by surgical procedure. Bipolar radiofrequency resulted to be the technique with the highest number of patients in NSR-off AAD at follow-up (p=0.001 v.s unipolar; p=0.001 vs. combined). The AF-recurrence cumulative incidence (Figure 2A) was significantly lower compared to either unipolar or bipolar-unipolar ablation. Furthermore, there was no difference in AF recurrence in patients who did or did not receive a roof line, an inferior line or a LAA to LPV line and cumulative incidences of AF recurrence were comparable (Figure 2B-D).

Similarly, a comparable number of patients having a mitral isthmus line were in NSR off-ADD with cumulative incidence of AF recurrence not significantly different between patients who had or did not have a connecting line to the mitral annulus (Figure 3A).

In contrast, a lower number of patients undergoing RA ablation showed a higher number of patients in NSR-off AAD with a cumulative incidence of AF recurrence

lower compared to patients undergoing only LA ablation (Figure 3B).
In contrast, LAA isolation, the choice of LAA exclusion or ligation showed a comparable number of patients in NSR at follow-up and the cumulative incidences were not significantly different (Figure 3C-D).
Similarly to GP ablation, the ablation system employed, the type of procedure on the mitral valve and the performance of concomitant cardiac procedures did not show a significantly different number of patients off-AF and off-AAD and cumulative incidences were similar (Figure 4A-D).
Multivariate analysis using competing risk regression (Table 4) revealed that use of unipolar RF (SHR 7.41[5.22-12.43], $p<0.001$), combined unipolar/bipolar ablation (SHR 3.93 [2.89-5.87], $p=0.003$) and absence of right atrial ablation (SHR 2.79[1.27-6.48], $p=0.011$) were independently associated with high incidence of AF recurrence.
The sub-group analyses showed that roof, inferior and LAA to PV lines performed with the bipolar clamp gained better long–term results compared with those carried out using the unipolar pen with a higher percentage of patients in NSR-off AAD (roof line, 78.6% vs. 46.7%, $p<0.001$; inferior line, 75.6 % vs. 50.2%, $p<0.001$; LAA to LPV line, 77.1% vs. 45.1%, $p<0.001$) and lower cumulative incidences (Figure 5A-C).
In contrast, the MI line performed with unipolar (60.1%), bipolar (62.2%) or made with a bipolar clamp and completed by an unipolar pen (66.6%) did not show statistical significance in the number of patients in NSR-off AAD at latest follow-up (unipolar vs. bipolar, $p=0.7$; unipolar versus combined, $p=0.06$; bipolar vs. combined 0.08) with comparable cumulative incidences (Figure 5D).

Echocardiographic results by Heart Rhythm

Echocardiographic data of patients in NSR and with AF recurrence are reported in Table 5. LA diameter ($p<0.001$), LA area ($p<0.001$), right atrium area ($p=0.001$) and estimated systolic pulmonary arterial pressure ($p<0.001$) resulted significantly lower in patients in NSR at follow-up.

Discussion

Most patients with AF have underlying cardiovascular disease and are candidates for open-heart surgery. In the presence of AF, the likelihood of NSR recovery after a conventional heart operation alone ranges from 4.5 to 36% and is even more unlikely in patients with left atriomegaly[20]. The first-line use of antiarrhythmic drugs to control AF resulted has not been an effective strategy due to reports of limited efficacy, poor patient compliance and contraindications[21]. As such, AF treatment has primarily been focused on treating the underlying rhythm pathology[22] and the Cox Maze III procedure resulted to be the most effective surgical technique for treating AF and its adverse consequences of altered haemodynamics, and increased thromboembolic risk[23]. Nonetheless, due to its high complexity, many surgeons are reluctant to perform the full cut and sew Maze technique. Therefore, the newest iteration is a Maze operation using surgical ablation rather than incisions replaced by lesions. It is performed using different energy source and ablation technologies and this version is sometimes called Cox-Maze IV.[8]

However, as far as we know, few studies in the literature actually address the long-term efficacy of the Cox-Maze concomitant mitral valve surgery and many previous reports are biased by the small number of patients, short follow-up and heterogeneity of patient cohorts[9]. Due to such a paucity of results, the long-term effectiveness of surgical ablation in mitral valve surgery is far for being fully established and the choice of lesion set remains still controversial.

In this multicentre study we analysed the long-term follow-up outcomes of patients undergoing concomitant RF ablation of AF during mitral valve surgery. The percentage of patients in NSR and off-AAD, in our experience, was 62.3% and cumulative incidence of AF recurrence was estimated to be 39.7%.

These figures are close to results reported by studies on surgical ablation with shorter follow-up intervals[8, 9] and they are also similar[21] or compare favourably[24] to data published on long-term results of Cox-Maze III. However, other authors[25] demonstrated that the cut and sew technique is still superior to surgery employing alternate energy sources.

Nonetheless, we do believe that the Maze III is still the most effective technique for curing AF but, requiring well-experienced and skilled surgeons, it is a ''niche'' surgery for the chosen few among the surgeons and patients. Notwithstanding, it represents a ''reference standard''[24] serving as a reliable comparator group as we move toward new technologies and approaches.[24]

The main objective of our study was to assess the impact of lesion set and surgical technique on long-term recurrence of AF.

Data from transcatheter ablation[26, 27] and AF surgery[14, 28] have demonstrated that clinical outcome is strongly influenced by completeness, transmurality and continuity 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 radiofrequency clamps are reliable and effective in creating transmural scars[29, 30]. Nonetheless, because of the clamping nature and the deep tissue penetration of bipolar radiofrequency, unipolar sources have been widely used to perform endocardial connecting lines during mitral surgery despite well-known limitations of this source such as high tissue temperature and no predictable transmurality[31]. In addition, apart from the uncertainty regarding the transmurality of the lesions, 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. Due to these limitations of unipolar energy sources, there is an apparent trend towards the implementation of the Cox-Maze IV through application of the bipolar RF clamp on a pattern of LA lesions[32].

Our findings confirm the superiority of the bipolar source. Indeed, the complete bipolar RF lesion setturned out to be the technique with the highest number of patients in NSR-off 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 (SHR 3.93, $p=0.003$) were independent predictors of AF recurrence.

The importance of completeness of the lesion set has been demonstrated by Gaita et al[33] 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[14] 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 did or did not receive a roof line, an inferior line or a LAA to LPV line and the absence of these lesions was not associated with a higher incidence of AF recurrence at multivariate competing risk analysis, independently of the type of preoperative AF. However our results could be explained by the higher number of patients in our series receiving a connecting

line with a unipolar RF device applied from the endocardial surface, which could have had significantly influenced these results. This is also confirmed by the sub-analysis carried out on patients having LA linear connecting lines either with an unipolar pen or bipolar clamp, which showed that a higher percentage of patients having LA lines performed with the bipolar clamp were in NSR with 10-year cumulative incidences significantly lower compared to those who had additional LA lesions made with the unipolar pen.

