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**Claudia Annemarie Josephine van der Heijden**

**Financial support**

Financial support granted by AtriCure for the publication of this thesis is gratefully acknowledged.

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Financial support by KM Innovations B.V. for the publication of this thesis is gratefully acknowledged.

**Printing**: Gildeprint

**Lay-out:** Claudia Annemarie Josephine van der Heijden

**Design cover**: Riva Boutylkova

**ISBN:** 978-94-6496-007-5

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DISSERTATION

To obtain the degree of Doctor at Maastricht University,

on the authority of the Rector Magnificus, Prof. dr. Pamela Habibovic

in accordance with the decision of the Board of Deans,

to be defended in public

on Friday February 2nd 2024 at 13:00 hours

by

**Claudia Annemarie Josephine van der Heijden**

Born on July 27th 1995, Maastricht, The Netherlands

**Promotor**

Prof. dr. J.G. Maessen

**Co-promotor**

Dr. B. Maesen

**Assessment committee**

Prof. dr. T. Hackeng, chair

Prof. dr. N.D. Bouvy

Prof. dr. M. Castellà, Hospital Clínic de Barcelona, Spain

Prof. dr. N.M.S. de Groot, Erasmus Medical Center Rotterdam, The Netherlands

# CONTENTS

# CHAPTER 1

## General Introduction

## Chapter 1

## Introduction

Atrial fibrillation (AF) was first discovered on an electrocardiogram by Willem Einthoven in 1906.[1] Currently, it is the most common sustained cardiac arrhythmia in adults and its prevalence increases with age. Atrial fibrillation is characterized by an irregular and often inappropriately rapid ventricular rate, potentially resulting in heart failure, and an increased risk for morbidity, stroke and overall mortality.[2,3] Since AF can occur for brief episodes or be continuously present, this supraventricular tachyarrhythmia is clinically classified based on its episode duration. Paroxysmal AF (pAF) is self-terminating, usually within 48 hours, but lasts no longer than 7 days. If prolonged, including episodes terminated by either chemical or electrical cardioversion after 7 days, AF is defined as persistent (persAF). Finally, longstanding-persistent AF is defined as persistent AF of greater than 12 months of duration.[3]

### 1. Pathophysiology of AF

Two important processes can be identified in the mechanisms underlying the initiation and perpetuation of AF. First, a "trigger" is needed for AF to be initiated and secondly, the development of an atrial "substrate" is required for AF to maintain.[4] As a consequence, an AF episode is likely to spontaneously convert to sinus rhythm (SR) in the absence of an underlying substrate.

#### 1.1 Triggers

Until the seminal discovery of Haïssaguerre et al. in 1998, it was long believed that the main mechanism of AF was based on reentrant wavefronts.[5,6] Instead, Haïssaguerre et al. identified the myocardial sleeves of atrial tissue within the pulmonary veins (PVs) as important triggers responsible for ectopic foci.[7] The mechanisms responsible for PV ectopy in patients are still unknown, also because an animal model displaying paroxysmal AF originating in the PVs is lacking. In principle, PV ectopy could result from cellular proarrhythmic events (triggered activity and afterdepolarizations) or from localized reentry localized within a small tissue area ('micro reentry'). Triggered activity, e.g., impulse initiation by spontaneous depolarization that occurs consequent to one or more preceding action potentials, can be caused by abnormalities in cellular $Ca^{2+}$ handling.[8] When the amplitude of early- and delayed afterdepolarization is large enough to reach the threshold potential, it causes a spontaneous action potential.[9] These triggered events can give rise to extrasystoles that can precipitate tachyarrhythmias,[10,11] and their likelihood is increased by acute stretch or rapid atrial pacing.[4] Besides triggered activity, also enhanced automaticity and abnormal induced automaticity may play a role in cellular proarrhythmic events.[10] Alternatively, rapid ectopic activity may result from micro reentry, possibly occurring in the PVs as a result of the tissue architecture of the myocardial sleeves.[4,12]

1.2 AF substrate

As mentioned earlier, AF requires not only a trigger, but also a substrate to perpetuate. On one hand, degenerative and fibrotic changes in the atria can be the result of ageing or cardiac diseases predisposing for AF, for example by directly involving the atria in the disease process or due to hemodynamic changes causing atrial volume and pressure overload. On the other hand, AF itself promotes the development of an atrial substrate, even without the presence of structural heart disease.[4] An important pathophysiological process in the development of an AF substrate is endomysial fibrosis, which leads to longitudinal and endo-epicardial dissociation of electrical activity.[13,14] This results in a transmural 3-dimensional substrate where propagation of waves goes from one layer to the other, which markedly increases the number of possible pathways for fibrillating waves to meander.[15,16] Especially in areas with a strong preferential fiber orientation, such as the left atrial (LA) posterior wall, electric fractionation and dissociation can be observed.[17,18] Moreover, according to the multiple wavelet theory, multiple fibrillation wavefronts interacting with each other result in wave breakdown and the generation of new wavefronts.[19] If the atrial mass is large enough and the wavelength sufficiently short, triggers that propagate into the atrial myocardium may initiate reentering wavelets, likely facilitating multiple reentrant waves.[20] Nowadays, it is suggested that both focal sources of AF and the coexistence of multiple waves are responsible for the uncoordinated activity that characterizes AF.

## 1.3 Remodeling

The healthy LA is a contractile compartment that has a reservoir, conduit and booster pump function.[21] Although the exact underlying mechanisms of AF are still incompletely understood, three types of LA remodeling can be distinguished: electrical, functional and structural remodeling (Figure 1).[4,18,22] The gradual and progressive process underlying atrial remodeling favors the occurrence of triggers and enhances the formation of a substrate, promoting the initiation and perpetuation of AF.[4]

### 1.3.1 Electrical remodeling

Within the first hours to days of AF, electrical remodeling takes place, which is characterized by shortening of the action potential duration caused by changes in ion channel expression (Figure 1).[22] Acute electrical remodeling is mainly promoted by AF itself and in this process, $Ca^{2+}$ hemostasis plays a central role.[4] As a result of the rapid atrial rates, AF leads to cellular calcium overload.[23] To reduce cytotoxic intracellular $Ca^{2+}$ levels, autoprotective mechanisms in $Ca^{2+}$ handling are enhanced. As a result, the cell is hyperpolarized and the action potential duration is shortened. Moreover, AF-induced changes in gap junction channels may be associated with atrial arrhythmogenicity.[24] Connexins, the proteins that form gap junction channels, allow electrical coupling between cardiomyocytes. When these channels are downregulated or dysfunctional due to disorganization and fragmentation of gap junctions, intra-atrial conduction velocity is reduced.[25] As a result of the decrease in the refractory period and conduction velocity, a reduction in atrial wavelength is expected. When the atrial mass is large enough, this in turn allows a larger number of re-entrant wavelets to meander and reactivate excitable tissue, thereby facilitating AF and increasing its complexity even further.[9] Interestingly, what initially seemed autoprotective has led to a chain of undesirable effects for the atrial myocardium.[26] As such, AF promotes its own maintenance in a vicious circle, and becomes more entrenched in the atria, as expressed in the seminal phrase “AF begets AF”.[27]

1.3.2 Functional remodeling

Functional remodeling is characterized by a loss of atrial contractility (Figure 1).[28] It is thought that the abnormal $Ca^{2+}$ handling in AF plays an important role in not only electrical remodeling, but also in functional remodeling. As a result of the atrial tachycardia induced $Ca^{2+}$ overload in atrial myocytes, the activation of myocardial proteases that break down $Ca^{2+}$ channels also results in the destruction of sarcomeres, causing atrial stunning and hypo-contractility.[29] After brief episodes of AF, a transient and fast, reversible phase of atrial hypo-contractility is induced, following the same time course as the reduction of the atrial action potential duration. As AF prolongs, the downregulation in $Ca^{2+}$ handling seems to be more related to a slower phase of (irreversible) structural remodeling. As such, it is suggested that the AF-induced electrical and contractile remodeling go hand-in-hand, as they share the same cellular mechanisms.[30] Moreover, AF itself decreases atrial mechanical performance.[31] As the volume and pressure overload can no longer be counteracted by the atrial muscle fibers, the atrial myocardial wall becomes too stretched and contractility is reduced, also known as the Frank-Starling mechanism. The loss of atrial myocardial contractility in turn increases atrial compliance, stiffness and dilatation, and vice versa.[32]

1.3.3 Structural remodeling

Over a time course of months to years, AF becomes more persistent and complex because structural remodeling takes place.[4] This phenomenon is characterized by alterations in atrial size (atrial dilatation) and tissue structure (apoptosis of cardiomyocytes, excess extracellular matrix production and enhanced fibroblast activation and proliferation) (Figure 1).[33] As a result of atrial stretch in long-lasting continuous AF, the development of endomysial fibrosis and the consequent dissociation of atrial bundles is enhanced.[14,16] The loss of atrial contractility of the fibrillating atria promotes atrial dilatation even further.[34]

Another important factor in structural remodeling is the role of epicardial adipose tissue (EAT).[35,36] First of all, due to the absence of fascial boundaries, EAT is able to directly infiltrate the myocardial wall and modify the normal atrial structure, leading to the generation of an electrophysiological substrate and electrical instability.[37] Secondly, EAT is a metabolic active tissue that exerts a paracrine and vasocrine function by the excretion of free fatty acids, pro- and anti-inflammatory adipokines.[36] Subsequently, these modulators enhance oxidative stress, fibrosis, myocardial inflammation, autonomic- and diastolic dysfunction and adipocyte-related atrial gene expression. Eventually, these factors combined can induce a slow but progressive process of structural remodeling, starting already early in this pathophysiological process.[38] Interestingly, the progression of AF from paroxysmal to persistent is accompanied by an increase in EAT quantity. This can be explained by the hypothesis that structural remodeling is more evident in persistent forms of AF compared to paroxysmal AF.[39]

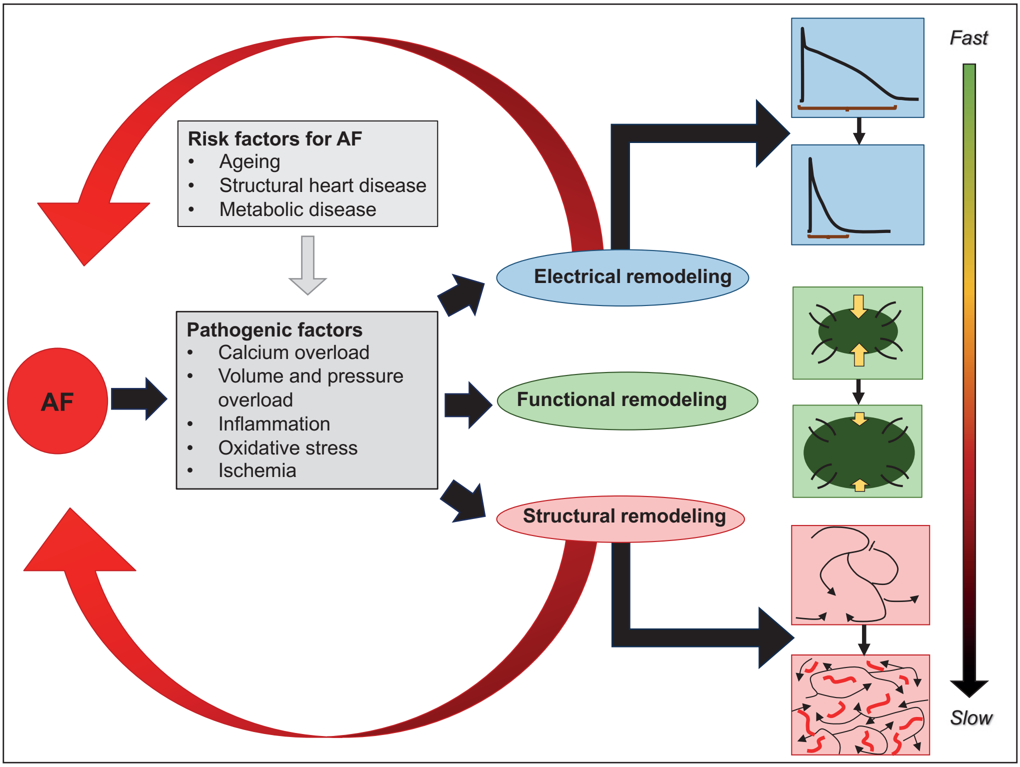


**Figure 1.** The feedback loop of remodeling during AF. Electrical remodeling: shortening of the refractory period. Functional remodeling: atrial dilatation and reduced contractility. Structural remodeling: development of a 3-dimensional substrate (fibrosis is highlighted in red, arrows depict multiple reentry waves). AF=atrial fibrillation.

## 1.4 Paroxysmal versus persistent AF

The classification of AF is based on episode duration, but the different types of AF are also characterized by differences in AF complexity. Initially, paroxysms of AF are often short and self-terminating, but AF episodes become longer and more frequent over time if left untreated. Those more persistent forms of AF go hand-in-hand with increased substrate complexity, thereby leading to an arrhythmia that is more refractory to intervention.[18,27,40]

Electrophysiological mapping studies have shown several important differences in AF complexity between the different AF phenotypes.[14,17,20] It is believed that triggers consisting of ectopic foci and/or micro-reentry are mainly responsible for the initiation of paroxysmal AF, leading to a hierarchical organization of AF. In more persistent forms of AF however, AF conduction is believed to consist of multiple propagating fibrillation waves, leading to an anarchical form of AF.[4] Based on computer models and electrophysiological mapping studies in goat and human, persistent forms of AF are characterized by highly fractionated electrograms, longitudinal- and endo- epicardial dissociation and epicardial breakthroughs due to electrical uncoupling within the atrial myocardium by endomysial fibrosis, leading to more complex activation patterns.[14,16,20] So while pAF is often characterized by self-terminating episodes that seem to be rather trigger-initiated, more persistent forms of AF depend on the development of an AF substrate characterized by multiple wave reentry (Figure 2).[37] These differences in AF complexity have important consequences for the successful treatment of AF.

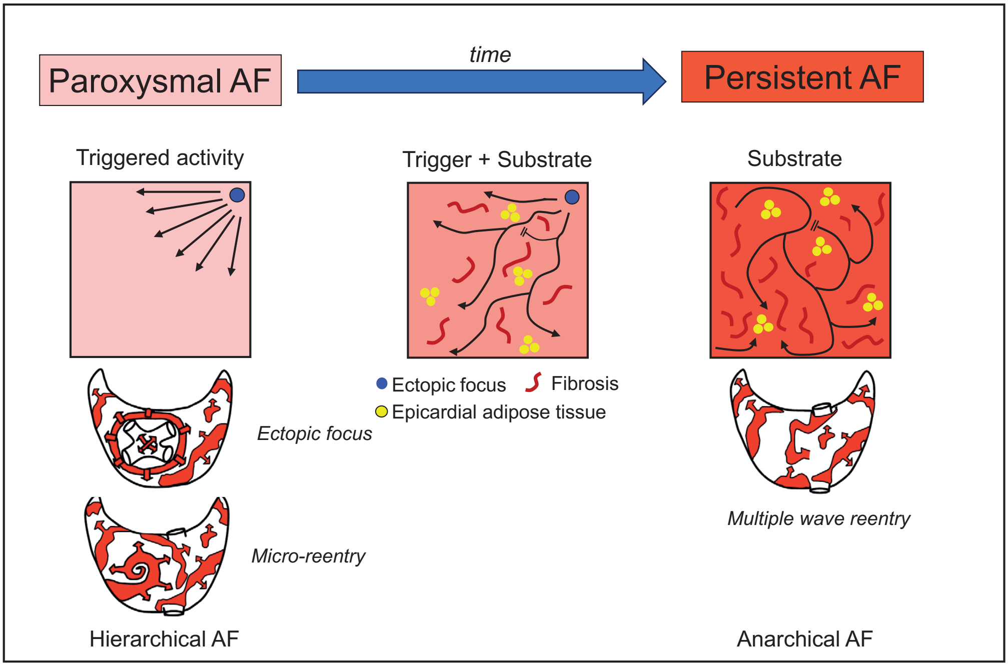


**Figure 2.** Differences in activation patterns based on the AF phenotype. While paroxysmal AF is characterized by a hierarchical activation pattern with triggered activity (ectopic focus or micro reentry), more persistent forms of AF are characterized by an anarchical activation pattern with multiple wave reentry.

## 2. Rhythm control strategies for AF

As described before, AF is a highly complex disease where different forms of remodeling result in the progressive development of an AF substrate. While some of the risk factors leading to AF can be managed, it remains a great challenge to address all of the underlying mechanisms in order to prevent AF. Even more worrying is the fact that once AF is present and becomes more complex over time, the atria may never fully recover to their healthy, pre-disease state. Electrical remodeling may be completely reversible with termination of the arrhythmia, even after years of AF,[41] but functional and structural remodeling are much slower processes that can take months to (partially) recover.[22] Due to the intertwined aspects of the electrophysiological, functional and structural changes in the atria, restoration of SR and improving quality of life in patient with complex AF remains challenging. In order to improve AF-related symptoms, rate control (controlling ventricular rate) and rhythm control (restoration of SR) are recommended to relieve symptoms.[3] Rhythm control strategies can be divided into antiarrhythmic drugs, electrical or chemical cardioversion and ablation strategies.

### 2.1 Catheter AF ablation

In 1998, Haïssaguerre et al. were the first to demonstrate that the myocardial sleeves of the pulmonary veins (PVs) harbor important triggers that are able to initiate AF paroxysms and that these foci can be successfully eliminated using radiofrequency (RF) ablation.[7,42] Ever since, PV isolation (PVI) using RF or cryo-energy has been the cornerstone for AF ablation (Figure 3).

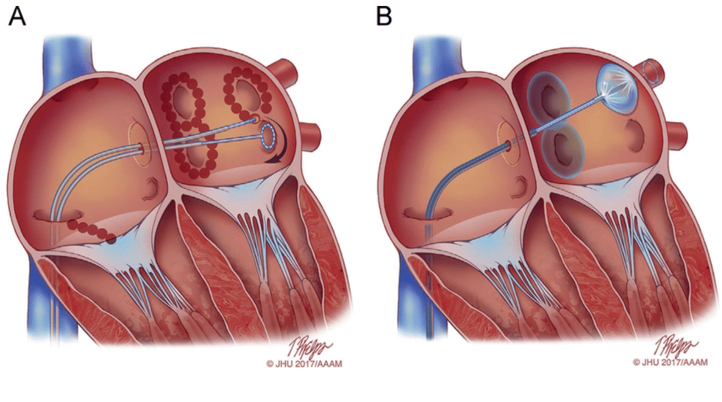


**Figure 3. A.** Radiofrequency ablation the pulmonary veins (and a cavotricuspid isthmus line for a typical flutter). **B.** Cryo-ablation of the pulmonary veins.

As such, transvenous endocardial ablation of triggered activity arising from the PVs is not only a safe, but also a very effective rhythm control strategy for patients with pAF and yields successful rhythm control outcomes exceeding 80%.[43] Unfortunately, results for persAF are far less satisfactory and success rates, independent of the ablation strategy applied, do not exceed 45%.[44] While several endocardial substrate modification techniques besides PVI only have been tested,[45-47] none of them were associated with high success rates and they may even be pro-arrhythmic if lesions fail to be transmural.[44,48,49] As AF progresses to (longstanding)-persAF, the atrial substrate becomes more complex (Figure 2). As such, ablation of localized triggers around the PVs is insufficient to adequately treat persistent AF and a more complex ablation strategy seems to be required.[18]

2.2 Thoracoscopic AF ablation

The anatomical lesion set of the surgical Cox-Maze III “cut and sew” procedure is still considered the gold standard today.[50] Based on electrophysiological mapping studies, the original Cox-Maze procedure was designed to divide the atria into multiple small and electrically isolated compartments to prevent sustained (multiple wave) re-entry and reduce the critical atrial mass.[51] Although the procedure was very effective in restoring SR, the procedure has not been widely adopted by surgeons because of its complexity, technical difficulty and significant degree of invasiveness.

To overcome the problem of non-transmural lesions in catheter ablation, while reducing the complexity and invasiveness of the Cox Maze procedure, surgical ablation has evolved into minimally invasive beating-heart alternatives.[52] Especially in patients with more complex and persistent forms of AF, minimally invasive surgical AF ablation must at least meet two requirements to restore SR: isolate triggers and modify substrate. First of all, taking into account that the PVs have been identified as important ectopic trigger sites, PV isolation (PVI) is the cornerstone for any AF ablation.[53] At the same time, epicardial PVI allows for isolation of the Ligament of Marshall, harboring Marshall’s vein that has also been identified as a trigger in persistent AF.[54] Secondly, since its complex atrial anatomy in combination with structural remodeling makes the LA posterior wall prone to multiple wavelet reentry and substrate formation, LA posterior wall isolation seems to be an important aspect of successful epicardial AF ablation. This box lesion consists of a roof and inferior line connecting both PV pairs. Thirdly, the LA appendage (LAA) is not only an important source for thrombus formation, but has recently also been identified as an arrhythmogenic trigger.[55] As such, LAA exclusion not only reduces stroke risk,[56] but also improves the success rates by isolating triggers originating from the appendage and by atrial mass reduction.[57] Furthermore, the role of neuromodulation has gained more and more interest in recent years. It has been proposed that ganglionated plexi (GP) play an important role in triggering ectopic foci causing paroxysms of AF.[58] Epicardial wide antral PVI automatically results in isolation of the most important GPs surrounding the PVs and may therefore contribute to its success. Therefore, epicardial PVI and box isolation in combination with LAA exclusion became the standard approach in stand-alone thoracoscopic ablation for persistent AF (Figure 4).

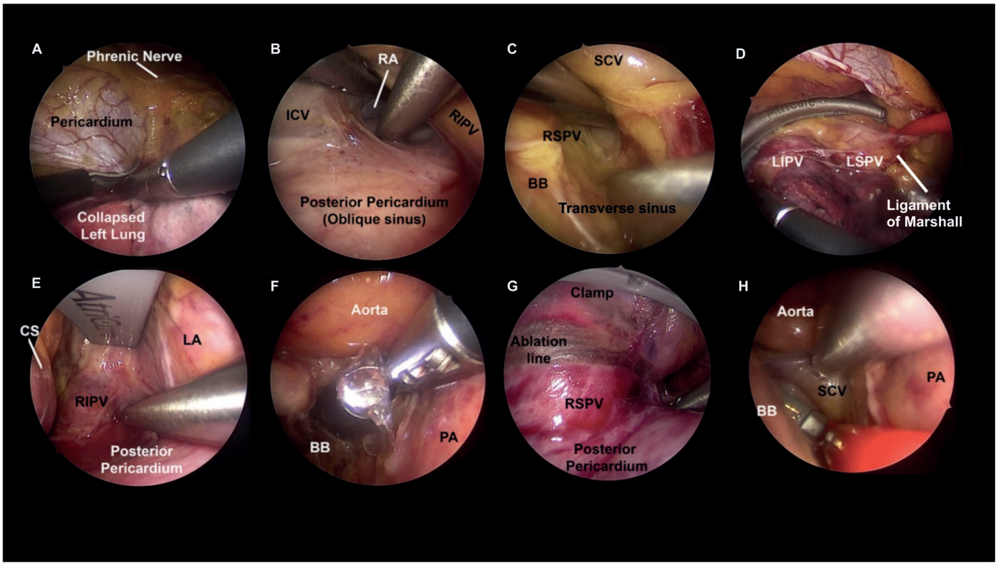


**Figure 4.** Example of unilateral left-sided thoracoscopic epicardial AF ablation. **A.** Opening of the pericardium posterior to the phrenic nerve. **B.** Opening the pericardial reflection between the RIPV and the ICV in the oblique sinus and **C.** between the RSPV and the SCV in the transverse sinus. **D.** Ablation of the left PVs. **E.** Creation of the inferior line as part of the box lesion set. **F.** Positioning of the lumitip and placement of the bipolar clamp around the right PVs. **G.** Result of the right PVI. **H.** Verification of the position of the clamps in the transverse sinus. BB=Bachmann bundle; LIPV=left inferior pulmonary vein; LSPV=left superior pulmonary vein; PV=pulmonary vein; PVI=PV isolation; RA=right atrium; RF=radiofrequency; RIPV=right inferior pulmonary vein; RSPV=right superior pulmonary vein; SCV=superior caval vein.

Rhythm outcomes after such a minimally invasive surgical approach are very convincing in patients with persAF and longstanding persAF, especially compared to catheter ablation.[59] An important factor contributing to its superiority is the ability to create durable and transmural epicardial lesions. Biparietal bipolar clamp devices using RF energy are most widely used for isolation of the PVs, as they allow PVI by applying RF energy between both jaws of the clamp. While unipolar uniparietal RF devices often create broad lesions in size and depth, they often fail to reach transmurality. On the contrary, biparietal bipolar RF devices create more narrow lesions that result in reliable transmural lesions.[60] Animal studies have shown that biparietal bipolar RF ablation of the PVs leads to transmural lesions in nearly 100% of all cases.[61] Hence, both the lesion set as well as the device used for the creation of those lesions are important determinants for obtaining a successful rhythm outcome. Although results for a thoracoscopic approach sound promising, one of the shortcomings of stand-alone thoracoscopic AF ablation is that some lesions cannot be created solely from the epicardium (for example a mitral isthmus line to treat a perimitral flutter or a cavotricuspid isthmus line for a typical flutter due to potential damage to the circumflex artery and the sinoatrial node respectively). Moreover, although the cardiac surgeon has direct vision of the anatomy, without extensive endocardial electrophysiological voltage mapping the surgeon is in fact blind for the underlying substrate and complexity of the arrhythmia. Moreover, epicardial testing may not always be as reliable as endocardial testing and lead to false-positive confirmation of entrance and exit block. For example, accidental epicardial testing on a fibrotic strand located in the box may lead to the false conclusion of box isolation.[62]

2.3 Hybrid AF ablation

Since patient-tailored identification and treatment of specific underlying mechanisms remains an unachievable goal and to overcome the shortcomings of catheter and thoracoscopic ablation, the hybrid AF procedure was developed in 2010 in our center (Maastricht University Medical Center – MUMC+).[63] The pioneers of the hybrid procedure suggested that the combination of both approaches may be more successful than either technique on its own (Figure 5).


**Figure 5.** Set-up in the hybrid operating room: surgical thoracoscopic (left) and transvenous catheter (right).

The complementary nature of the hybrid procedure is represented by the fact that the thoracoscopic surgical procedure, consisting of epicardial PVI, box isolation and LAA exclusion, is followed by a transvenous endocardial procedure. During the latter step, endocardial touch-up of incomplete epicardial lesions can be performed. Moreover, additional lesions including a mitral isthmus or cavotricuspid isthmus line can easily and safely be created from the endocardium (Figure 6).

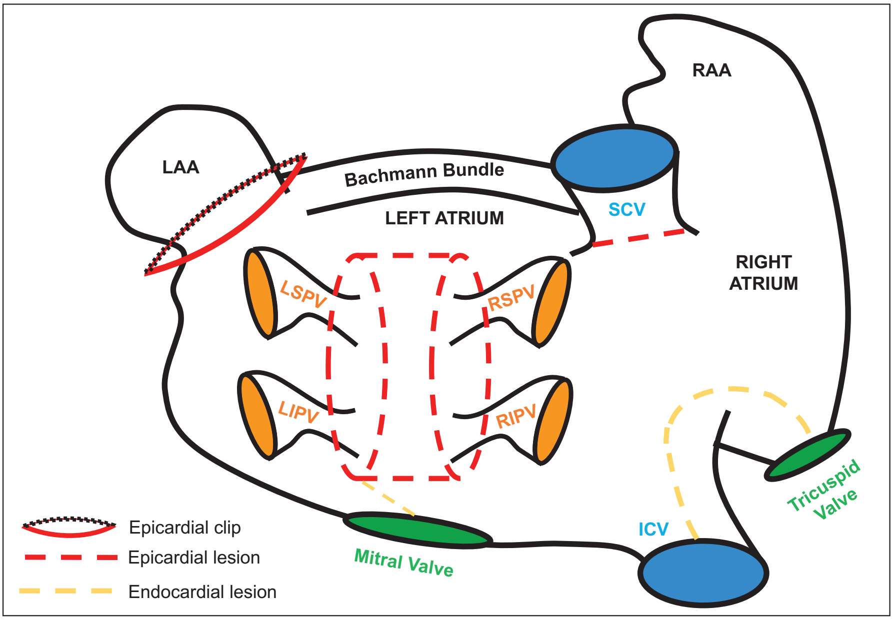


**Figure 6.** Schematic overview of epicardial and endocardial lesions during hybrid AF ablation. LAA=left atrial appendage; RAA=right atrium appendage; SCV=superior caval vein; ICV=inferior caval vein; LSPV=left superior PV; LIPV=left inferior PV; PV=pulmonary vein; RSPV=right superior PV; RIPV=right inferior PV.

Although the endocardial procedure is often performed directly after the surgical part during the same procedure (single staged), it can also be performed several months later (staged). An important advantage of a single-staged hybrid ablation procedure is the close cooperation between the cardiac surgeon and the electrophysiologist, where the extensive voltage map performed by the electrophysiologist can serve as a guide for the cardiac surgeon to complete and tailor gaps in epicardial lesions. Also, regular tachyarrhythmias that develop during the procedure can immediately be mapped from the endocardium and effectively be targeted from the endocardium. A staged procedure on the other hand has the logistical advantage of not necessitating both the cardiac surgeon and the electrophysiologist in a hybrid operation room at the same time. Moreover, some believe that an endocardial validation procedure that is performed once the epicardial lesions are matured and edema is regressed allows for more reliable endocardial testing.[64] However, those differences have never been demonstrated in comparative studies. An example of an endocardial electrophysiological voltage map of the LA atrium, showing complete isolation of the LA posterior wall during a single staged hybrid procedure, is depicted in Figure 6.

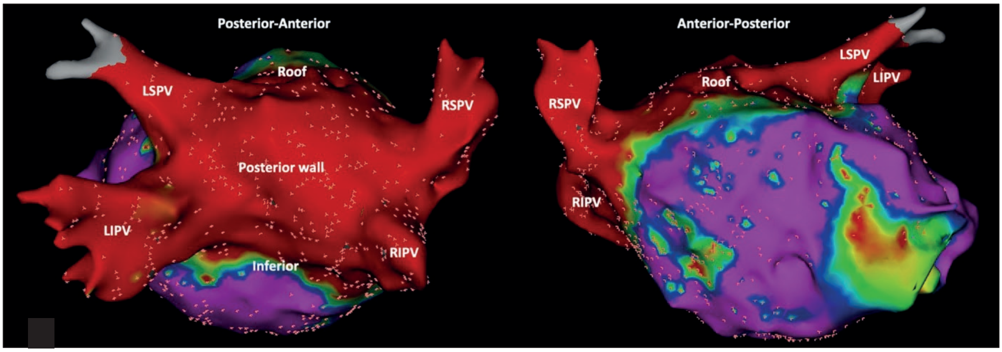


**Figure 7.** Endocardial electrophysiological mapping of entrance and exit block of the left atrium after thoracoscopic ablation during a hybrid AF procedure. The red color indicates that the left atrial posterior wall is successfully isolated.

### 3. Left atrial function

It is known that more persistent forms of AF lead to atrial stretch, dilatation and loss of synchronous atrial contractility.[22] Especially in patients with underlying heart disease, the decreased ventricular filling times due to the AF-induced tachycardia combined with the loss of atrial kick can reduce the cardiac output up to 25%.[65] This may in turn impair left ventricular diastolic filling, leading to (symptomatic) diastolic heart failure and a reduced quality of life, along with a higher risk for morbidity and mortality.[66] Also, loss of atrial contractility and increased inflammation in AF enhances stasis-related intracardiac thrombogenesis, leading to a four- to five-fold increasing risk of stroke.[3]

Although those changes are at least partially reversible, restoration of SR does not always translate in full recovery of atrial function or contractility. It is thought that by reversed electrical remodeling by SR restoration, LA $Ca^{2+}$ handling and consequently LA contractility can be normalized.[34] In that sense, it is important to limit the scarring created by ablation as much as possible to the essential lesion set, as isolated tissue does not contract. Also, while surgical exclusion of the LAA during thoracoscopic AF ablation significantly reduces the risk of thrombo-embolic stroke[56] and improves rhythm outcome in persAF,[57] the appendage is an important reservoir that contributes to the LA function and contractility. Therefore, one could wonder if the beneficial aspects of LAA exclusion always outweigh the negative effect on LA function (e.g., in young athletic patients passionate by endurance sports). Moreover, despite the fact that thoracoscopic hybrid ablation is successful in rhythm control,[67] the extensive fibrotic tissue in atria with advanced structural remodeling cannot be undone and atrial function might not improve despite restoration of SR.