Interestingly, also the MI ablation was not significant at competing risk regression (p=0.114) and a comparable number of patients having or not a MI line were in NSR off-ADD (63.0% vs. 62.0%, p=0.7) with non-stasticically significant cumulative incidences of AF recurrence (p=0.11).

Retrospective work by Gillinov et al has shown the significance of the left atrial isthmus lesion in patients with permanent AF[34] and Benussi et al[35] have confirmed this.

The mitral isthmus refers to the atrial myocardium between the MV annulus and the left-sided PVs[37]. Anatomically, since this isthmus extends into the LIPV, the width of the isthmus will depend on the extent of the myocardial sleeves associated with the vein. The wall of the isthmus ranges from 2-8 mm in myocardial thickness[38] and its endocardial surface may contain pits and troughs where the atrial wall becomes exceptionally thin[36]. 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 not easy 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 we tried to achieve a complete circumferential ablation of the coronary sinus by always making a second ablation line as suggested by Benussi et al[15]. Great attention was paid to individual coronary anatomy when performing a MI line with the bipolar clamp,

especially if patients had a left-dominant coronary system. A tangible marker (a needle or methylene blue) was employed to identify the coronary-free area of the atrio-ventricular groove.

Hence, although transmurality has been reported by an experimental study achieved with bipolar radiofrequency in this area[39], it was not confirmed by our findings. Furthermore, the use of a second unipolar device to complete the mitral line gained slightly better results but did not significantly improve rhythm outcome. For these reasons many surgeons prefer to complete a MI ablation with a cryoprobe because cryoablation should better preserve the fibrous skeleton of the heart, making it ideal for ablation near valvular tissue[40].

Further studies need to assess the effectiveness and safety of a MI lesion performed with a bipolar clamp and to make a comparison with results obtained using a combination of bipolar RF and cryothermal energy. This will be the object of an ongoing study.

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[42], who documented focal ectopies arising from the pulmonary veins, and of Sueda et al.[43] 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[44] observed, in explanted hearts, some striated muscle cells around the coronary sinus connecting the inferior right atrium. Furthermore, Lin et al[45] showed some specific right atrial "trigger zones" where paroxysmal AF may be induced and that the ablation of these sites may eliminate atrial fibrillation and recurrent atrial flutter or tachycardia.

Hereafter, these anatomic and electrophysiological features may be the basis for the inconsistent results reported for left atrial isolation and Cox- maze operations[46] 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 Cox-Maze procedure is difficult to define, as biatrial versus left atrial surgical ablation has never been compared in a randomised clinical trial. Therefore it is still matter of debate. Indeed, whereas some studies found no significant difference between left-side and biatrial ablation[47] or achieved comparable results to those of Maze III with the simple isolation of pulmonary veins[48], other studies confirmed the superiority of the biatrial approach compared to isolated left atrial ablation[12, 49].

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[12] 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[50]. This conclusion came out in our results: indeed, competing risk regression, corrected by pre-operative LA diameter and area, showed that 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. The 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 the right atrial appendage and terminal crest. Finally, some authors have demonstrated the advantage of autonomic denervation through ablation of the GP since autonomic ganglia within these plexi have been found to play a role in the initiation and maintenance of AF[51]. Nonetheless the long-term efficacy of ganglion ablation has been questioned[52].

Either way, autonomic ganglia adjacent to PVs are eliminated by PV-directed ablation procedures and there is substantial evidence for a key role of the tissue around PVs in the generation of vagally mediated arrhythmias[53]. However, it remains still difficult to clearly establish the real influence on long-term rhythm outcome of ablation of GP outside the pulmonary area, which is not systematically targeted during LA ablation.

In our experience, patients with or without GP ablation show similar percentages of NSR-off-AAD and 10-year cumulative incidence was not statistically significant (p=0.19).

Finally, the absence of GP ablation was not predictive of LA late recurrence at multivariate analysis (p=0.68). Our findings are in contrast with other authors[54] who reported improved early results with GP ablation added to the Maze procedure during mitral surgery. It has been demonstrated that AF inducibility is eliminated immediately after GP ablation, but this denervation effect is reversible due to reinnervation[55, 56] which could partially explain such a difference in the results in this series after a short follow-up period (16.7±0.95 months). Nonetheless, our findings must be interpreted in the light of the limitation of a small percentage of patients with GP ablation available at follow-up (40.9%). Hence, further larger randomised studies are warranted to reconfirm our observations.

Study limitations

The present paper has certain limitations that need to be addressed. First of all, the retrospective design of the study, its multicentre nature and the lack of randomisation do not provide a definitive causative link between type of surgical ablation technique associated with mitral valve procedures and long-term stable SR. However this study presented a large patient population with, to the best of our knowledge, one of the longest follow-up periods published in scientific literature.

Another drawback of our study is the heterogeneity of the patient population although this limitation is shared with other studies examining the outcomes of surgical ablation of AF. However, in our study the patient population is less varied, since patients undergoing isolated or associated cryothermy or ablation with other energy sources, were excluded.

In addition, continuous monitoring would have allowed a higher degree of confidence in detecting the real incidence of SR recovery and occurrence of transient attacks or arrhythmias and we acknowledge that we may have missed some patients with asymptomatic AF. This is an important limitation of our study. Nonetheless, all patients met the minimum criteria for follow-up, which is a 24-hour Holter monitoring.

Moreover, different ablation techniques were employed at the surgeon's discretion and this might have affected our results. Furthermore, the most single important variable is the surgeon's experience and technical proficiency with the different procedures: we did not account for the surgeon performing the ablation procedure.

Finally we did not compare monopole and bipolar sources employed for making right ablation lines. We are collecting data for another study to explore this aspect in more depth.

Conclusions

This study shows the favourable long-term results following surgical AF ablation during mitral surgery. Our experience suggests that a right-sided ablation should be routinely added. In addition, the use of a bipolar clamp improves electrophysiological long-term results. LA connecting lesions and MI lines did not result to be significant. Further studies are necessary to confirm our findings.

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Table 1. Baseline characteristics (n=685).