## 4. Quality of life

Besides rhythm and functional outcomes, patient reported outcomes such as quality of life (QOL) have gained more interest in the past years. Overall, more than 60% of all patients with AF report a significant decrease in QOL.[3] According to the World Health Organization, the most widely used health-related QOL measurement tool is the Short-Form 36 (SF-36), but also other questionnaires are frequently used for AF-related symptoms, including the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT), European Heart Rhythm Association (EHRA) or the EuroQol (EQ-5D-5L). In the treatment of AF, identifying symptom status and QOL is highly important, as AF-related symptoms may vary from none to disabling. Such symptoms include palpitations, dyspnea or reduced exercise tolerance. Importantly, the primary indication for rhythm control treatment strategies conform the ESC AF Guidelines is symptom relief and improvement in QOL.[3] While AF progression and the associated morbidity such as stroke or hospitalization are associated with a decrease in QOL, successful conversion to SR and freedom from AF recurrences have been associated with significant QOL improvement.

## 5. Thesis outline

This thesis describes different aspects related to minimally invasive (hybrid) ablation for AF as well as the underlying mechanisms related to AF in the postoperative setting. The efficacy and safety after hybrid and catheter ablation are compared in a meta-analysis and in a randomized controlled trial. Furthermore, efficacy- and safety outcomes after different thoracoscopic ablation approaches are discussed. Finally, also other endpoints for success are analyzed, including left atrial function and quality of life.

The **first chapter** comprises the General Introduction, where pathophysiological mechanisms underlying AF and minimally invasive rhythm control strategies are described.

It has been suggested that epicardial adipose tissue (EAT) plays a role early in the development of AF. Because of this early role and the fact that post-operative AF (POAF) seems to be an unmasking of an underlying AF substrate, we wondered if EAT might also be an important player in the occurrence of POAF after cardiac surgery (**chapter 2**).

Thereafter, we mainly focused on the beneficial aspects of hybrid AF ablation. Although we know from previous studies that hybrid ablation has very good rhythm and safety outcomes, direct comparisons between hybrid and catheter AF ablation were lacking. Our hypothesis that hybrid ablation is superior to catheter ablation in patients with complex and persAF was tested in **chapter 3** and **chapter 4**. Next, we evaluated whether the continuous drive for improving minimal invasiveness in surgical AF ablation also translates into good patient outcomes (**chapter 5**). To take it even further, we hypothesized that the combination of two minimally invasive cardiac procedures would reduce patient burden even more (**chapter 6**). Although restoration of sinus rhythm is an important efficacy outcome, restoration of LA function may never fully recover, but is also important for patient symptomatology. Therefore, we wondered how LA function relates to rhythm outcome and whether an improvement in LA function and contractility can be detected after concomitant thoracoscopic AF ablation and thoracoscopic hybrid ablation (**chapter 6** and **7**). In the end, the main reason why we believe that restoring sinus rhythm and improving LA function is so important, is because the goal of any rhythm control strategy remains to reduce AF-burden and symptoms for patients. Our hypothesis that quality of life improves after surgical AF ablation was tested in **chapter 8**.

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# CHAPTER 2

## Postoperative Atrial Fibrillation and Atrial Epicardial Fat: Is There a Link?

**Claudia A.J. van der Heijden*,** Sander Verheule*, Jules R. Olsthoorn, Casper Mihl, Lexan Poulina, Sander M. J. van Kuijk, Samuel Heuts, Jos G. Maessen, Elham Bidar, Bart Maesen

*Both authors contributed equally

*International Journal of Cardiology Heart and Vasculature. February 2022.*

## Abstract

**Background** Atrial Epicardial Adipose Tissue (EAT) is presumably involved in the pathogenesis of atrial fibrillation (AF). The transient nature of postoperative AF (POAF) suggests that surgery-induced triggers provoke an unmasking of a pre-existent AF substrate. The aim is to investigate the association between the volume of EAT and the occurrence of POAF. We hypothesize that the likelihood of developing POAF is higher in patients with high compared to low left atrial (LA) EAT volumes.

**Methods** Quantification of LA EAT based on the Hounsfield Units using custom made software was performed on pre-operative coronary computed tomography angiography scans of patients who underwent cardiac surgery between 2009 and 2019. Patients with mitral valve disease were excluded.

**Results** A total of 83 patients were included in this study (CABG=34, aortic valve=33, ascending aorta n=7, combination n=9), of which 43 patients developed POAF. The EAT percentage in the LA wall nor indexed EAT volumes differed between patients with POAF and with sinus rhythm (all $P>0.05$). In multivariable analysis, age and LA volume index (LAVI) were the only independent predictors for early POAF (OR: 1.076 and 1.056, respectively).

**Conclusions** As expected, advanced age and LAVI were independent predictors of POAF. However, the amount of local EAT was not associated with the occurrence of AF after cardiac surgery. This suggests that the role of EAT in POAF is rather limited, or that the association of EAT in the early phase of POAF is obscured by the dominance of surgical-induced triggers.


**Keywords** Postoperative atrial fibrillation • Epicardial adipose tissue • Computed tomography scan • Cardiac surgery

## Glossary of Abbreviations

| | |
|---|---|
| AF | Atrial fibrillation |
| AV | Aortic valve |
| BMI | Body mass index |
| BSA | Body surface area |
| CABG | Coronary artery bypass graft |
| CCTA | Coronary Computed Tomographic angiography |
| CM | Contrast management |
| CT | Computed tomography |
| EAT | Epicardial adipose tissue |
| EAT-V | EAT-volume |
| HU | Hounsfield units |
| kV | Kilovoltage |
| LA | Left atrial |
| LAVI | LA volume index |
| LVEF | Left ventricular ejection fraction |
| ml | Milliliter |
| MYO | Myocardial |
| MYO-V | MYO-volume |
| POAF | Post-operative AF |
| ROI | Regions of interest |
| SR | Sinus rhythm |

## Introduction

The onset of atrial fibrillation (AF) after cardiac surgery is associated with an increased risk of stroke, higher hospitalization costs and decreased short- and long-term survival.[1,2] In addition, the occurrence of postoperative AF (POAF), although often considered to be a transient phenomenon, is a predictor of later recurrences of AF.[3] For example, patients with a single episode of early POAF have an eightfold increased risk in developing AF later on.[2] Although the exact pathophysiological mechanisms underlying this arrhythmia are still incompletely understood, it is believed that POAF is the result of an interplay between acute factors related to the early postoperative period, and pre-existent substrate related to e.g. heart disease and ageing of the heart.[4]

Epicardial adipose tissue (EAT),[5] defined as the volume of adipose tissue between the myocardium and the visceral pericardium, can lead to structural remodeling and AF substrate development.[6] However, the association between EAT and AF after cardiac surgery remains unclear. Given the transient character of early postoperative AF (POAF), and the role of EAT early in the development of the AF substrate, it is interesting to evaluate the role of EAT in the occurrence of AF after cardiac surgery. Therefore, this study aims to investigate the association between EAT and early POAF in patients undergoing cardiac surgery. We hypothesize that patients with higher EAT volumes are more likely to develop POAF after cardiac surgery than patients with low EAT volumes.

## Patients and Methods

Study design and setting

This retrospective study was approved by the Institutional Review Board (IRB) and Ethics Committee (METC 2018-0448), and analyzed anonymously in accordance with IRB guidelines. The study complies with the ethical principles of the Helsinki Declaration.

Consecutive patients undergoing coronary artery bypass graft (CABG), ascending aorta surgery or surgical aortic valve replacement (AVR) at the Maastricht University Medical Centre+ (the Netherlands) from the 1st of November 2009 until the 31st of December 2019 were potential candidates. We included patients who had undergone a preoperative coronary computed tomographic angiography (CCTA) prior to the surgical procedure. Patients with a history of AF were included in the study to compare baseline characteristics with non-AF patients, but excluded from the primary analysis comparing EAT between POAF and SR to reduce confounding.

Data selection

POAF was defined as an (a)symptomatic episode of supraventricular arrhythmia of at least 30 seconds detected by continuous rhythm monitoring or a 12-lead ECG.[7] Postoperative continuous monitoring was used at least three and four days in patients who underwent CABG or aortic (valve) surgery respectively. In the case of symptoms such as palpitations a 12-lead ECG was obtained.

Computed tomographic imaging protocol

All CT scans were conducted using a standardized protocol, using a second-generation dual source CT scanner (Somatom Definition Flash, Siemens Medical Solutions, Erlangen, Germany; slice collimation 128x0.6mm) or a third-generation dual source CT-scanner (Somatom Force, Siemens Healthineers, Forchheim, Germany; slice collimation 192x0.6mm). Tube voltage of scan protocols varied between 80–120kV. The contrast management (CM) injection protocol consisted of 300 mg I/ml Iopromide (Ultravist, Bayer Healthcare, Berlin, Germany), prewarmed to body temperature (37 ˚C; 99 ˚F), injected using a dual-head CT power injector (Stellant, Bayer).

Depending on the heart rate, a different scan protocol was used. In patients with a stable heart rate <60bpm, a prospectively ECG-triggered "high pitch" spiral protocol was used

("Flash"-technique). A prospectively triggered "adaptive sequence" protocol (prospective sequential data acquisition) was used in patients with a stable heart rate between 60-90bpm. A retrospectively gated helical protocol was used in patients with an irregular heart rhythm or with a heart rate ≥90bpm. To reduce confounding factors in the analysis, all patients who were scanned with an older generation CT-scanner (Brilliance 64, Philips, Healthcare, Best, Netherlands) were excluded, as differences in scan and CM injection parameters (e.g., tube voltage [kV], total injected CM volume, flow rate) have an effect on the attenuation of EAT as measured by Hounsfield Units (HU).

Atrial delineation

LA EAT was manually delineated using an image processing program designed for scientific multidimensional images (ImageJ software, U.S. National Institutes of Health, Bethesda, MD, USA) and a pen tablet (Wacom, Kazo, Saitama, Japan).[8] The regions of interest (ROI) were manually delineated, starting at the basal slice above the mitral valve annulus. In addition to this the left atrial appendage was delineated.[8] Delineation of LA EAT was performed by an independent assessor (C.A.J. van der H.) blinded for patient characteristics and rhythm outcome. In the case of inconclusive quantification, scans were reviewed by a second assessor (B.M.) (Figure 1A and D).

Epicardial adipose tissue calculation

Custom-made semi-automated software developed in ImageJ (AdipoQuant, developed by S.V.) was used to quantify the number of pixels of EAT and myocardial tissue (MYO) based on the HU per ROI. A range within -30 to -190 HU was defined as EAT, while MYO was defined as pixels ranging from 10 to 120 HU (Figure 1B-C and E-F).[8, 9] Thereafter, total LA EAT and MYO volumes (EAT-V and MYO-V) in milliliter (ml) were calculated using several parameters obtained from the metadata of the CCTA, including pixel size, slice thickness and the spacing between slices. EAT-V and MYO-V were used to calculate the percentage of EAT in the LA myocardial wall (EAT-V/[EAT-V+MYO-V] *100).

Consequently, EAT-V and EAT-V indexed to LA-volume (ml) (EAT-LA) were indexed to several clinical parameters that potentially influence the volume of EAT, including body surface area (BSA), body mass index (BMI), MYO-V and left atrial dimension. To determine whether EAT location differed within and between groups, a separate EAT-V analysis at the LA roof was performed. Subsequently, roof EAT-V and non-roof EAT-V (total EAT-V minus roof-EAT-V) were compared (Figure 1D–F).

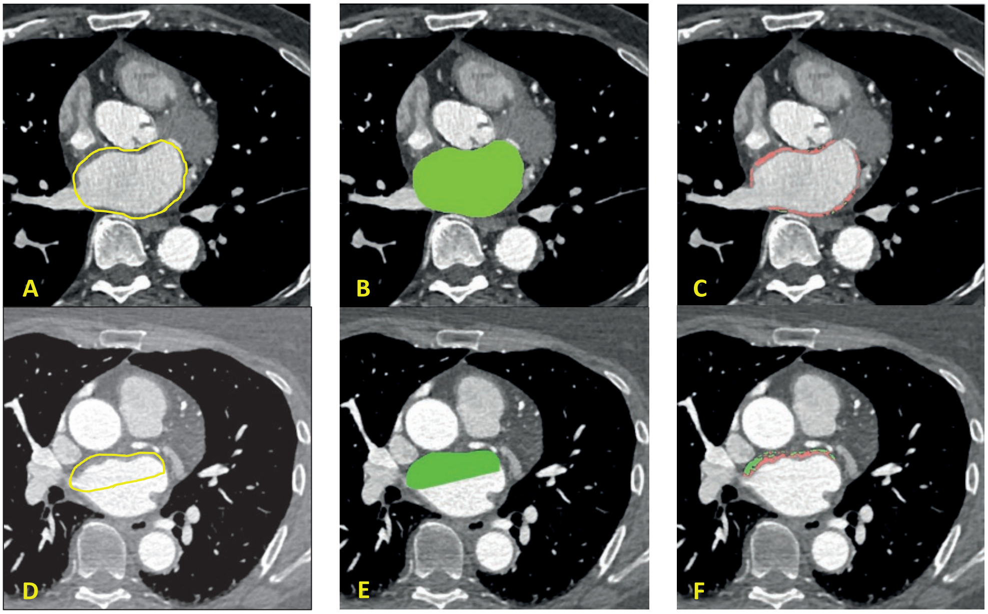


**Figure 1.** Coronary computed tomography angiography images with LA EAT and MYO measurements in the whole wall (**A–C**) and the roof specifically (**D–F**). (**A and D**) Manual delineation of the LA (yellow line). (**B and E**) Selection of the region of interest (green color). (**C and F**) Pixels containing MYO (red color) and EAT (green color) based on HU ranging from 10 to 120 HU and -30 to -190 HU respectively. EAT=epicardial adipose tissue; MYO=myocardial tissue; LA=left atrium; HU=Hounsfield unit.

Statistical analysis

Statistical analysis was performed based on rhythm outcome (POAF versus SR) using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Normality of distribution of continuous variables was tested using the Shapiro-Wilk test and by visual inspection of histograms. A student's t-test was performed for continuous means in case of normality (mean ± standard deviation) and a Mann-Whitney-U test in case of non-normally distributed data (median and interquartile range). A Pearson's $\chi^2$ test or Fisher's exact test was performed to compare categorical variables between both groups. Univariate analyses were performed using Pearson's r or Spearman's Rho, depending on data distribution, between clinical characteristics and EAT variables. Finally, multivariable regression analysis was performed to identify independent predictors of POAF. For all analyses, differences were considered statistically significant if $P<0.05$.

## Results

<u>Study population</u>

Of the screened population, 107 patients that underwent cardiac surgery at Maastricht University Medical Centre between 2009 and 2019 had a preoperative CCTA. Eleven patients were excluded due to incomplete or suboptimal quality of the images and 13 patients were excluded due to being scanned with an older scanner, as outlined in the methods. In addition, 12 patients had a history of AF and were therefore excluded from the EAT analysis only. In total, 83 patients were retrospectively included in our analysis.

Patients were on average 61±10 years old, 24% was female and 42% underwent stand-alone CABG surgery. Patients with POAF had a greater LA volume (82±28ml vs. 68±21ml, $P$=0.039) and LA volume index (LAVI) (41±13 vs. 35±10ml/m$^2$, $P$=0.043). On the other hand, no significant differences were seen in the baseline characteristics age (64±9 vs. 61±11years), BMI (27.3±3.7 vs. 27.2±3.8 kg/m$^2$), BSA (2.0±0.2 vs. 2.0±0.2m$^2$) history of AF (19% vs. 10%) or prior ablation for AF (9% vs. 8%) (all $P$>0.05). However, after stratification based on age (≤60y, 61-64y, 65-70y and ≥71y), there was more POAF in the oldest subgroup (≥71y) (POAF n=15 vs. SR n=7) compared to the youngest subgroup (≤60y) (POAF n=14 vs. SR n=20) (Table 1). Furthermore, there were no significant differences in preoperative drug use between POAF and non-POAF (Table S1).

**Table 1**. Baseline characteristics comparing patients with POAF to SR during hospitalization.

| | POAF (n=43) | SR (n=40) | *P*-value | History of AF (n=12) |
|---|---|---|---|---|
| **Demographics n=83)** | | | | |
| Age (years) | 64 ± 9 | 61 ± 11 | 0.089 | 69 ± 7 |
| ≤60 | 14 (33%) | 20 (50%) | 0.036 | 1 (8%) |
| 61–64 | 9 (21%) | 3 (8%) | | 2 (17%) |
| 65–70 | 5 (12%) | 10 (25%) | | 3 (25%) |
| ≥71 | 15 (35%) | 7 (18%) | | 6 (50%) |
| Female | 10 (23%) | 10 (25%) | 0.853 | 3 (25%) |
| BMI ($kg/m^2$) | 27.3 ± 3.7 | 27.2 ± 3.8 | 0.868 | 27.6 ± 2.5 |
| BSA (Dubois) | 2.0 ± 0.2 | 2.0 ± 0.2 | 0.542 | 1.99 ± 0.1 |
| Logistic Euroscore | 3.3 (2.2 – 4.7) | 2.5 (1.5 – 4.4) | 0.102 | 3.4 (2.6 – 12.8) |
| Euroscore-II | 1.2 (0.9 – 2.4) | 1.2 (0.7 – 1.6) | 0.382 | 1.7 (1.0 – 3.2) |
| Additive Euroscore | 4.0 (3.0 – 6.0) | 3.5 (2.0 – 5.0) | 0.110 | 4.5 (4.0 – 8.5) |
| **AF history** | | | | |
| Paroxysmal | 8 (19%) | 4 (10%) | 0.354 | 12 (100%) |
| Prior ablation | 4 (9%) | 3 (8%) | 1.000 | 4 (33%) |
| **Comorbidities** | | | | |
| $CHA_2DS_2$-VASc | 2 (1 – 3) | 2 (1 – 3) | 0.695 | 3 (2 – 5) |
| COPD | 5 (12%) | 4 (10%) | 1.000 | 1 (8%) |
| OSAS | 3 (7%) | 7 (18%) | 0.185 | 1 (8%) |
| **Echocardiographic measurements** | | | | |
| LA diameter (mm) | 40 ± 6 | 40 ± 6 | 0.743 | 43 ± 6 |
| LA volume (ml) | 82 ± 28 | 68 ± 21 | 0.039 | 74 ± 26 |
| LAVI ($ml/m^2$) | 42 ± 13 | 35 ± 11 | 0.043 | 37 ± 13 |
| LVEF (%) | 59 ± 9 | 57 ± 8 | 0.437 | 58 ± 8 |

Data are presented as mean ± standard deviation, median (interquartile range) or frequencies: n (%). AF=atrial fibrillation; BMI=body mass index; BSA=body surface area; COPD=chronic obstructive pulmonary disease; LA=left atrial; LVEF=left ventricular ejection fraction; LAVI=left atrial volume index; OSAS=obstructive sleep apnea syndrome; POAF=postoperative atrial fibrillation; SR=sinus rhythm.

### Procedural characteristics

All procedures were carried out at Maastricht University Medical Centre. Cardiac surgery consisted of surgery of the ascending aorta (with or without aortic valve repair n=7, with aortic valve repair n=6), isolated aortic valve surgery (repair n=4, replacement n=29) or stand-alone coronary artery bypass graft (CABG) (on-pump n=28, off-pump n=6). A combination of CABG and aortic valve surgery was performed in 9 patients.

Following the procedure, 43/83 (52%) patients developed POAF during hospitalization. The incidence of POAF was lower following isolated CABG surgery (32% POAF vs. 68% SR, *P*=0.003), while no significant difference was seen for aortic valve (64% POAF vs. 36% SR, *P*=0.080) or ascending aorta (86% POAF vs. 14% SR, *P*=0.111) surgery. Of all patients undergoing CABG, only 6 patients received off-pump surgery (17% POAF vs. 83% SR, *P*=0.101). No other surgery or perfusion-related aspects differed between the POAF and SR group (Table 2).

**Table 2**. Procedural characteristics of all patients undergoing cardiac surgery compared by rhythm outcome.

| Characteristics | POAF (n=43) | SR (n=40) | *P*-value |
|---|---|---|---|
| **Type of surgery** | | | |
| Ascending aorta surgery (n=7) | | | |
| With aortic valve replacement or repair | 6 (86%) | 1 (14%) | 0.111 |
| With aortic valve repair | 5 (83%) | 1 (17%) | 0.203 |
| Aortic valve surgery (n=33) | | | |
| All | 21 (64%) | 12 (36%) | 0.080 |
| Repair | 2 (50%) | 2 (50%) | 1.000 |
| Replacement | 19 (66%) | 10 (34%) | 0.067 |
| CABG (n=34) | | | |
| All | 11 (32%) | 23 (68%) | 0.003 |
| Off pump | 1 (17%) | 5 (83%) | 0.101 |
| Combination (n=9) | | | |
| CABG + aortic valve surgery | 5 (56%) | 4 (44%) | 1.000 |
| **Perfusion** | | | |
| Lowest temperature (°C) | 36 (34 – 36) | 36 (36 – 36) | 0.573 |
| Perfusion time (min) | 87 (72 – 120) | 84 (62 – 109) | 0.252 |
| Aortic clamp time (min) | 63 (48 – 84) | 52 (41 – 74) | 0.242 |

Data are presented as frequencies: n (%) or median (interquartile range). CABG=coronary artery bypass graft; POAF=postoperative atrial fibrillation; SR=sinus rhythm.

## Epicardial adipose tissue measurements

EAT-V and MYO-V were calculated for all patients, with exclusion of the patients known with a history of AF (n=12). An example of a patient with a relatively low and high EAT-V on CCTA is shown in figure 2. When comparing the volume of EAT between those with POAF and SR, no significant difference was seen (0.68ml POAF vs. 0.67ml SR, $P$=0.431). Moreover, the percentage of EAT in the LA wall (19.15±8.84 % vs. 19.34±8.30 %) nor EAT-V indexed to BMI (2.67 [1.79–3.61] vs. 2.24 [1.36–3.79]), BSA (0.37 [0.27–0.49] vs. 0.33 [0.19–0.50]), LA volume (1.13 [0.83–1.56] vs. 0.93 [0.72–1.30]), LAVI (2.25 [1.51–3.04] vs. 1.83 [0.86–2.51]) and MYO-V (25.21±14.46 vs. 25.26±12.99) differed between both groups (all $P$>0.05). Also EAT-V indexed to LA (ml) (EAT-LA) indexed to BSA, BMI, LAVI and MYO did not differ between groups either (Table 3). Furthermore, the percentages of EAT of the total LA wall, roof and non-roof did not statistically differ between POAF and SR (all $P$>0.05), but patients with POAF did have a higher percentage of EAT in the roof compared to non-roof (23.28±12.65 vs. 18.23±8.91, $P$=0.020) (Tables 3–4). Followingunivariate analyses, EAT-V variables were positively correlated with MYO-V and the percentage in the LA wall, but not with POAF. A weak positive trend was seen for age and EAT-V normalized to LA volume normalized to BSA, but this was not significant (r=0.270, $P$=0.053). After multivariable logistics regression analysis (with the exclusion of patients with pre-operative AF) using age, LAVI (ml/m$^2$), the total percentage of EAT and the percentage of EAT in the roof, only age and LAVI were independent predictors for developing POAF (odd's ratio (OR)=1.076 [1.007–1.149], $P$=0.030 and 1.056 [1.001–1.115], $P$=0.047, respectively), while the percentages of total EAT and EAT in the roof were not (OR=0.975 [0.883–1.077], $P$=0.621 and 1.070 [0.990–1.156], $P$=0.089, respectively) (Table S2).

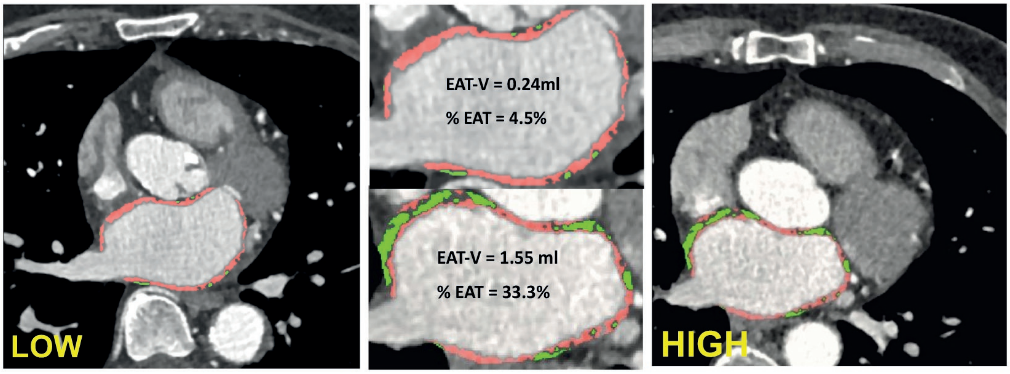


**Figure 2**. Differences in EAT-V (green) and MYO-V (red) between a low and high percentage of EAT in the LA wall, based on the Hounsfield Units. Left and upper middle: low EAT% in the LA wall (EAT-V=0.22 ml, MYO-V=4.63 ml, LA volume measured by TTE=103 ml, EAT%=4.5 %). Right and upper middle: high EAT% in the LA wall (EAT-V=1.55 ml, MYO-V=3.11 ml, LA volume measured by TTE=43 ml, EAT%=33.3 %). EAT-V=epicardial adipose tissue volume; MYO-V=myocardial volume; LA=left atrial; TTE=transthoracic echocardiogram.

**Table 3**. EAT-V and EAT percentage in the LA wall, based on post-operative rhythm outcome. EAT-V were also indexed to BSA, BMI, LAVI and MYO-V.

| Variables | POAF (n=35) | SR (n=36) | *P*-value |
|---|---|---|---|
| **EAT LA wall** | | | |
| EAT-V (ml) | 0.68 (0.51 – 1.04) | 0.67 (0.41 – 0.97) | 0.431 |
| MYO-V (ml) | 2.87 (2.36 – 3.80) | 2.88 (2.09 – 3.62) | 0.265 |
| % EAT | 19.15 ± 8.84 | 19.34 ± 8.30 | 0.929 |
| EAT-V (ml)/BMI (kg/m$^2$) | 2.67 (1.79 – 3.61) | 2.24 (1.36 – 3.79) | 0.577 |
| EAT-V/BSA (m$^2$) | 0.37 (0.27 – 0.49) | 0.33 (0.19 – 0.50) | 0.505 |
| EAT-V/LAVI (ml/m$^2$) (%) | 2.25 (1.51 – 3.04) | 1.83 (0.86 – 2.51) | 0.210 |
| EAT-V (ml)/MYO-V (ml) (%) | 25.21 ± 14.46 | 25.26 ± 12.99 | 0.987 |
| EAT-V/LA (ml) (%) (=EAT-LA) | 1.13 (0.83 – 1.56) | 0.93 (0.72 – 1.30) | 0.203 |
| EAT-LA/BMI (%) | 3.84 (3.13 – 6.19) | 3.39 (2.25 – 5.00) | 0.431 |
| EAT-LA/BSA | 0.57 (0.42 – 0.82) | 0.49 (0.35 – 0.67) | 0.272 |
| EAT-LA/MYO-V | 0.36 (0.16 – 0.53) | 0.32 (0.25 – 0.45) | 0.942 |
| MYO-V/LAVI (%) | 7.94 (6.39 – 11.08) | 7.81 (5.66 – 10.71) | 0.490 |
| **EAT LA wall roof** | | | |
| EAT-V (ml) | 0.12 (0.06 – 0.21) | 0.09 (0.06 – 0.16) | 0.120 |
| MYO-V (ml) | 0.50 (0.34 – 0.70) | 0.46 (0.31 – 0.60) | 0.227 |
| % EAT | 23.28 ± 12.65 | 19.62 ± 10.88 | 0.196 |
| EAT-V roof/LA (%) (=EAT-roof-LA) | 0.19 (0.08 – 0.36) | 0.13 (0.08 – 0.21) | 0.131 |
| (EAT-roof-LA)/BMI (%) | 0.66 (0.32 – 1.29) | 0.46 (0.36 – 0.71) | 0.235 |
| (EAT-roof-LA)/BSA (%) | 8.87 (4.02 – 17.47) | 6.33 (4.77 – 10.25) | 0.168 |
| (EAT-roof-LA)/MYO (%) | 0.37 (0.24 – 0.73) | 0.30 (0.16 – 0.43) | 0.318 |
| **EAT LA wall non -roof** | | | |
| EAT-V (ml) | 0.54 (0.34 – 0.87) | 0.53 (0.32 – 0.85) | 0.760 |
| MYO-V (ml) | 2.46 (1.95 – 3.57) | 2.33 (1.81 – 2.99) | 0.204 |
| % EAT | 18.23 ± 8.91 | 19.19 ± 8.51 | 0.524 |

Data are presented as median (interquartile range) or mean ± standard deviation. EAT-V=epicardial adipose tissue volume; MYO-V=myocardial volume; LA=left atrial; BMI=body mass index; BSA=body surface area; LAVI=left atrial volume index; POAF=postoperative atrial fibrillation; SR=sinus rhythm.

**Table 4**. Comparison of the percentage EAT of the total LA wall, in the roof and non-roof for POAF and SR.

| Groups | % EAT roof | % EAT non-roof | *P*-value |
|---|---|---|---|
| POAF (n=35) | 23.28 ± 12.65 | 18.23 ± 8.91 | 0.020 |
| SR (n=36) | 19.62 ± 10.88 | 19.19 ± 8.51 | 0.753 |

Data are presented as mean ± standard deviation. POAF=postoperative atrial fibrillation; SR=sinus rhythm.

## Discussion

In this study we quantified EAT-V in the left atrial wall. We found that no local EAT-V variables were associated with POAF following cardiac surgery, while advanced age and LAVI were independent predictors of POAF.

Mechanisms underlying EAT and AF

Although previous studies have highlighted the role of EAT in AF, the exact mechanisms of the underlying pathophysiological process remain unclear.[10] In this process, two main potential arrhythmogenic mechanisms can be distinguished. First, EAT directly influences atrial electrophysiological properties by fatty infiltration into the contiguous epicardial layer of the myocardium,[11] resulting in shortening of the atrial refractoriness, thereby favoring local conduction block and micro re-entry circuits.[12, 13] Secondly, paracrine secretion of factors such as adipokines can influence the direct adjacent myocardium, thereby leading to oxidative stress, autonomic- and diastolic dysfunction and adipocyte-related atrial gene expression.[14-16] Eventually, a combination of these factors can induce myocardial inflammation and fibrosis, resulting in slow but progressive structural remodeling and stabilization and perpetuation of AF.[17] On the contrary, Antonopoulos et al. reported a potential protective effect of atrial EAT in relation to oxidative stress.[18] During AF oxidative stress leads to an alteration in gene expression in EAT, such as the adipokine adiponectin. In the human heart, adiponectin in turn decreases myocardial oxidative stress via endocrine or paracrine effects, thereby representing a novel defense mechanism against myocardial oxidative stress. In addition to its role in inflammation and oxidative stress, EAT is involved in lipid and energy homeostasis by secreting free fatty acids.[17] Compared to other visceral depots, it has lower glucose utilization and also has brown fat properties that are hypothesized to protect the myocardium against hypothermia by producing free fatty acids.[17] Non-invasive imaging techniques can be used to measure adipose tissue as a surrogate marker of inflammation.[19] As the attenuation of inflamed adipocytes increases, inflamed cells can be distinguished from non-inflamed cells by CT-scan analyses based on the HU. Furthermore, PET-scan analysis could be used to provide real-time visualization of metabolic and inflammatory activity by the uptake of radioactive tracers within adipose tissue, thus providing more information on the metabolic characteristics of adipose tissue in a certain region of interest.[22] Unfortunately, these kinds of analyses have only been described on peri-coronary adipose tissue and not yet on fatty tissue on the atrial level. Subsequently, these analyses have not yet been validated for atrial adipose tissue and therefore not yet applicable in our population.

<u>EAT and POAF</u>

Since EAT is involved in the early phase of structural remodeling leading to AF, but has also shown to have cardioprotective effects, it is interesting to investigate the role of these early remodeling processes of EAT in the onset of POAF, especially given the transient occurrence of early POAF. In the postoperative setting, Opolski et al.[20] studied independent predictors of POAF after CABG in 108 patients. They found that LA EAT, measured by a comprehensive CCTA analysis using semi-automated software, is a significant predictor of POAF (OR: 1.21). It must be noted that 7% of the included study population had paroxysmal AF, while we excluded patients with diagnosed AF from the EAT analysis as it is known that EAT is associated with the occurrence and severity of AF by the release of adipokines leading to various alterations of the structural and functional properties of the atrial myocardium.[17] Furthermore, in the study by Drossos et al. a strong association between pericardial adipose tissue and POAF was reported following CABG.[21] However, the authors analyzed a mixture of epicardial and pericardial fat and performed whole heart instead of selective atrial analysis. However, in the pathogenesis of AF, the arrhythmic effects of EAT seem local rather than systemic. Furthermore, our study used 2D source data for analysis, while the study of Drossos et al. performed their analysis based on a 3D reconstruction, which may have altered the morphological composition of EAT.[21]

Kogo et al. analyzed the association between EAT and POAF based on local EAT analysis, and did not find an association.[22] Also we did not find a significant correlation between EAT and POAF incidence. It seems that local EAT analysis does not allow to find an association between the quantification of EAT and the onset of POAF, while whole heart analysis of EAT does suggest that there is an association. As such, it might be that analysis of local EAT is not sensitive enough to find an association between EAT and the onset of POAF, but EAT analysis on the level of the whole heart is. On the other hand, it is known that in the acute postoperative phase, surgical induced factors (such as sympathetic activation, oxidative stress and inflammation) and hemodynamic and biochemical instability are known to elicit POAF also in patients with less severe AF substrates.[4, 5] As we performed our EAT analysis in a relatively low-risk population without a history of AF and a LAVI of 38±12 ml/m$^2$, the dominance of these acute factors might obscure the effects of a predisposing substrate in this low risk population.