Age	65.0±9.3
Sex (M/F)	454/231 (66.2/33.8)
Diabetes	163 (23.7)
Hypertension	450 (65.6)
COPD	245 (35.7)
CVD	97 (14.1)
Redo Cardiac Surgery	32 (4.6)
NYHA	2.9 [2.1-3.4]
Additive EuroScore	6.3 [4.9-7.5]
$CHADS_2$ Score	1.6 [1.1-2.1]
Type of AF	
Long-Standing Persistent	267 (39.0)
Persistent	377 (55.0)
Paroxysmal	41 (6.0)
Duration of AF (Months)	35.6±40.3
Previous ECV	247 (36.0)
Mitral Valve Disease	
Degenerative	249 (36.3)
Rheumatic	150 (21.9)
Ischemic	161 (23.5)
Functional	89 (13.0)
Other/Unknown	36 (5.3)
Associated Cardiac Disease	
CAD	103 (15.0)
AVD	171 (24.9)
TVD	289 (42.1)
Other	30 (4.3)
LVEF (%)	49.7±10.4
LA diameter (mm)	52.9±7.8
LA area (cm^2)	33.4±7.5
RA area (cm^2)	21.9±6.5
Systolic PAP (mmHg)	45.0±11.8
LVEDD (mm)	51.0±9.1
LVESD (mm)	39.4±10.0

Values are shown as mean ± standard deviation for normally distributed data, median [Interquartile range] for not normally distributed data or number (percentage) for categorical data.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CVD, Cerebrovascular disease; NYHA, New York Heart Association; CHADS, Congestive Heart Failure, Hypertension, Age, Diabetes, prior Stroke; AF, Atrial Fibrillation; ECV, Electrical Cardioversion; CAD, Coronary Artery Disease; AVD, Aortic Valve Disease; TVD, Tricuspid Valve Disease; LVEF, Left Ventricular Ejection Fraction; LA, Left Atrium; RA, Right Atrium; PAP, Pulmonary Artery Pressure; LVEDD, Left Ventricular End-Diastolic Diameter; LVESD, Left Ventricular End-Systolic Diameter.

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

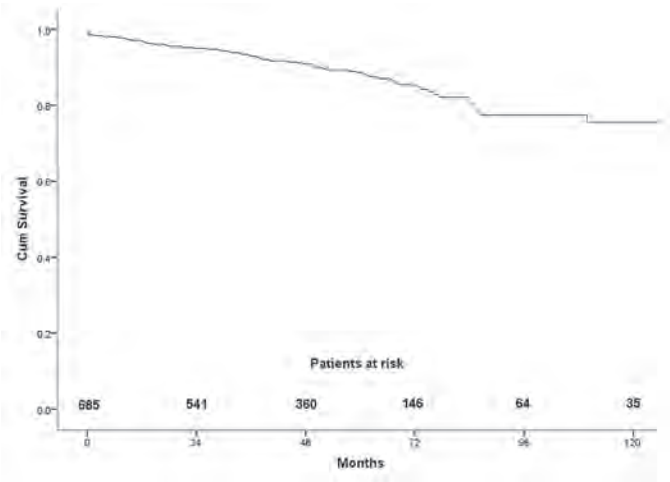


Figure 2. A-D
Ten-year cumulative cncidence of recurrent atrial fibrillation by type of radiofrequency ablation and left atrial lesion lines. The cumulative incidence was reported with the 95% confidence interval (parentheses) and the standard error (SE).
Abbreviations: RF, Radiofrequency; AF, Atrial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

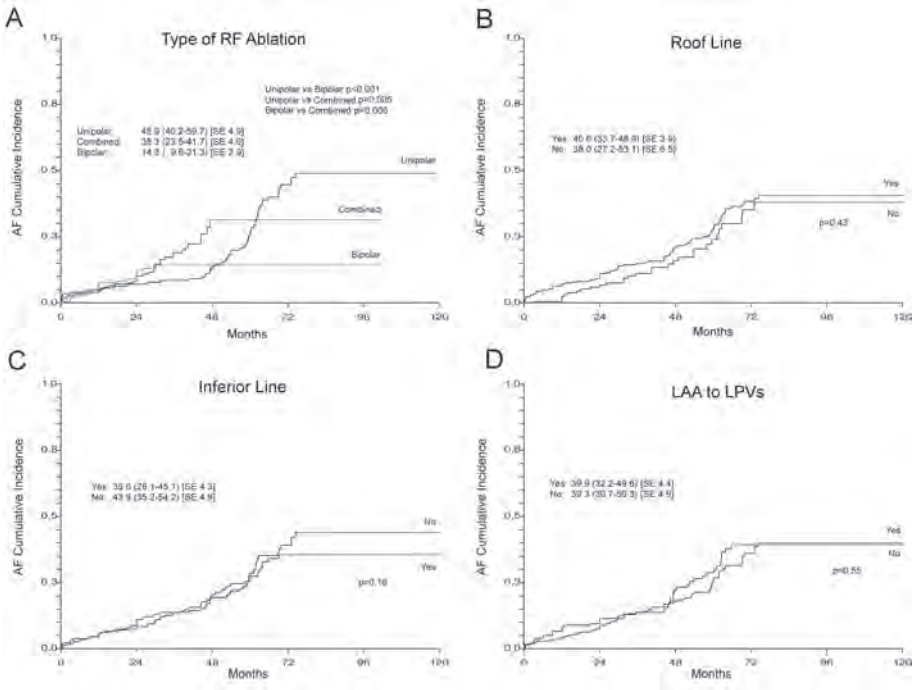


Figure 3.A-D
Ten-year cumulative incidence of recurrent atrial fibrillation by performance of mitral isthmus line, right atrial ablation, left atrial appendage isolation and left atrial appendage ligation/stitching. The cumulative incidence was reported with the 95% confidence interval (parentheses)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

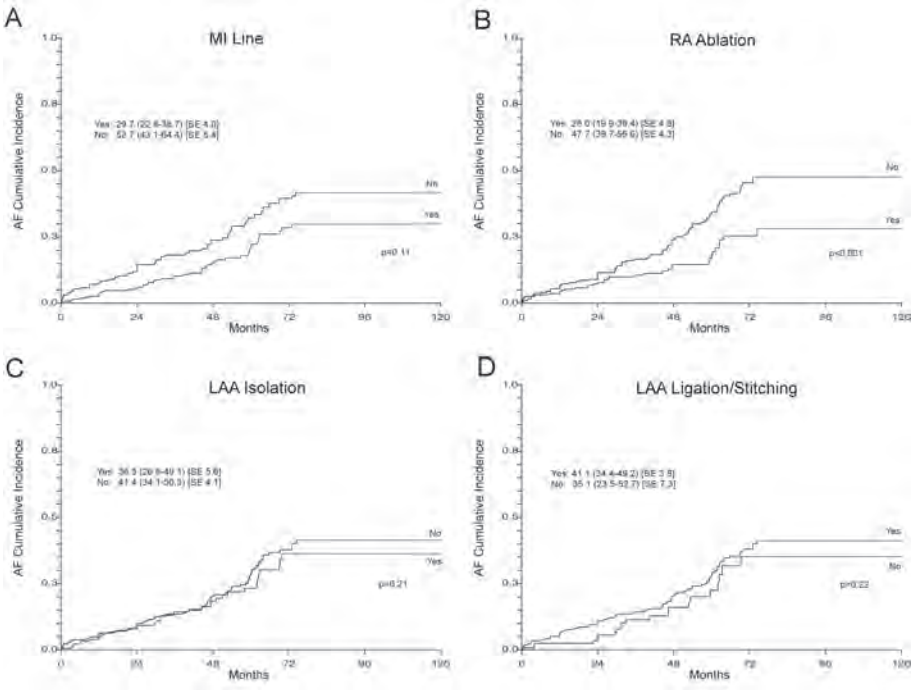


Figure 4.A-D
Ten-year cumulative incidence of recurrent atrial fibrillation by ganglionated plexi ablation, type of ablation system employed, type of main procedure performed on mitral valve and performance of concomitant heart procedures. The cumulative incidence was reported with the 95% confidence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