**Limitations**

This study has some limitations. First, the retrospective character of the study combined with a small number of patients included in this analysis limits drawing valid conclusions. Patients with mitral valve disease were excluded since the underlying etiology of AF is probably different as mitral valve disease causes significant left atrial (LA) dilatation as the result of mitral regurgitation.[23] However, despite this, predictors of POAF such as LA dimension and age were also found to be predictive for POAF in the present study. Secondly, while manual CT-scan analysis is considered a valid technique for measuring EAT and semi-automated quantification in custom made software allows for manual delineation of all regions of interest,[9] no 'gold standard' overcoming human error in the analysis of EAT is yet available to compare our results with. Not only is manual delineation using semi-automated software time consuming (±45 minutes per scan), it can also be difficult to determine the exact anatomic borders of the ROI, such as the caudal and cranial part of the LA, as well as the entry points of the pulmonary veins into the LA. Finally, since both scan and CM injection parameters are patient specific and may differ between scanners, potential bias based on the heterogeneity in the attenuation of EAT as measured in HU cannot be excluded in this study. Although probably less important than LA EAT, as AF most often derives from the PV ostia and the posterior LA, right atrial EAT could not adequately be analyzed in the present study due to the lack of contrast in the right atrium at the time of scanning.

## Conclusion

This study found that advanced age and LAVI were independent predictors of POAF and that patients with POAF have significantly more EAT in the roof compared to non-roof. However, local EAT analysis was not associated with the occurrence of early POAF following cardiac surgery. This might suggest that early postoperative triggers dominate the ignition of early POAF, which potentially obscure the association of POAF with EAT, or that general rather than local effects of EAT play a role in the onset of POAF. Furthermore, perhaps not only the quantification of LA EAT is interesting to analyze, but also its metabolic and inflammatory properties. Therefore, it would be interesting if larger and prospective future studies combined PET-CT scan volume with inflammatory and/or metabolic activity analyses to compare not only the quantity of EAT between POAF and non-POAF, but also the metabolic and inflammatory characteristics of EAT, both systemic and local.

## Acknowledgments and disclosures

None.

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## Supplementary Materials

### Tables

**Table S1**. Drug use in patients with POAF, SR and AF.

| | POAF (n=43) | SR (n=40) | *P*-value | History of AF (n=12) |
|---|---|---|---|---|
| Ace-inhibitor | 11 (31%) | 7 (19%) | 0.246 | 3 (25%) |
| Antibiotic | 5 (14%) | 2 (6%) | 0.260 | 2 (17%) |
| Anti-diabetic | 6 (17%) | 2 (6%) | 0.151 | 3 (25%) |
| Antidepressant | 1 (3%) | 6 (17%) | 0.107 | 2 (17%) |
| Angiotensin-receptor blocker | 7 (20%) | 8 (22%) | 0.819 | 5 (42%) |
| Benzodiazepine | 2 (6%) | 7 (19%) | 0.151 | 1 (8.3%) |
| Beta-blocker | 20 (57%) | 17 (47%) | 0.403 | 5 (42%) |
| Calcium antagonist | 12 (34%) | 8 (22%) | 0.259 | 5 (42%) |
| Diuretic | 8 (23%) | 8 (22%) | 0.949 | 8 (67%) |
| HCN channel blocker | 0 (0%) | 2 (6%) | 0.493 | 0 (0%) |
| Lowering cholesterol | 19 (54%) | 23 (64%) | 0.411 | 11 (92%) |
| Nitrate | 4 (11%) | 8 (22%) | 0.225 | 2 (17%) |
| Oral-anticoagulation | 2 (6%) | 1 (3%) | 0.614 | 5 (42%) |
| Proton pump inhibitor | 12 (34%) | 17 (47%) | 0.268 | 6 (50%) |

Data are presented as frequencies: n (%). AAD=antiarrhythmic drug; HCN=hyperpolarization-activated cyclic nucleotide-gated.

**Table S2.** Multivariable logistic regression analysis.

| Clinical variables | POAF | |
|---|---|---|
| | OR [95% CI] | *P*-value |
| Age (years) | 1.076 [1.007 – 1.149] | *P*=0.030 |
| LAVI (ml/m$^2$) | 1.056 [1.001 – 1.115] | *P*=0.047 |
| Total LA EAT (%) | 0.975 [0.883 – 1.077] | *P*=0.621 |
| EAT LA roof (%) | 1.070 [0.990 – 1.156] | *P*=0.089 |

Data are presented as OR [95% CI], *P*-value. CI=confidence interval; EAT=epicardial adipose tissue; LAVI=left atrial volume index; OR=odd's ratio; POAF=postoperative atrial fibrillation.

# CHAPTER 3

## Hybrid Versus Catheter Ablation in Patients with Persistent and Longstanding Persistent Atrial Fibrillation: A Systematic Review and Meta-Analysis

**Claudia A.J. van der Heijden*,** Mindy Vroomen*, Justin G.L.M. Luermans, Rein Vos, Mark La Meir, Laurent Pison, Bart Maesen

*Both authors contributed equally

*European Journal of Cardiothoracic Surgery. January 2019.*

*Cited in ESC 2020 Atrial Fibrillation Guidelines. 2020.*

**Abstract**

**Introduction** As the mechanisms underlying persistent atrial fibrillation (AF) are still incompletely understood, a ‘golden standard’ ablation strategy is lacking. The results of catheter ablation, independent of the ablation strategy applied, are disappointing. Hybrid ablation, combining a thoracoscopic epicardial and transvenous endocardial approach, has shown more favorable outcomes. To date, studies comparing both techniques are lacking. Therefore, we conducted a systematic review and meta-analysis of hybrid versus catheter ablation in patients with persistent or longstanding persistent AF.

**Methods** A systematic literature search of studies reporting on catheter and hybrid ablation of persistent or longstanding persistent AF was performed in the PubMed database. All identified articles were screened and checked for eligibility. A meta-analysis was performed on inter-study heterogeneity and pooled correlation between baseline characteristics, primary- and secondary outcomes of hybrid and catheter studies.

**Results** From the 520 articles identified by the search, 34 papers could be included in the analysis. Hybrid ablation resulted in higher freedom of atrial arrhythmias in patients with persistent and longstanding-persistent AF than catheter ablation (70.7% vs 49.9%, $P<0.001$). While hybrid ablation had a slightly higher complication rate than catheter ablation, overall morbidity and mortality were low.

**Conclusion** In conclusion, hybrid ablation is more effective than catheter ablation in maintaining sinus rhythm in patients with persistent or longstanding persistent AF. However, data directly comparing both techniques are lacking and small, heterogenic, single-arm studies in a random-effects model hinder to draw definite conclusions. Therefore, larger randomized controlled trials directly comparing both techniques are needed.

**Keywords** Persistent Atrial Fibrillation • Hybrid Ablation • Catheter Ablation • Systematic Review and meta-analysis

## Introduction

Atrial fibrillation (AF) is the most common sustained form of arrhythmia and represents a growing health problem worldwide.[1] The prevalence of AF is estimated to be approximately 3% in all adults >20 years old.[1] While paroxysmal AF is believed to originate from pulmonary vein (PV) ectopy,[2] pathophysiological mechanisms driving persistent AF (persAF) and longstanding persistent AF (LSPAF) are less understood.[3,4] As a consequence, catheter ablation of persAF and LSPAF is far less successful than of paroxysmal AF.[3] One of the major concerns with catheter ablation is the inability to create long-lasting transmural lesions.[5] Stand-alone surgical AF ablation of persAF and LSPAF has been associated with more favorable outcomes.[6] Over the past years, hybrid ablation has gained more attention, because it combines the strengths of endocardial catheter and epicardial surgical ablation.[7, 8]

Although the results of hybrid and catheter ablation have been well reported separately, the outcomes of both procedures have not been compared before. Therefore, we performed a systematic review and meta-analysis comparing the effectiveness between catheter and hybrid ablation in maintaining the sinus rhythm (SR) in patients with persAF or LSPAF after at least 12 months of follow-up.

## Methods

<u>Literature search</u>

This systematic review and meta-analysis is written according to PRISMA standards.[9] In November 2018, a systematic literature search was conducted with both structured MeSH and free terms in the PubMed database: ((((((atrial fibrillation [MeSH Terms]) OR Atrial Fibrillation)) AND ((longstanding persistent atrial fibrillation) OR persistent atrial fibrillation)) AND ((((hybrid ablation) OR hybrid approach) OR hybrid procedure) OR endocardial- epicardial ablation))) OR ((Therapy/Narrow[filter]) AND ((((((atrial fibrillation [MeSH Terms]) OR Atrial Fibrillation)) AND ((catheter ablation [MeSH Terms]) OR catheter ablation)) AND ((longstanding persistent atrial fibrillation) OR persistent atrial fibrillation)))). No forward search was used.

Study selection

All identified studies were screened based on their title and abstract by 2 reviewers. All articles published ≤10 years, reporting in English on simultaneous hybrid ablation, staged hybrid ablation or catheter ablation in humans with persAF and LSPAF were found eligible. In case of uncertainty, full text reports were read. The search was supplemented by manually screening the reference lists of the articles, which were selected based on the search. Next, full texts were read and if they still met the eligibility criteria, the manuscript was included.

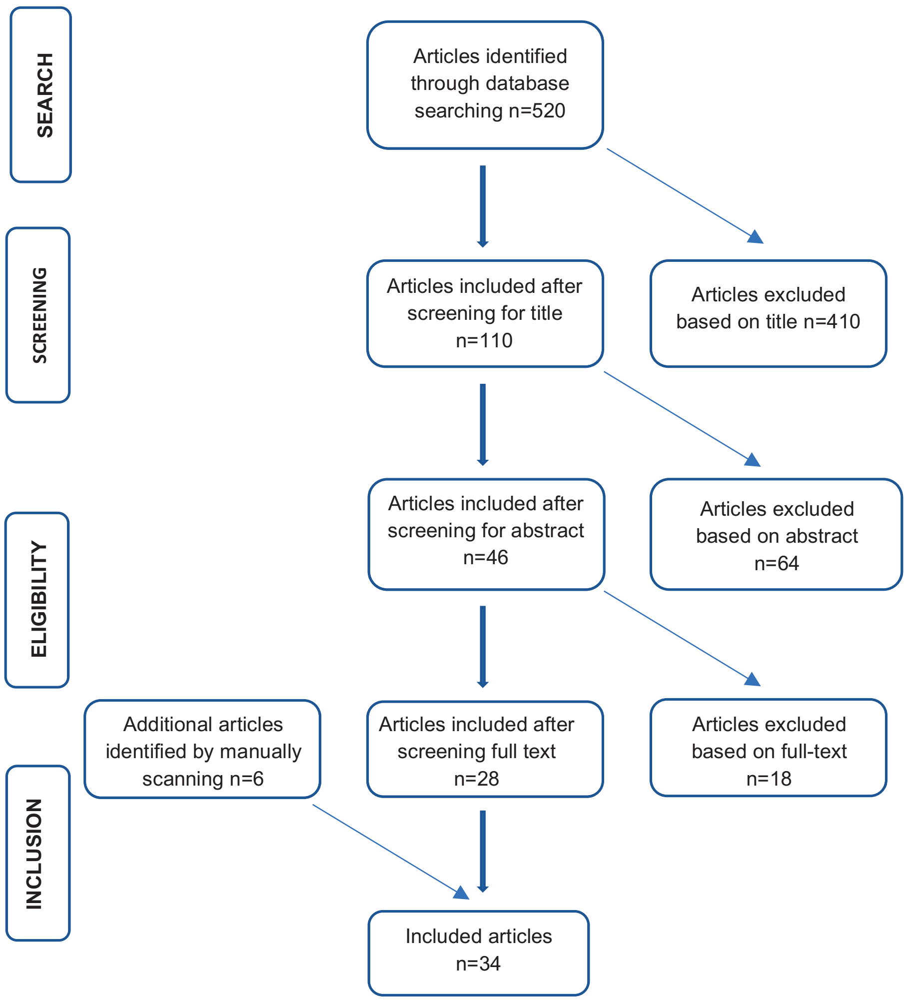


**Figure 1.** Study flow diagram.

Risk of bias

In all observational studies and non-randomized clinical trials, the risk of bias was assessed with the use of the ROBINS-I tool.[10] In articles reporting randomized controlled trials (RCTs), the risk of bias was assessed using the Cochrane Checklist.[11]

Endpoints

The primary outcome was defined as the percentage of patients in SR off antiarrhythmic drugs (AADs) after at least 12 months of follow-up. Secondary outcome measures were hospital mortality and other perioperative major and minor complications.

Statistical analysis

The metric 'Untransformed Proportions', defined as the count of successes in the sample divided by the size of that sample, was used to analyze primary outcomes using study type as a covariate factor.[12] If studies have not specifically differentiated between a primary outcome with or without the use of AADs, primary outcomes were interpreted as without AADs in the meta-analysis.[12] Because of the relatively low complication rates, secondary outcomes were analyzed using the metrics 'Untransformed Proportion' and 'Freeman–Tukey Double Arcsine Proportion'. *P*-values of continuous baseline characteristics were computed using the weighted mean difference (μ) of each group using the metric 'TX Mean', while again 'Untransformed Proportions' were used for *P*-values of continuous data. All statistical values were computed with a 95% confidence interval (CI) in a binary random-effects model, and the 2-tailed *P*-value thresh- old for statistical significance was set at 0.05.

Heterogeneity between hybrid outcomes, catheter outcomes and the combination, was tested and visualized in forest plots. A statistical *P*-value <0.10 and/or $I^2$ >50% was used as cut-off point for significant heterogeneity. All statistical analyses were performed using the Meta-Analyst for Mac software (2009)[12] (version Beta 1.0). Furthermore, publication bias was tested by visual inspection of a funnel plot made in Excel.

## Results

### Study selection

Following the literature search, 34 articles[3, 13-45] were included (Fig. 1, Supplementary Material, Table S1). Reasons for exclusion based on title and abstract were lack of actual results, irrelevant data for this review, different patient population (paroxysmal AF), focus on different outcome measures and performance of catheter ablation only after surgical ablation in case of a recurrence. According to its definition, this is not considered a hybrid ablation procedure.[1] Reviews and meta-analysis were also excluded.

After full text reading, 17 more articles were excluded. Of 17 hybrid studies concerning overlapping patients, 5 studies[13, 15, 19, 21, 23] reporting on the biggest patient population were included. Of 2 catheter studies with overlapping patients, the one with the smallest population was excluded.[41, 46] Four more catheter studies were excluded because success rates after a single procedure without AADs after at least 12 months of follow-up were not reported. Six studies could be added by manually screening the reference lists.[19, 22, 31, 34, 39, 42]

### Risk of bias

The risk of bias in most of the observational and non-randomized studies was estimated to be low. Bias due to con- founding was highest among the studies, followed by measurement of outcomes and missing data. The overall risk of bias of the RCTs seemed low, though not as low as the observational studies, due to selection of participants into the study, blinding, attrition and reporting.
Concerning the publication bias, the funnel plot in Fig. 2 shows that the effect estimates of both hybrid and catheter studies are spread along the x-axis. This indicates that studies with high and low success rates were included, and no publication bias occurred in this review. Figure 2 also shows that most included studies have a relatively high standard error, as the triangular shape along the y-axis is not evident.[47] This could be explained by the poor methodological study designs. Consequently, the dispersion of estimates between studies is high, including the variance within each study. In the included catheter studies, a wide distribution of effect estimates with low standard error is present and only few outliers with high standard error are reported. On the other hand, hybrid studies are

pointed more towards a higher standard error, meaning that the variance between catheter studies and within each study was lower than for hybrid studies, possibly because sample sizes were bigger. However, the forest plots illustrate that both hybrid and catheter ablation showed marked heterogeneity (*P*<0.001).