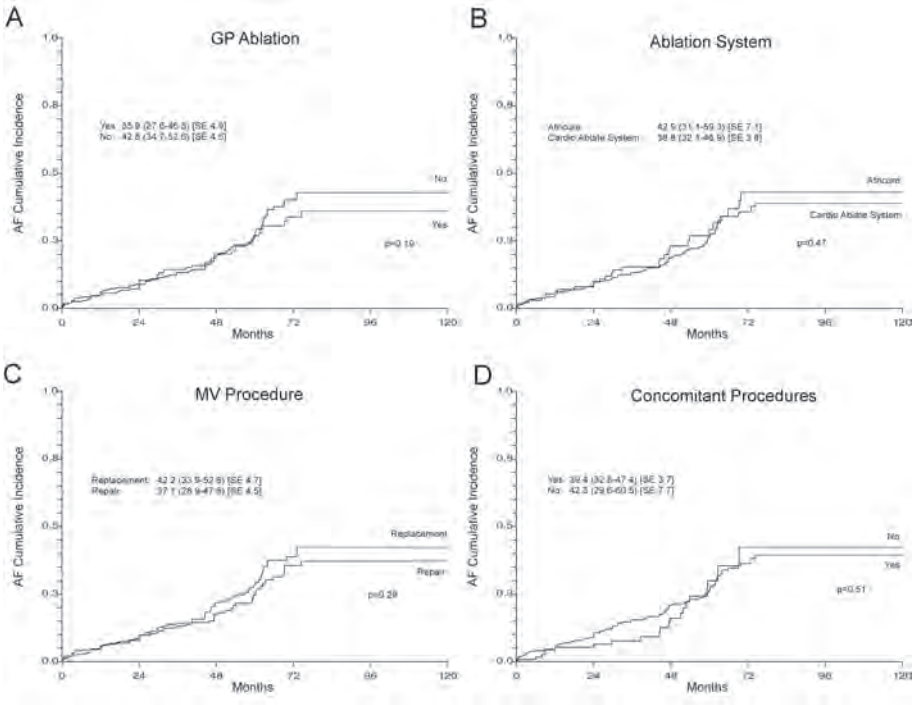
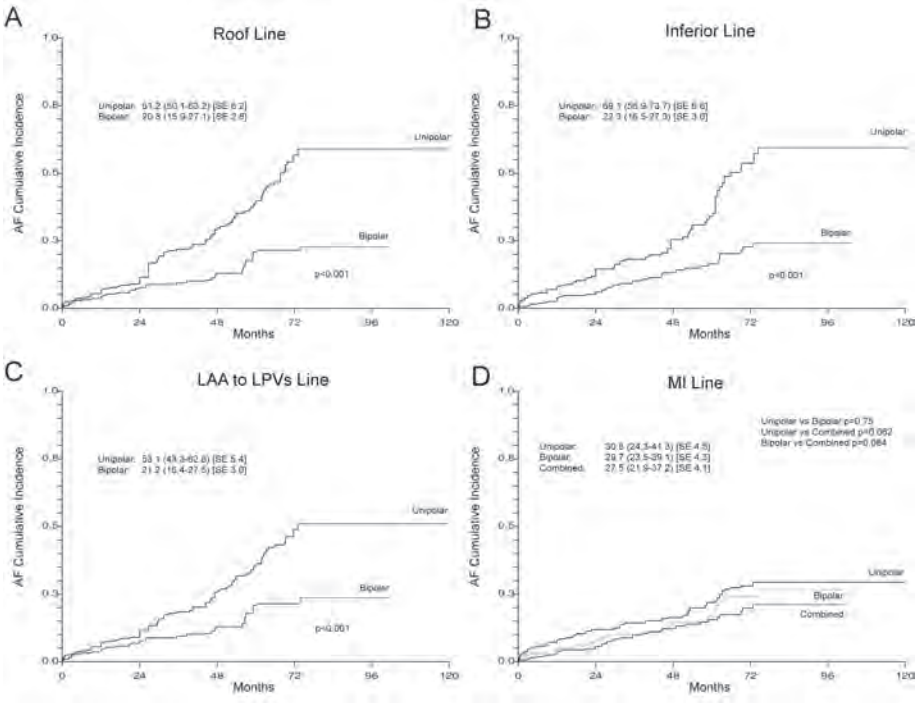


Figure 5.A-D
Ten-year cumulative incidence of recurrent atrial fibrillation by RF source employed for left atrial linear lesions. The cumulative incidence was reported with the 95% confidence interval (parentheses) and the standard error (SE).
Abbreviations: LAA, Left Atrial Appendage; LPVs, Left Pulmonary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