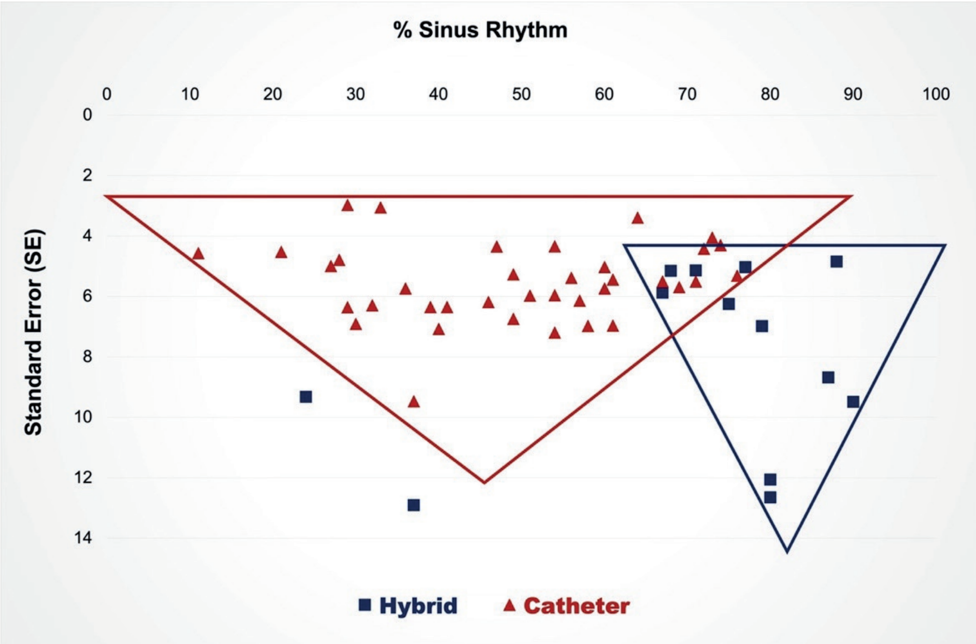


**Figure 2.** Funnel plot. The percentage in sinus rhythm at the end of follow-up plotted against the standard error of that study.

### Baseline characteristics

Differences in baseline characteristics between hybrid and catheter studies are presented in Table 1. Study size samples were bigger in the catheter studies. Age, gender distribution, type of AF, body mass index and comorbidities including hypertension and diabetes mellitus were comparable (60.2 vs. 59.9 years, *P*=0.765; 20.4% vs. 24.3% females, *P*=0.129; 53.5% vs. 49.6% LSPAF, *P*=0.771, 29.4 vs. 28.6 kg/$m^2$, *P*=0.394; 60.3% vs. 56.1% hypertension, *P*=0.387; 20.4% vs. 13.2% diabetes, *P*=0.096). Left atrial dimension was significantly larger in patients undergoing hybrid ablation compared to the patients undergoing catheter ablation (49.2 vs. 45.4 mm, *P*=0.001). Furthermore, the left ventricle ejection fraction was significantly lower in patients undergoing hybrid ablation (52.5% vs. 57.9%, *P*=0.001). More baseline characteristics are summarized in

Supplementary Table S2. Due to incomplete reporting of baseline data, no differences in AF duration, LA volume or other comorbidities could be studied.

**Table 1.** Differences in characteristics between hybrid and catheter studies at baseline.

| Characteristics | Hybrid (total patients n=574) | Catheter (total patients n=3291) | *P*-value |
|---|---|---|---|
| **Age (years)** | 60.2 [58.3 – 62.2] | 59.9 [58.9 – 60.9] | 0.765 |
| **Females (%)** | 20.4 [15.9 – 24.9] | 24.3 [22.0 – 26.6] | 0.129 |
| **Longstanding persistent AF (%)** | 53.5 [30.8 – 76.1] | 49.6 [36.3 – 62.8] | 0.771 |
| **Left Atrial Dimension** | 49.2 [47.6 – 50.7] | 45.4 [44.7 – 46.2] | 0.001 |
| **LVEF (%)** | 52.6 [49.9 – 55.3] | 57.9 [56.4 – 59.4] | 0.001 |
| **Body Mass Index (kg/m$^2$)** | 29.4 [27.7 – 31.1] | 28.6 [27.5 – 29.7] | 0.394 |
| **Hypertension (%)** | 60.3 [51.9 – 68.6] | 56.1 [51.6 – 60.6] | 0.387 |
| **Diabetes mellitus (%)** | 20.4 [13.1 – 27.7] | 13.2 [8.7 – 17.6] | 0.096 |

AF=atrial fibrillation, LVEF=left ventricular ejection fraction. Data is presented as adjusted means or proportions followed by the 95% confidence interval. *P*-value of the meta-regression was computed using the metric 'Untransformed Proportion' in a binary random-effects model using study type as covariate factor.

### Perioperative data

All hybrid and catheter ablation studies performed at least PV isolation (PVI). In 13 studies, patients were randomized into 2 or 3 groups with different ablation strategies.[3, 28-33, 35, 38, 40, 43-45] Nine out of 13 hybrid studies occluded or excluded the left atrial appendage (LAA) in some or all of the patients on top of standard ablation, and 2 out of 21 catheter ablation studies electrically isolated the LAA. See the Supplementary Material, Table S3 for more perioperative data.

Primary outcome

The primary outcome of all studies reporting on hybrid or catheter ablation was the percentage of patients in SR after at least 12 months of follow-up, without the use of AADs (Table 2). Hybrid ablation was more effective in maintaining SR than a single catheter ablation (70.7% vs 49.9%, $P<0.001$). This is also illustrated in the Forest plots (Fig. 3A and 3B). Two hybrid studies (Edgerton et al.[17] and La Meir et al.[21]) showed remarkably poor results (24% and 37%, respectively). Most probably, this is related to the use of unipolar radiofrequency (RF). The plot also shows a high inter-study variance between the measured effects in hybrid and catheter ablation studies. Majority of the included studies, mostly hybrid studies, have a broad 95% CI. Although point estimates are higher in hybrid studies, the broad 95% CI indicates a less reliable result with a high degree of within-study variance.[48] When statistically testing for the degree of heterogeneity, this was proven to be highly significant [hybrid: $\tau^2 = 0.016$, $\chi(df = 12) = 54.980$, $P<0.001$, $I^2 = 78.2\%$; catheter: $\tau^2 = 0.030$, $\chi(df = 38) = 464.742$, $P<0.001$, $I^2 = 91.8\%$].

Moreover, most studies reported a mean follow-up duration of 12 months, though overall follow-up in the hybrid studies seemed longer. Because of incomplete reporting of this variable in the majority of included studies, available data were insufficient to perform an analysis to confirm this difference. Also, in hybrid studies the monitoring during follow-up was more extensive, mostly a 7-day Holter was performed compared to a 48-h Holter in catheter ablation studies.

**Table 2.** Follow-up.

| **Study** | Follow-up (months ± SD) | Follow-up reached (%) | Patients at follow-up (n) | Sinus rhythm at follow-up after a single procedure (%) | | Monitoring at the end of follow-up |
|---|---|---|---|---|---|---|
| | | | | With AADs | Without AADs | |
| **Hybrid** | | | | | | |
| *Bisleri (2013)* | 28±2 | 100 | 45 | **88*** | **88*** | ILR |
| *Budera (2017)* | 12 | 89 | 34 | **82** | **79** | 24-h Holter |
| *Bulava (2017)* | 12 | 100 | 70 | - | **77** | 7-day Holter |
| *de Asmundis (2017)* | 23±14 | 100 | 64 | - | **67** | 24-h Holter |
| *Edgerton (2016)* | 12 | 88 | 21 | **24*** | **24*** | 7-day Holter |
| *Gehi (2013)* | 12 | 98 | 82 | **58** | **68** | 24-h Holter |
| *Gersak (2012)* | 12 | 96 | 45 | **88** | **75** | ILR |
| *Krul (2011)* | 12 | 71 | 11 | - | **80** | 24-h Holter |
| *La Meir (2012)* | 12 | 100 | 14 | **63** | **37** | 7-day Holter |
| *Mahapatra (2011)* | 16±2 | 100 | 15 | **93** | **87** | 24-h Holter |
| *Pison (2014)* | 24 (12-36) | 100 | 49 | - | **73** | 7-day Holter |
| *Richardson (2016)* | 12 | 95 | 78 | **71*** | **71*** | ILR or pacemaker |
| *Zembala (2012)* | 12 | 37 | 10 | - | **80** | 7-day Holter or ILR |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Catheter** | | | | | | |
| *Bassiouny (2016)* | 12 | 100 | 44 | - | **30** | 24- or 48-h Holter |
| *Boersma (2012)* | 12 | 100 | 26 | **43** | **37** | 7-day Holter |
| *Di Biase (2016)*[1] | 12 | 100 | 85 | - | **56** | 48-h or 7-day Holter |
| *Di Biase (2016)*[2] | 12 | 100 | 88 | - | **28** | 48-h or 7-day Holter |
| *Dixit (2012)*[1] | 12 | 100 | 55 | - | **49** | NS |
| *Dixit (2012)*[2] | 12 | 100 | 50 | - | **58** | NS |
| *Dixit (2012)*[3] | 12 | 100 | 51 | - | **29** | NS |
| *Dong (2015)*[1] | 12 | 100 | 73 | **67** | - | 48-h Holter |
| *Dong (2015)*[2] | 12 | 100 | 73 | **60** | - | 48-h Holter |
| *Elayi (2008)*[1] | 17±2 | - | 47 | - | **11** | 48-h Holter |
| *Elayi (2008)*[2] | 16±1 | - | 48 | - | **40** | 48-h Holter |
| *Elayi (2008)*[3] | 16±1 | - | 49 | - | **61** | 48-h Holter |
| *Elayi (2011)*[1] | 17±5 | 100 | 48 | **69** | **54** | 48-h Holter |
| *Elayi (2011)*[2] | 17±5 | 100 | 50 | **72** | **58** | 48-h Holter |
| *Fink (2017)*[1] | 12 | 97 | 59 | - | **39** | 24-h Holter |
| *Fink (2017)*[2] | 12 | 96 | 55 | - | **32** | 24-h Holter |
| *Gaita (2008)* | 12 | 100 | 79 | - | **27** | 24-h Holter |
| *Kim (2015)* | 12 | 100 | **120** | **73*** | **73*** | 48-h Holter |
| *Kim (2017)*[1] | 23 [17-28] | 100 | 29 | - | **76** | 24-h Holter |
| *Kim (2017)*[2] | 21 [10-33] | 100 | 54 | - | **72** | 24-h Holter |
| *Kim (2017)*[3] | 26 [10-35] | 100 | 54 | - | **61** | 24-h Holter |
| *Mont (2014)* | 12 | 97 | 95 | **60*** | **60*** | 24-h Holter |
| *Pokushalov (2013)*[1] | 12 | - | 132 | - | **54** | ILR |
| *Pokushalov (2013)*[2] | 12 | - | 132 | - | **47** | ILR |
| *Rostock (2011)* | 27±7 | - | 81 | **27** | **21** | Holter |
| *Schmidt (2017)*[1] | 12 | 92 | 66 | - | **69** | 72-h Holter |
| *Schmidt (2017)*[2] | 12 | 91 | 68 | | **71** | 72-h Holter |
| *Singh (2016)* | 12 | 95 | 90 | **51** | **49** | 7-to-24-day Holter |
| *Tilz (2012)* | 56 (49-67) | 99 | 200 | **64*** | **64*** | 24-h Holter |
| *Verma (2015)*[1] | 18 | 90 | 60 | **49** | **41** | Holter |
| *Verma (2015)*[2] | 18 | 90 | 237 | **41** | **33** | Holter |
| *Verma (2015)*[3] | 18 | 90 | 233 | **37** | **29** | Holter |
| *Wang (2013)*[1] | - | - | 70 | **54*** | **54*** | 7-day Holter |
| *Wang (2013)*[2] | - | - | 70 | **51*** | **51*** | 7-day Holter |
| *Wang (2013)*[3] | - | - | 70 | **36*** | **36*** | 7-day Holter |
| *Wong (2015)*[1] | 12 | 100 | 65 | - | **57** | Holter |
| *Wong (2015)*[2] | 12 | 100 | 65 | - | **46** | Holter |
| *Yang (2017)*[1] | 18 | 91 | 104 | - | **74** | 24-h Holter |
| *Yang (2017)*[2] | 18 | 90 | 103 | - | **72** | 24-h Holter |

AADs=antiarrhythmic drugs, ILR=implanted rhythm monitoring, h=hour, *=unclear whether this is with or without the use of AADs.

| Study | Estimate | 95 % C.I. | Ev/Trt |
|---|---|---|---|
| Bisleri 2013 | 0.889 | (0.797, 0.981) | 40/45 |
| Budera 2017 | 0.794 | (0.658, 0.930) | 27/34 |
| Bulava 2017 | 0.771 | (0.673, 0.870) | 54/70 |
| de Asmundis 2017 | 0.672 | (0.557, 0.787) | 43/64 |
| Edgerton 2016 | 0.238 | (0.056, 0.420) | 5/21 |
| Gehi 2013 | 0.683 | (0.582, 0.784) | 56/82 |
| Gersak 2012 | 0.756 | (0.630, 0.881) | 34/45 |
| Krul 2011 | 0.818 | (0.590, 1.000) | 9/11 |
| La Meir 2012 | 0.357 | (0.106, 0.608) | 5/14 |
| Mahapatra 2011 | 0.867 | (0.695, 1.000) | 13/15 |
| Pison 2014 | 0.735 | (0.611, 0.858) | 36/49 |
| Richardson 2016 | 0.705 | (0.604, 0.806) | 55/78 |
| Zembala 2012 | 0.800 | (0.552, 1.000) | 8/10 |
| **Overall (I^2=7817%, P<0.001)** | **0.710** | **(0.630, 0.790)** | **385/538** |

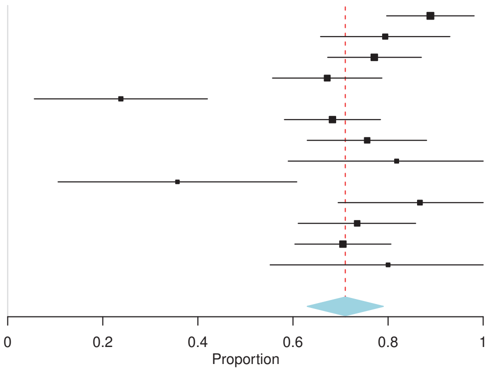


**Figure 3A.** Forest plot showing success rates after hybrid ablation.
Forest plot illustrating the weight given to each study (area of the black box), point effect estimate (mid-point of the black box) and the degree of variance per study (horizontal line through the black box). The overall effect estimate is represented by the diamante shape. A greater width line indicates a greater 95% confidence interval for the effect estimates. Heterogeneity: $\tau^2 = 0.016$, $\chi(df = 12) = 54.980$, $P<0.001$, $I^2 = 78.2\%$.

| Study | Estimate | 95 % C.I. | Ev/Trt |
|---|---|---|---|
| Bassiouny 2016 | 0.295 | (0.161, 0.430) | 13/44 |
| Boersma 2012 | 0.385 | (0.198, 0.572) | 10/26 |
| Di Biase_PVI + lines 2016 | 0.565 | (0.459, 0.670) | 48/85 |
| Di Biase_PVE + lines 2016 | 0.284 | (0.190, 0.378) | 25/88 |
| Dixit_PVI 2012 | 0.491 | (0.359, 0.623) | 27/55 |
| Dixit_PVI + lines 2012 | 0.580 | (0.443, 0.717) | 29/50 |
| Dixit_PVI + CFAE 2012 | 0.294 | (0.169, 0.419) | 15/51 |
| Dong_fixed approach 2015 | 0.671 | (0.563, 0.779) | 49/73 |
| Dong_stepwise approach 2015 | 0.603 | (0.490, 0.715) | 44/73 |
| Elayi_CPVI 2008 | 0.106 | (0.018, 0.195) | 5/47 |
| Elayi_PVI 2008 | 0.396 | (0.257, 0.534) | 19/48 |
| Elayi_PVI + CFAE 2008 | 0.612 | (0.476, 0.749) | 30/49 |
| Elayi_PVI 2011 | 0.542 | (0.401, 0.683) | 26/48 |
| Elayi_ PVI + CFAE 2011 | 0.580 | (0.443, 0.717) | 29/50 |
| Fink_PVI 2017 | 0.390 | (0.265, 0.514) | 23/59 |
| Fink_PVI + lines 2017 | 0.327 | (0.203, 0.451) | 18/55 |
| Gaita 2008 | 0.266 | (0.168, 0.363) | 21/79 |
| Kim 2015 | 0.733 | (0.654, 0.812) | 88/120 |
| Kim_PVI + lines (SR) 2017 | 0.759 | (0.603, 0.914) | 22/29 |
| Kim_PVI + lines (AF) 2017 | 0.722 | (0.603, 0.842) | 39/54 |
| Kim_PVI + lines + CFAE (AF) 2017 | 0.611 | (0.481, 0.741) | 33/54 |
| Mont 2014 | 0.600 | (0.501, 0.699) | 57/95 |
| Pokushalov_PVI + GP 2013 | 0.538 | (0.453, 0.623) | 71/132 |
| Pokushalov_ PVI + LL 2013 | 0.470 | (0.385, 0.555) | 62/132 |
| Rostock 2011 | 0.210 | (0.121, 0.299) | 17/81 |
| Schmidt_1 2017 | 0.697 | (0.586, 0.808) | 46/66 |
| Schmidt_2 2017 | 0.706 | (0.598, 0.814) | 48/68 |
| Singh 2016 | 0.489 | (0.386, 0.592) | 44/90 |
| Tilz 2012 | 0.640 | (0.573, 0.707) | 128/200 |
| Verma_PVI 2015 | 0.417 | (0.292, 0.541) | 25/60 |
| Verma_PVI + CFAE 2015 | 0.329 | (0.269, 0.389) | 78/237 |
| Verma_PVI + lines 2015 | 0.292 | (0.233, 0.350) | 68/233 |
| Wang_ PVI + lines + CFAE 2013 | 0.543 | (0.426, 0.660) | 38/70 |
| Wang_PVI + lines + CFAE 2013 | 0.514 | (0.397, 0.631) | 36/70 |
| Wang_PVI + CFAE 2013 | 0.357 | (0.245, 0.469) | 25/70 |
| Wong_ PVI + lines 2015 | 0.569 | (0.449, 0.690) | 37/65 |
| Wong_ PVI + lines + CFAE 2015 | 0.462 | (0.340, 0.583) | 30/65 |
| Yang_PVI + lines 2017 | 0.740 | (0.656, 0.825) | 77/104 |
| Yang_PVI + lines + CFAE 2017 | 0.718 | (0.632, 0.805) | 74/103 |
| **Overall (I^2=9182%, P<0.001)** | **0.500** | **(0.442, 0.557)** | **1571/3178** |