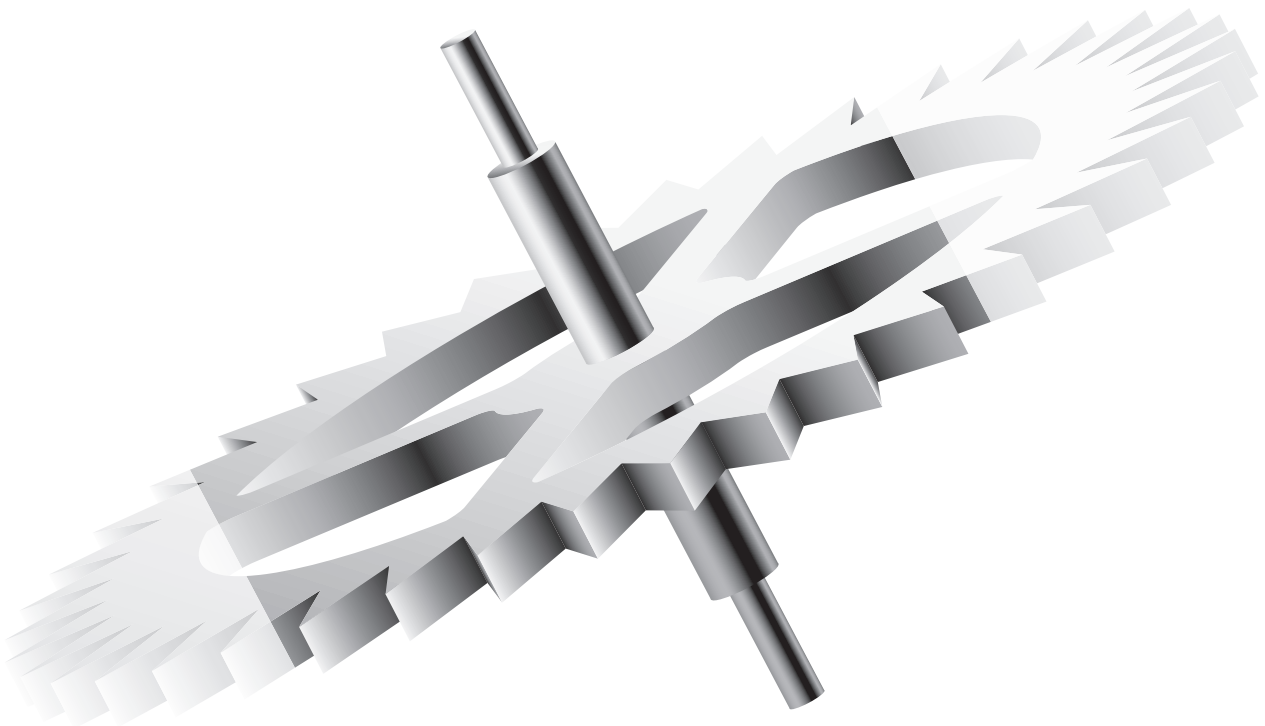


Appendix 1

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

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Abstract

The hybrid approach combines an epicardial ablation with a percutaneous endocardial ablation in a single-step or sequential procedure. This study provides an overview of the hybrid procedure for the treatment of stand-alone atrial fibrillation (AF). Papers selected for this review were identified on PUBMED and the final selection included nine studies. The total number of patients was 335 (range 15-101). Mean age ranged from 55.2 to 62.9 years. The hybrid approach achieved satisfactory results, with AF-antiarrhythmic drug-free success rates higher than isolated procedures. In particular, the bilateral approach with a bipolar device showed a high success rate independently of the AF type and seems to be the better choice for the hybrid procedure. Despite good preliminary results, large, multicentre trials of hybrid AF ablation that target a population of patients with long-standing-persistent disease are necessary to establish whether this approach may represent a gold-standard treatment for AF in the future.

Introduction

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia and it is associated with increased morbidity and mortality[1]. Despite often being inadequate, medical treatment is still considered the "first-step" approach[2, 3]. Nevertheless, non-pharmacological strategies, surgical or interventional, have gained an increasing interest among both cardiac surgeons and electrophysiologists[4-9].
Because of suboptimal results of catheter ablation and surgery[10, 11], a so-called hybrid approach has recently been introduced. This procedure combines an epicardial and endocardial ablation, either staged or as a single procedure, through a partnership between the surgeon and the electrophysiologist (EP).
Data related to this approach are still scarce and it has not yet been established whether the hybrid approach will produce more favourable outcomes regardless of the type of AF. Therefore, we carried out a systematic literature overview to explore the safety and effectiveness of hybrid surgical ablation for the treatment of stand-alone AF.

Review criteria

Studies selected for this review were identified on PUBMED (last search 1 April 2013) using the following search terms "hybrid procedure AND atrial fibrillation", "hybrid approach AND atrial fibrillation" and "endocardial-epicardial ablation AND atrial fibrillation". Exclusion criteria were animal studies, reviews, case reports, concomitant surgery, not stand-alone (lone) atrial fibrillation, not hybrid, not performed on the beating heart, not English, no full-text availability. These criteria were chosen to make a selection based on title and/or abstract. Inclusion criteria were studies with >10 patients, follow-up of >3 months, minimally invasive beating heart surgery and transcatheter ablation either staged or as a single procedure for the treatment lone atrial fibrillation (LAF). The search returned a total of 111 papers. A total of 14 articles were selected. Two met inclusion criteria but were excluded because they had <10 patients[12, 13]. Two were excluded because they might have reported on overlapping patients[14, 15]. Finally one was excluded because it reported a joint surgical-electrophysiological approach only for confirmation of conduction block across pulmonary vein ablation during total thoracoscopic surgery[16]. The final selection included nine studies.

Baseline characteristics

Baseline characteristics of the selected studies are presented in Table 1. Studies were published between 2011 and 2013; all studies were observational in nature and none was prospective-randomised. Furthermore, all studies were performed in a single centre. The total number of patients was 335 (range 15-101). Mean age ranged from 55.2 to 62.9 years.

Six papers[17-19, 21, 22, 24] reported AF duration in years, which ranged from five to eight years. Three papers[20, 23, 25] reported AF duration in months, which ranged from 67 to 83 months.

One hundred and fourteen patients (34%) had undergone one or more previous percutaneous catheter ablation (PCA). A total of 69 patients (20.6%) with paroxysmal AF (pAF) underwent a hybrid procedure, 104 (31.0%) had persistent AF, and 162 (48.4%) long-standing-persistent (LSP) AF. One paper[25] reported only patients with LSP-AF.

Surgery

Mahapatra et al employed [17]a sequential approach combining minimally invasive surgical ablation followed three to five days later with planned catheter ablation. In the studies from Muneretto et al[23] and Bisleri and co-workers[25] all patients underwent a staged catheter procedure 30-45 days after the surgical ablation. The others authors describe a "one step" approach with the catheter ablation following surgical ablation during the same procedure.

Three studies[21, 23, 25] employed a right thoracic monolateral approach, four a bilateral thoracic approach[17-21], one a subxiphoid approach[24] and one a laparoscopic approach[22].

Four authors[17-20] utilized bipolar RF whereas five[21-25] monopolar RF as ablation source. Six groups carried out ganglionated plexi (GP) ablation in 162 patients (48.3%) and one hundred and two patients (30.4%) underwent excision/ligation of the left atrial appendage (LAA). Nonetheless, only a few groups clearly stated the indications for LAA removal: La Meir et al[19] performed a LAA stapler/clip in patients with $CHADS_2$ score ≥ 1 (see supplemental material), in the presence of rapid firing coming from the LAA and when the procedure was deemed safe.

Pulmonary vein isolation (PVI) was performed in all cases. Additional left atrial lesions (Figure 1) were reported in all studies. They consisted of a roof line connecting superior pulmonary veins[17-20, 22-25], an inferior line connecting inferior pulmonary veins[18-25], a connecting line between the superior line and the left

fibrous trigone[17], a connecting line from the superior pulmonary vein and the LAA[17, 19-21] and a line from the right inferior pulmonary vein to the coronary sinus (CS)[24].

Additional right lesions were reported in four papers and lesions consisted of a superior vena cava (SVC) and inferior vena cava (IVC) circumferential lesion[17,19] and a SVC to IVC line[19]. La Meir et al[19] specified that SVC to IVC and SVC circumferential lesions were added when patients with persistent and long-standing persistent AF had right atrial volume ≥ 58 mL whereas IVC circumferential isolation was only performed in patients in which it was feasible to extend the SVC-IVC line to the IVC in order to prevent an incomplete linear lesion.

Only few papers clearly described the endocardial ablation lines[23, 25]. Mahapatra and coworkers[17], La Meir et al[19, 21], Pison et al[20] and Gehi et al[24] described a cavo-tricuspid isthmus line performed in 105 patients (31.3%). A mitral isthmus line was carried out in 94 (28%) patients[19, 20, and 24]. Finally, only two papers[17, 24] reported a coronary sinus line, which was carried out in 88 (26.2%) patients.

Follow-up, rhythm monitoring, anticoagulation and antiarrhythmic therapy

Three hundred and fifteen patients (94 %) reached the maximum follow-up, which was 100% complete in six papers[17, 19, 21, 23-25]. In the others[18, 20, 22] the follow-up completeness was 66.6%, 70.9% and 92.3% (Table 3). The longest follow-up was 38 months[23] and, however, all studies reported a follow-up of at least 12 months, which is the minimum, recommended to evaluate procedural efficacy[26]. All studies employed at least one method of long-term monitoring. Four studies[17, 18,22,24] (44.4%) utilized 24-hour Holter monitoring (HM), three (33.3%) 7-day HM[19-21], two (22.2%) an insertable cardiac monitor[23, 25] and one (11.1%) a continuous auto-triggered monitor associated with another long-term monitoring[17].

Six papers clearly described the adopted protocol for AADs during the follow-up: AADs were withdrawn in patients in sinus rhythm (SR) after three months in five studies[17-19, 21,23] and at six months in one study[20]. In addition, in two studies[22, 24] AADs were withdrawn at the discretion of the referring cardiologist whereas the AAD protocol was not specified in one paper[25].

Similarly, a standard protocol was not followed for oral anticoagulation (OAC) therapy: it was discontinued at three months if $CHADS_2$ score was ≥ 2 by Mahapatra et al[17], La Meir et al[19] and Zembala et al[22]. In another three papers[18, 20,23] OAC was discontinued after three months if patients were in SR. Finally in two

studies[22, 24] OAC was withdrawn at the discretion of the referring cardiologist whereas the OAC protocol was not specified in one paper[25].
Patients taking AADs at latest follow-up were shown or could be calculated in six of nine (66.6%) studies. The range was from 6.6% to 37% (mean 20.2 ± 9.2%). Patients still under OAC therapy at follow-up could be obtained from four of nine (44.4%) studies. The range was from 11.1 % to 48.3 % (mean 34.1 ± 17.8%).

Results

All papers defined the primary efficacy endpoint of surgery as suggested by current guidelines [freedom from AF, off AADs at one year (Table 4)] [26]. Six studies[18-21,23,25] reported ≥ 12-month AAD-free success rate. Two studies[22, 24] reported outcomes as freedom from AF and AAD at 6 months or 12 months. The success rate ranged from 85.7 % to 92 % in papers employing bipolar RF and from 36.8 % to 88.9% in those utilizing monopolar RF.
Zembala et al[22] reported results at 3-months follow-up (after blanking period) 6-, 12- and 24-month follow-up. The rates of patients in SR were 63.2% (n=19), 72.2% (n=18), 80% (n=10) and 100% (n=6) and freedom from AAD rates were 68%, 66.5%, 90% and 100% at 3, 6, 12 and 24 months, respectively[22].
With specific reference to the different type of AF, only four papers reported AAD-free success rate by type of AF[18-21], which ranged from 60% to 91.6% in pAF, from 50% to 77.7% in persistent AF and from 20% to 100% in LSP. In addition, four papers[17, 21-23] reported freedom from AF on AAD, which ranged from 63.1% to 93.3%.
Mahapatra et al[17] showed that the sequential approach compared favourably to a control group of patients who underwent repeat catheter ablation in terms of freedom from any atrial arrhythmias either off AAD (p=0.04) or on ADD (p=0.01).
La Meir and coworkers[19] compared early results of the hybrid versus standard minimally invasive approach. The hybrid group yielded better results in LSP-AF (p=0.01) whereas freedom from AF-off AAD was significantly higher in persistent and pAF (both, p=0.04).
Finally, reporting their experience with monopolar RF source La Meir et al[21] employed a method suggested by the Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons, with results expressed as time-related

prevalence of AF[27]. Time-related prevalence of post-operative AF after a monolateral-monopolar hybrid procedure peaked at 44.4% (41.3–47.4) at two weeks, was 30.4% (27.3–34.9) at three months, fell to 14.2% (11.6–18.1) by six months and was 13.3% (11.0–17.4) at twelve months.

Complications

There were three early deaths (0.8%) and three patients (0.8%) required conversion to sternotomy (Table 5). Overall, fourteen (4.1%) patients experienced complications. In addition, no patient died during the follow-up and none underwent repeated ablation. Finally, four patients (1.1%) had an electric cardioversion and none experienced any thromboembolic event.

Echocardiographic results and quality of life (QoL)

Only a few papers[19, 22] reported echocardiographic results before and after hybrid procedures. La Meir and co-workers[19] showed a significant 12-month LA reverse remodeling (p=0.02) with a reduction in LA volume index and an increase in LA emptying fraction occurring more in LSP patients. Zembala et al[22] showed statistically significant improvements in both LA size and LVEF one year post procedure. A greater change in left ventricular function was noted in patients with a baseline LVEF < 35% than in patients with a baseline LVEF greater than 40%.
Finally, (QoL) assessment was carried out by Gehi et al[24] employing the Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) scale and showing an improvement after hybrid ablation regardless of recurrence.

Discussion

Surgical treatment of AF has undergone dramatic changes over the last decade. A better knowledge of functional anatomy[28] as well as the development of new technologies[29] has allowed the creation of transmural lesions on a beating heart through alternative, less-invasive incisions which are being increasingly employed in clinical practice[30]. Hybrid procedures are further advancing the state of the art. This hybrid approach combines minimally invasive surgical techniques with the latest advances in catheter ablation.
There exists a clear rationale for this approach[31], as some ablation lesions that are incorporated into the well-established Cox-Maze lesions[32, 33] cannot be

accomplished using a minimally invasive, off-pump surgical approach. Indeed, while some lesions can be easily performed through the transverse sinus, efficacy and safety of other ablation lesions on the full beating heart (i.e, the ablation line to the mitral annulus) are the main challenges[34].

At the same time, other lesions that are part of the Cox maze ablation strategy may be more successfully applied using currently available epicardial surgical ablation tools (i.e., PVI, where the rate of permanent long-term PVI with catheter ablation is limited).

In addition, lesions are more likely to be transmural when ablating from the inside outwards and from the outside inwards simultaneously and the EP can add an endocardial 'touch-up' in the case of incomplete isolation of one of the pulmonary veins, or if the connecting lesions are not transmural. Moreover, from the EP point of view, there is no risk of phrenic nerve and esophageal injury because these structures can be protected by the surgeon, the possibility of tamponade is low since the pericardium is open and the risk of embolism is potentially reduced due to a lower number of endocardial ablations required.