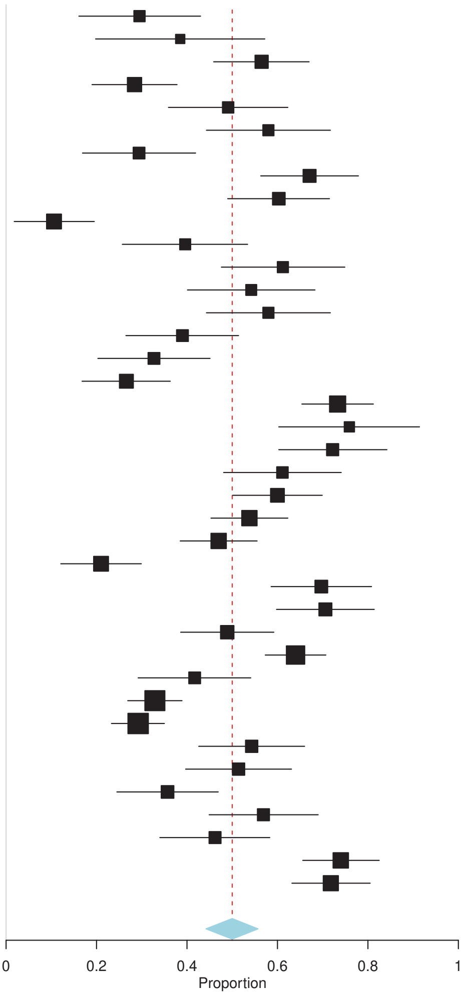


**Figure 3B.** Forest plot showing success rates after catheter ablation.
Heterogeneity: $\tau^2 = 0.030$, $\chi(df = 38) = 464.742$, $P<0.001$, $I^2 = 91.8\%$.

### Secondary outcomes

Differences in complication rates between hybrid and catheter ablation are presented in Table 3. Complications that were significantly higher among hybrid studies include: bleeding requiring transfusion (1.6% vs. 0.4%, *P*=0.000), conversion to sternotomy (1.1% vs. 0.4%, *P*=0.010), cardiac tamponade (1.7% vs. 0.7%, *P*=0.049), hospital mortality (1.1% vs. 0.5%, *P*=0.007), pacemaker implantation (1.0% vs. 0.4%, *P*=0.041), phrenic nerve injury (1.2% vs. 0.4%, *P*=0.002), pneumothorax (1.0% vs. 0.4%, *P*=0.033) and PV stenosis not requiring stenting (1.0% vs. 0.4%, *P*=0.007). Cardiac tamponade was reported in all except 6 catheter ablation studies. Most complications resulting from catheter ablation included groin hematoma requiring therapy and thromboembolic events, though incidences were not significantly higher compared to hybrid studies (0.9% vs. 0.6%, *P*=0.602 and 0.9% vs. 0.8%, *P*=0.302, respectively). More information is presented in the Supplementary Material, Table S4.

**Table 3.** Differences in outcome and complications between hybrid and catheter studies.

| | **Hybrid** | | **Catheter** | | ***P*-value** |
|---|---|---|---|---|---|
| **Primary outcome** | | | | | |
| SR after ≥12 months of follow-up | 70.7% [61.2-80.2] | | 49.9% [44.7-55.2] | | 0.000 |
| **Complications** | Number of patients of total group (n= 574) | Adjusted mean [95% CI] | Number of patients of total group (n= 53291) | Adjusted mean [95% CI] | |
| Bleeding: reoperation | n=1 | 0.9% [0.1-1.7] | n=0 | 0.4% [0.2-0.6] | 0.074 |
| Bleeding: transfusion | n=17 | 1.6% [0.6-2.7] | n=0 | 0.4% [0.2-0.7] | 0.000 |
| Conversion to sternotomy | n=7 | 1.1% [0.2-1.9] | n=0 | 0.4% [0.2-0.7] | 0.010 |
| Groin hematoma | n=1 | 0.9% [0.2-1.7] | n=35 | 0.6% [0.3-0.9] | 0.602 |
| Hospital mortality | n=7 | 1.1% [0.3-2.0] | n=1 | 0.5% [0.2-0.7] | 0.007 |
| PM implantation | n=3 | 1.0% [0.2-1.8] | n=3 | 0.4% [0.2-0.7] | 0.041 |
| Phrenic nerve injury | n=10 | 1.2% [0.3-2.1] | n=3 | 0.4% [0.2-0.7] | 0.002 |
| Pneumothorax | n=4 | 1.0% [0.2-1.8] | n=1 | 0.4% [0.2-0.7] | 0.033 |
| PV narrowing: stenting | n=1 | 0.9% [0.2-1.7] | n=1 | 0.5% [0.2-0.7] | 0.074 |
| PV narrowing, insignificant | n=7 | 1.0% [0.2-1.8] | n=4 | 0.4% [0.2-0.7] | 0.007 |
| Stroke/TIA | n=4 | 0.9% [0.2-1.7] | n=27 | 0.8% [0.5-1.1] | 0.302 |
| Tamponade | n=9 | 1.7% [0.6-2.7] | n=32 | 0.7% [0.4-1.0] | 0.049 |

#Data are presented as the total number of patients of all hybrid and catheter studies per complication, followed by the adjusted mean of proportion and the 95% confidence interval (CI) in a binary random-effects model. Statistical tests primary outcome: one-arm meta-regression “Untransformed Proportion”. Statistical test secondary outcomes: one-arm meta-regression “Untransformed Proportion” and “Freeman-Tukey Double Arcsine Proportion”. PM=pacemaker; PV=pulmonary vein; SR=sinus rhythm, TIA=transient ischemic attack.

## Discussion

To the best of our knowledge, this is the first systematic review comparing rhythm outcome and complications between hybrid ablation and catheter ablation in patients with persAF and LSPAF. At 12-months follow-up or more, hybrid ablation resulted in a significantly higher rate of freedom from atrial arrhythmias without the use of AAD than catheter ablation. Although hybrid ablation was associated with a slightly higher complication rate compared to catheter ablation, the overall rate of complications was low.

### Primary outcome

Both hybrid and catheter ablation improve SR in patients with persAF or LSPAF, with or without the use of AADs. Even though patients undergoing hybrid ablation had significantly larger left atria and a diminished left ventricular ejection fraction, hybrid ablation was more effective in maintaining SR than catheter ablation (70.7% vs 49.9%, $P<0.001$). There are several explanations for this difference. First, the bipolar RF PV clamp is very effective in creating acute and long-lasting transmural lesions of PV.[16, 49] Secondly, hybrid ablation offers the opportunity of endocardial touch-up of conduction gaps after epicardial ablation alone.[21, 50] Also, a surgical approach allows direct visual identification of the targeted structures.

Based on the results of this review, the outcome is not affected whether the endocardial part of the hybrid procedure is done simultaneously (single procedure) or after a predefined period (staged procedure).[13] Arguments favoring a single procedure are the intensive collaboration between the cardiac surgeon and electrophysiologist and the fact that it is more patient friendly. Arguments favoring a staged approach are avoiding the logistic challenge of facilitating a single-procedure approach and avoiding the possibility of only temporary conduction block due to tissue edema.[24, 50] The relevance of the latter argument, however, is limited, because we found no difference in the outcome between single and staged hybrid procedures. While overall success rates were higher after a hybrid procedure, Edgerton et al.[17] reported remarkably low success rates and a complication rate (20.8%). Besides the fact that all included patients had LSPAF and significant atrial enlargement (left atrial dimension of 52±3mm), the use of a unipolar RF device might explain their poor results. This might also account for the study by La Meir et al.[21], who reported success rates of 63% and 37% (with and without the use of AADs, respectively). Bipolar RF devices (AtriCure, OH, USA) have proven to be more effective than unipolar devices in creating transmural lesions.[51] In the catheter group, multiple procedures are often necessary to improve success rates, thereby increasing risks of complications. It should be noted that catheter ablation is a contemporary mainstream therapy, whereas hybrid ablation is still limited to a few expert centers with extraordinary collaboration and very good in-hospital logistics. A possible interpretation of the results of this review could be that LSPAF should not be targeted anymore by catheter ablation and that building more centers of excellence for collaboration between electrophysiologists and cardiac surgeons to perform a hybrid ablation should be encouraged.

**Lesion types**

In all studies reporting on catheter and hybrid ablation, PVI is performed. For paroxysmal AF, it is recognized that triggers initiating paroxysmal AF are frequently located in and around the PVs.[2] Even though its underlying mechanism is less understood, in persAF, PVI also represents the cornerstone of AF ablation.[6] Besides the PVs, also other parts of the left atrium seem to play a role in maintaining AF. As reported by Saad and Slater,[52] PVI does not prevent AF recurrences in patients with persAF and especially LSPAF. Creating the so-called box lesion (i.e. connecting inferior and roof lines between both isolated PV pairs, leading to complete posterior wall isolation) has proven to enhance success rates in patients with persAF and LSPAF.[8] This finding probably only applies if a long-lasting PVI has been performed.[6] While PV reconduction following endocardial ablation in patients with LSPAF is high (76% showed reconnection 5 years after ablation[42]), epicardial ablation using a bipolar RF clamp is associated with a much higher degree of transmurality. According to Velagic et al.[49], only 7% of the box lesions were incomplete and 9% of the PVs were reconnected in patients with LSPAF after a single hybrid procedure. Next to substrate modification by adding linear lines CFAE ablation was also used in several studies. CFAE ablation was only executed in 1 hybrid study conducted by Gehi et al.[18], but the authors failed to show improved effectiveness in SR maintenance with or without AADs (58% and 68%) at the end of the follow-up in comparison to the other hybrid studies.

In catheter ablation, the role of CFAE was more thoroughly investigated. In the study by Elayi et al.,[31] the strategy of combining PVI with CFAE ablation was most effective in AF termination and SR maintenance off AAD compared to circumferential PVI and PVI only

(61% vs 11% and 40%, respectively). The incremental value of CFAE ablation on long-term SR maintenance is thought to be due to the diminishment of non-PV triggers, reduction of vast atrial mass leading to a smaller proportion of the atrium able to fibrillate and ablation of regions that sustain perpetuation of AF. On the other hand, no benefit of CFAE ablation was observed in the STAR-AF II trial.[3] It should be noted that extensive CFAE ablation may actually cause new iatrogenic areas of arrhythmogenesis if a complete transmural isolation block is not achieved.[53]

Left atrial appendage

A major advantage of the hybrid ablation is the unique possibility to simultaneously treat the LAA. In most hybrid studies, surgical LAA occlusion and thus consequent ‘electrical isolation’ was performed using a clipping or stapling device. Although the role of the LAA in arrhythmogenesis has not been widely reported, it is considered to be a common site of non-PV sources in initiating or maintaining AF.[54] Surgical exclusion (amputation, stapler or clip) of the LAA does not only induce electrical isolation but also prevent the formation of clots, thereby potentially reducing the stroke risk.[55]

As for catheter ablation, 2 of 21 included studies performed electrical LAA isolation, but none of the LAAs were occluded. Compared to Tilz et al.[42] who isolated the LAA only in 10% of patients, Di Biase et al.[28] examined the role of empirical LAA isolation to a greater extent. In the BELIEF Trial, empirical electrical isolation of the LAA improved long-term (2-years) freedom from atrial arrhythmias compared to extensive ablation alone (56% vs. 24%, respectively)[28]. As a major drawback, electrical isolation without occlusion of the LAA might induce an elevated stroke risk and the need for lifelong oral anticoagulation therapy.[28] Surprisingly, Di Biase et al. reported a 0% and 4.5% stroke in the group that did and did not receive electrical LAA isolation, respectively.[28] On the other hand, Edgerton et al. performed electrical LAA isolation without occlusion in all patients and reported a stroke incidence of 8.3%.[17]

**Meta-analysis and meta-regression**

The marked heterogeneity variance in this review can be explained by several factors. First, all effect estimates of the included studies are based on single-arm studies in a random-effects model. As such, reported results of intervention groups were not compared with controls; hybrid ablation was not directly compared with catheter ablation in one RCT. Per definition, single-arm studies come with a high degree of inter-study variance. Secondly, the type of lesion and/or technique differed between studies. Because some techniques have been illustrated to be more effective in creating transmural lesions than others, inter-study outcome variance increases. Other possible reasons for heterogeneity in this review on a patient, technical or surgical level include differences in left atrial dimension, the surgeon's learning curve, small sample sizes and outliers with poor results that lead to scattering of results.[17, 21]

**Secondary outcomes**

The incidence of major complications, including bleeding requiring transfusion, conversion to sternotomy, hospital mortality, insignificant pulmonary vein narrowing, pacemaker implantation, phrenic nerve injury, pneumothorax and tamponade was significantly higher in hybrid than in catheter studies. First, it should be noted that hybrid ablation is a combination of a surgical and a catheter procedure. Secondly, the hybrid procedure, although minimally invasive, remains a surgical procedure. When considering full anesthesia, single-lung ventilation and thoracoscopic surgical dissection, we believe that the complication rate for the hybrid procedure is far from excessive.

Finally, 6/13 studies in the hybrid arm, but none in the catheter arm, reported on first experiences or complications that mainly occurred in the first patients.[15-18, 20, 22] In the catheter arm, several studies specified that they were conducted in experienced centers.[3, 35-37, 39, 40, 45] As such, the learning curve seems to have played a significant role in the complication rate reported in the hybrid group, but not in the catheter group. For example, Edgerton et al. reported on the first series of hybrid procedures conducted at their center and the complication rate was surprisingly high (12.5% mortality) compared to other studies.[17]

**Limitations**

The main limitation of this systematic review is that all included studies reported on the outcomes of 2 different procedures separately, as data directly comparing both techniques are lacking. Furthermore, estimation of the interval is difficult with such extreme low risks as intervals are not completely reliable with such low numbers. Another important limitation is the risk of bias of the included studies, which may compromise their validity. Bias due to confounding, selection, missing/unspecified data and differences in mean follow-up most frequently occurred. Risk of bias seemed higher in the studies reporting on catheter than hybrid ablation. This variation may largely be attributed to the difference in study designs and the use of different tools to assess this risk. All studies reporting on hybrid ablation were prospective or retrospective observational designs. While their overall risk of bias was assessed low, the validity of measured outcomes of observational studies was less evidence based than that of RCTs. Based on the criterion for hierarchical rankings, observational studies (effectiveness studies) are methodologically less evidence based compared to the gold-standard RCT, as RCTs (efficacy studies) eliminate selection bias.[56]

## Conclusion

In patients with persistent and longstanding persistent AF, this meta-analysis demonstrates that hybrid ablation is associated with higher success rates in maintaining SR compared to catheter ablation. Although overall mortality and morbidity of both techniques is low, hybrid ablation has a slightly higher complication rate than catheter ablation. However, data directly comparing both techniques have only been minimally described in literature and small, heterogenic single-arm studies hinder drawing definite conclusions. Therefore, larger randomized controlled trials that directly investigate the effectiveness and safety of both techniques are needed to recommend future treatments.