Nonetheless, despite theoretical advantages, preliminary results from the Contact[36], the first trial on the hybrid method recently reported by Edgerton[37], are not encouraging and seem to demonstrate that this combined technique increases complication rates and does not improve outcomes in patients with a large atrium and LSP-AF. In addition, some authors raise serious concerns about such a time-consuming procedure that is significantly longer than surgery/trancatheter-alone techniques. Furthermore, others think that the hybrid treatment might represent a "logistical nightmare"[39] since it requires that experts in both catheter ablation and surgical ablation be available in the same hospital, on the same day and at the same time. Therefore, the key purpose of this review is to summarize and discuss results from published articles about hybrid thoracoscopic and transvenous catheter ablation for the treatment of stand-alone AF to establish the efficacy of this procedure as well as its potential superiority over catheter ablation or standard surgical technique. From this overview the hybrid treatment appears to be a safe technique. Indeed, both mortality (0.8%) and complications rates (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 pAF, 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 RF (100%, 100%, 81.8%) and compare favourably either with minimally invasive-beating heart surgery[11, 35] or percutaneous catheter ablation[10, 17]. In contrast, with the exclusion of the paper from Bisleri et al[25], AF-freedom rate was lower in papers employing monoploar RF. La Meir et al[21] reported unsatisfactory results with monopolar RF in the entire patient population and, more evidently, in LSP-AF. The same authors, in another paper (excluded from our analysis because of overlapping patients) compared results of the hybrid monopolar versus the hybrid bipolar RF ablation and showed that the hybrid bilateral approach with a bipolar device had a good 1-year success rate independently of AF. In contrast, the hybrid monolateral approach was less effective in long-standing persistent and persistent AF. Although these findings must be read in light of inherent limitations[39] (for instance, the higher number of paroxysmal patients in the bipolar group and the right-sided lesions exclusively delivered in the group undergoing bipolar hybrid ablation) and despite the potential advantages of a monolateral right-thoracoscopic approach, these results undoubtedly confirm the existing concerns about the ability of monopolar devices to create transmural lesions with bidirectional conduction block on the beating heart[29] and are a strong call for further research.

Moreover, from this review it is noticeable that, although it is well known that a more extensive lesion set beyond PVI is often necessary (mainly in persistent and LSP-AF), the only standard lesion applied to all patients was PVI. Indeed, despite the theoretical benefit of a hybrid approach to accomplish a complete mitral line and cavotricuspid line, these lesions were created in only a relatively small percentage of patients and, in most cases, ablation lesions with the exception of PVI were "tailored" on the basis of different factors (e.g. concomitant patient diseases, AF type, operator preference). As a result, there is not a standard technique which can be applied to most patients and that can be replicable by all centres and it is not clear which lesions or lesion sets are needed and what is the best end point for the procedure.

Finally, it is also matter of debate if it would be preferable to perform simultaneous surgical /EP procedures or to carry out the surgical ablation with PVI first and the catheter ablation afterwards. Indeed, the timing between the surgical and electrophysiological procedures might be a topic of utmost importance and for some authors[39,40] simultaneous epicardial/endocardial procedures may

be associated with false negative results (such as acute demonstration of a bidirectional block which could be only transient and not potentially confirmed in the chronic setting), as well as with false positive results in terms of early inducible arrhythmias, which usually require further "maturation" of the ablative lesion.

Limitations

This review has some important limitations, which must be pointed out. First of all, the small number of studies and the limited patient population, due to the recent introduction of the technique, do not allow us to draw any final conclusions. Second, a meta-analysis could not be carried out because of the heterogeneity and the small number of the papers as well as the lack of individual patient data. Third, the unavailability of data from prospective randomised studies on the hybrid procedure and its comparison to minimally invasive as well as trancatheter ablation was a drawback of this systemic review. Finally, not all results are uniformly reported which made a comparison of the different studies difficult.

Conclusions

Hybrid thoracoscopic and transvenous catheter ablation achieved satisfactory results with AAD-free success rates higher than isolated procedures. In particular, the bilateral approach with a bipolar device showed a high success rate independently of the AF type and it seems to be the better choice for the hybrid procedure. These results emphasize that success in the treatment of AF will probably rely on a close collaboration between the surgeon and the electrophysiologist. Nonetheless, large, multicentre trials of hybrid AF ablation that target a population of patients with LSP-AF are necessary to establish whether this approach may represent a gold-standard treatment for AF in the future.

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Table 1. Baseline characteristics

First Author	Year	Pts.	Age	AF duration	LA diameter (mm)	PCA	PX	PR	LSP
Mahapatra S.[17]	2011	15	59.5±2.4	5.4±0.6 y	52.3±10.3	15	-	9	6
Krul S.P.J[18]	2011	31	57 (43-77)	8 [1-25] y	47.0±7.0	14	16	13	2
La Meir M.[19]	2012	35	57.1±9.5	5[4.2-9.0] y	52.0±5.0	21	16	8	11
Pison L.[20]	2012	26	56.8 ±8.6	67.2±47.6 m	43.1±5.5	11	15	10	1
La Meir M. [21]	2012	19	61.2±8.6	5[3-8.5] y	49±20	9	5	4	10
Zembala M.[22]	2012	27	55.2±11	3.5±2.5 y	45.5±4.7	8	-	5	22
Muneretto C.[23]	2012	36	62.3±10	72.8 (7-240) m	50.3±5.5	-	-	8	28
Gehi A.K[24].	2013	101	62.9±9.6	5.9±5.5 y	51±10	36	17	47	37
Bisleri G.[25]	2013	45	62.3±9.8	83.8±69.1 m	51.3±9.7	-	-	-	45

Studies were presented by year of publication.

Abbreviations: Age is expressed as mean ± SD or (range); AF duration expressed as mean ± SD or (range) or median [Interquartile Range]; y: years; m: months; LA: Left atrial diameter expressed as mean ± SD; PCA: (Previous) Percutaneous Catheter Ablation; PX: Paroxysmal atrial fibrillation; PR: Persistent atrial fibrillation; LSP: Long-standing Persistent atrial fibrillation.

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).

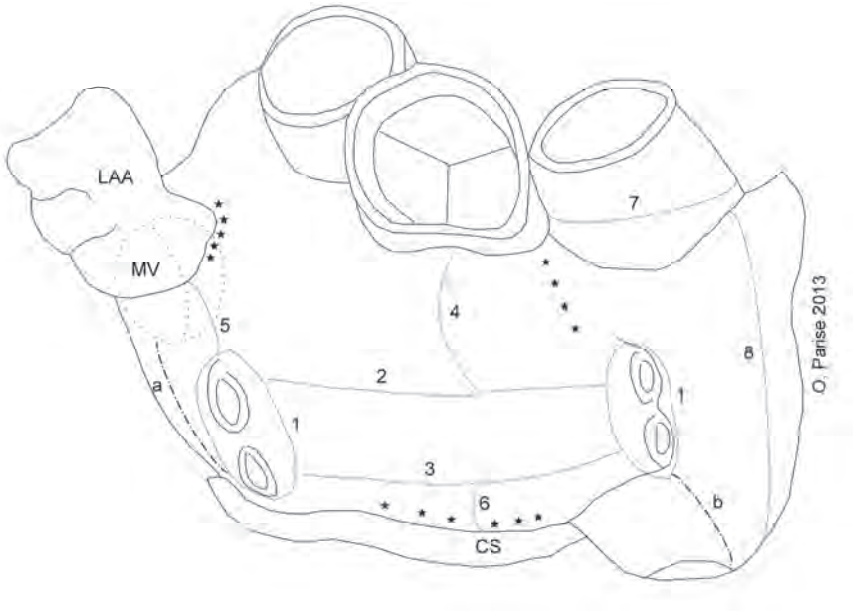
Table 5. Early and late outcome

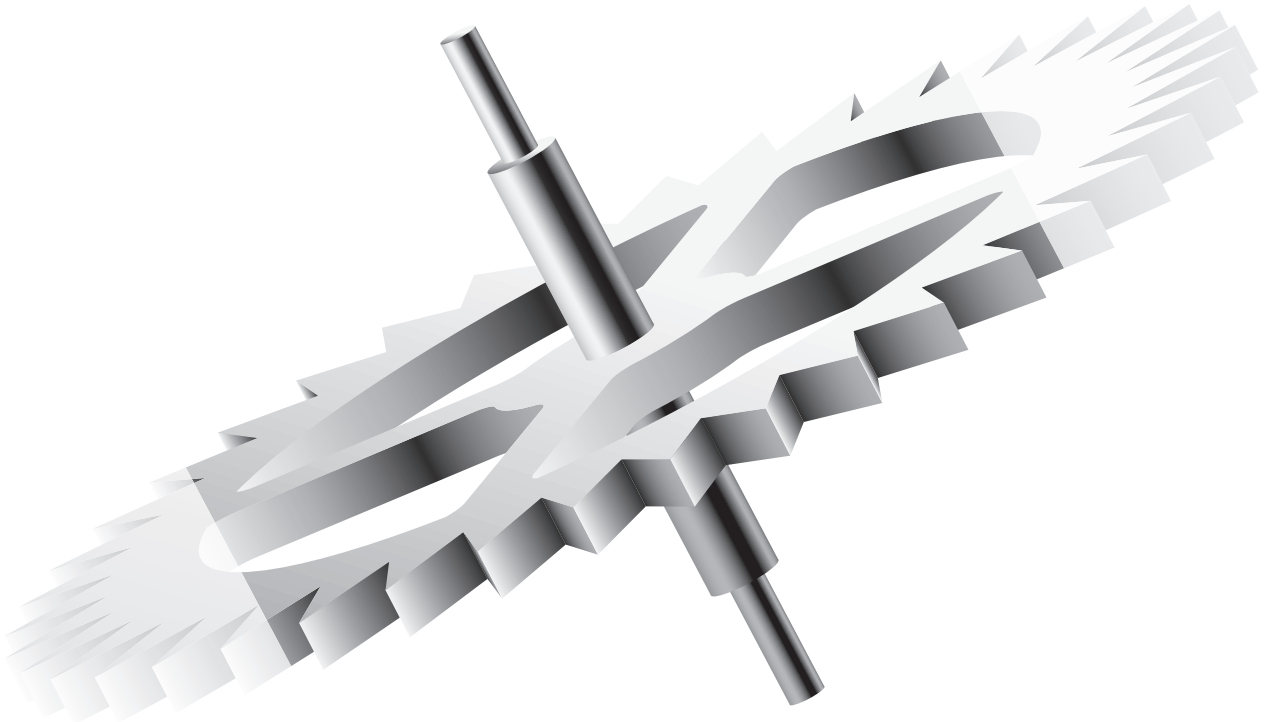
First Author	Early death	Conversion*	Complications	Late death	Repeated ablation	ECV	TEs
Mahapatra S.[17]	0	0	T	0	0	2	0
Krul S.P.J[18]	0	3	B(3) HeTX PNX PN	0	0	0	0
La Meir M.[19]	0	0	0	0	0	2	0
Pison L.[20]	0	0	PLE	0	0	0	0
La Meir M. [21]	0	0	0	0	0	0	0
Zembala M.[22]	1	0	T B	0	0	0	0
Muneretto C.[23]	0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

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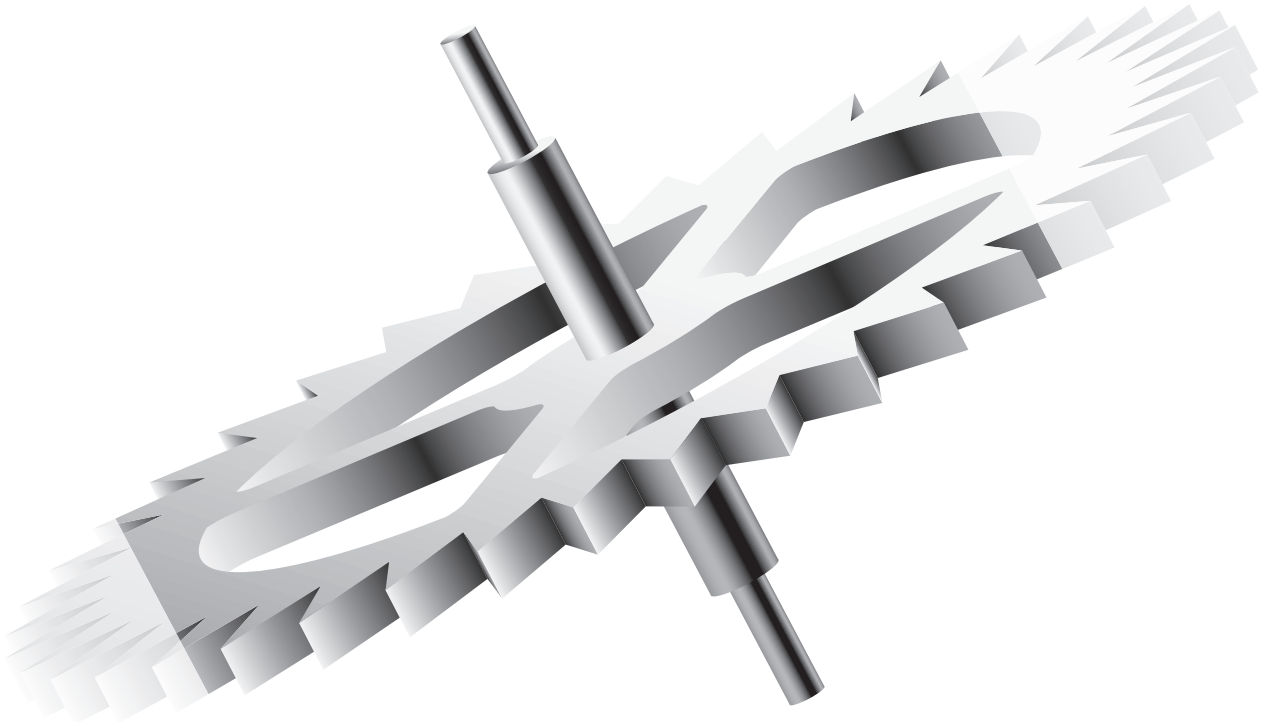

Addendum

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.

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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

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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.