## Funding

No sources of funding were involved.

## Conflicts of interest

None declared.

## Acknowledgements

We thank Dr. Stef Zeemering for his kind contribution regarding Fig. 3 (protocol43-xxx-z).

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## Supplementary Materials

**Table S1.** Overview of all included studies.

| First author | Year of publication | Title | Journal | Volume number | Pages |
|---|---|---|---|---|---|
| **Hybrid** | | | | | |
| *Bisleri*[1] | 2013 | Hybrid Approach for The Treatment of Long-Standing Persistent Atrial Fibrillation: Electrophysiological Findings and Clinical Results† | European Journal of Cardio-Thoracic Surgery | Vol. 44 No. 5 | 919-23 |
| *Budera*[2] | 2017 | Two-Staged Hybrid Ablation of Non-Paroxysmal Atrial Fibrillation: Clinical Outcomes and Functional Improvements After 1 Year | Interactive Cardiovascular and Thoracic Surgery | Vol. - No. - | - |
| *Bulava*[3] | 2017 | Correlates Of Arrhythmia Recurrence After Hybrid Epi- And Endocardial RF Ablation for Persistent Atrial Fibrillation | Circulation: Arrhythmia and Electrophysiology | Vol. 10 No. 8 | E005273 |
| *de Asmundis*[4] | 2017 | Midterm Clinical Outcomes of Concomitant Thoracoscopic Epicardial and Transcatheter Endocardial Ablation for Persistent and Long-Standing Persistent Atrial Fibrillation: A Single-Centre Experience | Europace | Vol. 19 No. 1 | 58-65 |
| *Edgerton*[5] | 2016 | Hybrid Procedure (Endo/Epicardial) Versus Standard Manual Ablation in Patients Undergoing Ablation of Longstanding Persistent Atrial Fibrillation: Results from A Single Center | Journal Of Cardiovascular Electrophysiology | Vol. 27 No. 5 | 524-30 |
| *Gehi*[6] | 2013 | Hybrid Epicardial-Endocardial Ablation Using a Pericardioscopic Technique for The Treatment of Atrial Fibrillation | Heart Rhythm | Vol. 10 No. 1 | 22-8 |
| *Gersak*[7] | 2012 | Low Rate of Atrial Fibrillation Recurrence Verified by Implantable Loop Recorder Monitoring Following A Convergent Epicardial And Endocardial Ablation Of Atrial Fibrillation | Journal Of Cardiovascular Electrophysiology | Vol. 23 No. 10 | 1059-1066 |
| *Krul*[8] | 2011 | Thoracoscopic Video-Assisted Pulmonary Vein Antrum Isolation, Ganglionated Plexus Ablation, And Periprocedural Confirmation of Ablation Lesions: First Results of a Hybrid Surgical-Electrophysiological Approach for Atrial Fibrillation | Circulation: Arrhythmia and Electrophysiology | Vol. - No. - | - |
| *La Meir*[9] | 2012 | The Hybrid Approach for The Surgical Treatment of Lone Atrial Fibrillation: One-Year Results Employing a Monopolar RF Source | Journal Of Cardiothoracic Surgery | Vol. 7 No. 1 | 71 |
| *Mahapatra*[10] | 2011 | Initial Experience of Sequential Surgical Epicardial-Catheter Endocardial Ablation for Persistent and Long-Standing Persistent Atrial Fibrillation with Long-Term Follow-Up | Annals Of Thoracic Surgery | Vol. 91 No. 6 | 1890-8 |
| *Pison*[11] | 2014 | Effectiveness And Safety of Simultaneous Hybrid Thoracoscopic and Endocardial Catheter Ablation of Lone Atrial Fibrillation | Annals Of Cardiothoracic Surgery | Vol. 3 No. 1 | 38-44 |
| *Richardson*[12] | 2016 | Staged Versus Simultaneous Thoracoscopic Hybrid Ablation for Persistent Atrial Fibrillation Does Not Affect Time to Recurrence of Atrial Arrhythmia | Journal Of Cardiovascular Electrophysiology | Vol. 27 No. 4 | 428-434 |
| *Zembala*[13] | 2012 | Minimally Invasive Hybrid Ablation Procedure for The Treatment of Persistent Atrial Fibrillation: One Year Results | Kardiologia Polska (Polish Heart Journal) | Vol. 70 No. 8 | 819-828 |

| Catheter | | | | | |
|---|---|---|---|---|---|
| *Bassiouny*[14] | 2016 | Randomized study of persistent atrial fibrillation ablation: ablate in sinus rhythm versus ablate complex-fractionated atrial electrograms in atrial fibrillation | Circulation: Arrhythmia and Electrophysiology | Vol. 9 No. 2 | E003596 |
| *Boersma*[15] | 2012 | Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment (Fast): A 2-Center Randomized Clinical Trial | Circulation: American Heart Association | Vol. 125 No. 1 | 23-30 |
| *Di Biase*[16] | 2016 | Left Atrial Appendage Isolation in Patients with Longstanding Persistent AF Undergoing Catheter Ablation: BELIEF Trial | Journal Of the American College Of Cardiology | Vol. 68 No. 18 | 1929-1940 |
| *Dixit*[17] | 2012 | Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study | Circulation: Arrhythmia and Electrophysiology | Vol. 5 No. 2 | 287-94 |
| *Dong*[18] | 2015 | Prospective Randomized Comparison Between a Fixed ‘2C3L’ Approach Vs. Stepwise Approach for Catheter Ablation of Persistent Atrial Fibrillation | Europace | Vol. 17 No. 12 | 1798-1806 |
| *Elayi*[19] | 2008 | Ablation For Longstanding Permanent Atrial Fibrillation: Results from A Randomized Study Comparing Three Different Strategies | Heart Rhythm | Vol. 5 No. 12 | 1658-1664 |
| *Elayi*[20] | 2011 | Identifying the relationship between the non-PV triggers and the critical CFAE sites post-PVAI to curtail the extent of atrial ablation in longstanding persistent AF | Journal of Cardiovascular Electrophysiology | Vol. 29 No. 11 | 1199-205 |
| *Fink*[21] | 2017 | Stand-Alone Pulmonary Vein Isolation Versus Pulmonary Vein Isolation with Additional Substrate Modification as Index Ablation Procedures in Patients with Persistent and Long-Standing Persistent Atrial Fibrillation: The Randomized Alster-Lost-AF Trial (Ablation At St. Georg Hospital For Long-Standing Persistent Atrial Fibrillation) | Circulation: Arrhythmia and Electrophysiology | Vol. 10 No. 7 | E005114 |
| *Gaita*[22] | 2008 | Long-Term Clinical Results Of 2 Different Ablation Strategies in Patients with Paroxysmal and Persistent Atrial Fibrillation | Circulation: Arrhythmia and Electrophysiology | Vol. 1 No. 4 | 269-275 |
| *Kim*[23] | 2015 | Does Isolation of The Left Atrial Posterior Wall Improve Clinical Outcomes After Radiofrequency Catheter Ablation for Persistent Atrial Fibrillation? A Prospective Randomized Clinical Trial | International Journal of Cardiology | Vol. 181 No. - | 277-283 |
| *Kim*[24] | 2017 | Does Additional Electrogram-Guided Ablation After Linear Ablation Reduce Recurrence After Catheter Ablation for Longstanding Persistent Atrial Fibrillation? A Prospective Randomized Study | Journal of the American Heart Association | Vol. 6 No. 2 | E004811 |
| *Mont*[25] | 2014 | Catheter Ablation Vs. Antiarrhythmic Drug Treatment of Persistent Atrial Fibrillation: A Multicentre, Randomized, Controlled Trial (SARA Study) | European Heart Journal | Vol. 35 No. 8 | 501-507 |
| *Pokushalov*[26] | 2013 | Ganglionated Plexus Ablation Vs Linear Ablation in Patients Undergoing Pulmonary Vein Isolation for Persistent/Long-Standing Persistent Atrial Fibrillation: A Randomized Comparison | Heart Rhythm | Vol. 10 No. 9 | 1280-1286 |
| *Rostock*[27] | 2011 | Long-Term Single- And Multiple-Procedure Outcome and Predictors of Success After Catheter Ablation for Persistent Atrial Fibrillation | Heart Rhythm | Vol. 9 No. 8 | 1391-7 |
| *Schmidt*[28] | 2017 | Laser balloon or wide-area circumferential irrigated radiofrequency ablation for persistent atrial fibrillation: a multicenter prospective randomized study | Circulation: Arrhythmia and Electrophysiology | Vol. 10 No. 12 | E005767 |
| *Singh*[29] | 2016 | The modified stepwise ablation guided by low-dose ibutilide in chronic atrial fibrillation trial (The MAGIC-AF Study) | European Heart Journal | Vol. 37 No. 20 | 1614-21 |
| *Tilz*[30] | 2012 | Catheter Ablation of Long-Standing Persistent Atrial Fibrillation: 5-Year Outcomes of The Hamburg Sequential Ablation Strategy | Journal of The American College of Cardiology | Vol. 60 No. 19 | 1921-1929 |
| *Verma*[31] | 2015 | Approaches To Catheter Ablation for Persistent Atrial Fibrillation | New England Journal of Medicine | Vol. 372 No. 19 | 1812-1822 |
| *Wang*[32] | 2013 | Evaluation Of Linear Lesions in The Left and Right Atrium in Ablation of Long-Standing Atrial Fibrillation | Pacing and Clinical Electrophysiology | Vol. 36 No. 10 | 1202-1210 |
| *Wong*[33] | 2015 | No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: benefit of complex ablation study | Circulation: Arrhythmia and Electrophysiology | Vol. 8 No. 6 | 1316-24 |
| *Yang*[34] | 2017 | STABLE-SR (electrophysiological substrate ablation in the left atrium during sinus rhythm) for the treatment of nonparoxysmal atrial fibrillation: a prospective, multicenter randomized clinical trial | Circulation: Arrhythmia and Electrophysiology | Vol. 10 No. 11 | E005405 |

**Table S2.** Baseline characteristics.

| Study | Patients (n) | Age (years) (mean ± SD or median [IQR]) | Female (%) | AF duration (years) (mean ± SD or median [IQR]) | AF duration (months) (mean ± SD or median [IQR]) | LA dimension (mm) (mean ± SD or median [IQR]) | LA volume (mL or mL/m$^2$) (mean ± SD) | Type of AF (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | persAF | LSPAF |
| **Hybrid** | | | | | | | | | |
| *Bisleri (2013)* | 45 | 63 ± 10 | 27 | - | 84 ± 70 | 51 ± 10 | - | 0 | 100 |
| *Budera (2017)* | 38 (incl. n=3 with only epicardial) | 62 ± 9 | 26 | - | 33 ± 33 | 47 ± 4 | - | 34 | 66 |
| *Bulava (2017)* | 70 | 62 ± 8 | 30 | - | 42 ± 35 | 49 ± 5 | 150 ± 34 mL | 100 | 0 |
| *de Asmundis (2017)* | 64 | 60 ± 9 | 13 | - | 62 ± 45 | 50 ± 7 | 82.4 ± 22 mL | 33 | 67 |
| *Edgerton (2016)* | 24 | 64 ± 9 | 8 | 7 ± 4 | - | 52 ± 3 | - | 0 | 100 |
| *Gehi (2013)* | 84 | 63 ± 10 | 22 | 6 ± 6 | - | 51 ± 10 | - | 56 | 44 |
| *Gersak (2012)* | 47 (incl. n=5 with only epicardial) | 56 ± 11 | 16 | 5 ± 5 | - | 48 ± 1 | - | 17 | 83 |
| *Krul (2011)* | 15 | 57 ± 7 | 19 | 8 [1-25] | - | 47 ± 7 | - | 87 | 13 |
| *La Meir (2012)* | 14 | 61 ± 9 | 16 | 5 [3-9] | - | 49 ± 20 | 47 ± 11 mL/m$^2$ | 29 | 71 |
| *Mahapatra (2011)* | 15 | 60 ± 2 | 47 | 5 ± 1 | - | 52 ± 10 | - | 60 | 40 |
| *Pison (2014)* | 49 | 61 [53-66] | 23 | 4 [2-7] | - | 45 [42-48] | - | 69 | 31 |
| *Richardson (2016)* | 82 | 63 [57-68] | 18 | - | - | 49 [42-53] | - | 100 | |
| *Zembala (2012)* | 27 | 53 ± 11 | 22 | 3 ± 3 | - | 46 ± 5 | - | 19 | 81 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Catheter** | | | | | | | | | |
| *Bassiouny (2016)* | 44 | 65 ± 9 | 25 | - | 8 [4–12] | 42 ± 10 | - | 72 | 28 |
| *Boersma (2012)* | 26 | 56 ± 7 | 13 | - | - | 43 ± 5 | - | 100 | 0 |
| *Di Biase (2016)* | 85 | 64 ± 8 | 12 | - | - | 48 ± 6 | - | 0 | 100 |
| *Di Biase (2016)* | 88 | 64 ± 9 | 17 | - | - | 48 ± 7 | - | 0 | 100 |
| *Dixit (2012)* | 55 | 59 ± 8 | 13 | - | 56 ± 65 | 48 ± 7 | - | 100 | 0 |
| *Dixit (2012)* | 50 | 57 ± 10 | 16 | - | 44 ± 44 | 47 ± 6 | - | 100 | 0 |
| *Dixit (2012)* | 51 | 60 ± 9 | 10 | - | 43 ± 40 | 49 ± 8 | - | 100 | 0 |
| *Dong (2015)* | 73 | 55 ± 11 | 26 | - | 20 ± 9 | 42 ± 5 | - | 19 | 81 |
| *Dong (2015)* | 73 | 56 ± 10 | 23 | - | 22 ± 11 | 43 ± 6 | - | 16 | 84 |
| *Elayi (2008)* | 47 | 60 ± 10 | 36 | 7 ± 3 | - | 45 ± 7 | - | 0 | 100 |
| *Elayi (2008)* | 48 | 58 ± 10 | 31 | 6 ± 4 | - | 45 ± 7 | - | 0 | 100 |
| *Elayi (2008)* | 49 | 59 ± 12 | 35 | 6 ± 3 | - | 46 ± 6 | - | 0 | 100 |
| *Elayi (2011)* | 48 | 61 ± 9 | 21 | 8 ± 6 | - | 48 ± 7 | - | 0 | 100 |
| *Elayi (2011)* | 50 | 62 ± 10 | 18 | 9 ± 6 | - | 47 ± 7 | - | 0 | 100 |
| *Fink (2017)* | 61 | 62 ± 10 | 31 | - | 12 [7 - 24] | 47 ± 5 | - | 57 | 43 |
| *Fink (2017)* | 57 | 61 ± 10 | 26 | - | 12 [7 - 24] | 47 ± 4 | - | 60 | 40 |
| *Gaita (2008)* | 79 | 55 ± 10 | 20 | 5 ± 4 | - | 49 ± 7 | - | 100 | 0 |
| *Kim (2015)* | 120 | 57 ± 11 | 27 | - | - | - | 75 ± 2 mL | 100 | 0 |
| *Kim (2017)* | 29 | 64 ± 12 | 28 | - | 46 ± 42 | 45 ± 5 | 43 ± 14 mL/$m^2$ | 0 | 100 |
| *Kim (2017)* | 54 | 63 ± 10 | 35 | - | 62 ± 64 | 45 ± 6 | 47 ± 15 mL/$m^2$ | 0 | 100 |
| *Kim (2017)* | 54 | 60 ± 11 | 18 | - | 57 ± 51 | 45 ± 5 | 43 ± 13 mL/$m^2$ | 0 | 100 |
| *Mont (2014)* | 98 | 55 ± 9 | 22 | - | - | 41 ± 5 | - | 100 | 0 |
| *Pokushalov (2013)* | 132 | 55 ± 6 | 27 | 6 ± 4 | - | 49 ± 7 | - | 67 | 33 |
| *Pokushalov (2013)* | 132 | 54 ± 7 | 31 | 5 ± 4 | - | 48 ± 7 | - | 70 | 30 |
| *Rostock (2011)* | 81 | 59 ± 11 | 27 | - | 16 ± NS | - | - | 69 | 31 |
| *Schmidt (2017)* | 77 | 66 ± 10 | 33 | - | 35 ± 45 | 43 [31–46] | - | 100 | 0 |
| *Schmidt (2017)* | 75 | 65 ± 9 | 40 | - | 26 ± 37 | 43 [31–46] | - | 100 | 0 |
| *Singh (2016)* | 95 | 60 ± 9 | 24 | - | 10 + 22 | 46 + 8 | - | 77 | 23 |
| *Tilz (2012)* | 202 | 61 ± 9 | 21 | - | 99 ± 64 | 49 ± 6 | - | 0 | 100 |
| *Verma (2015)* | 67 | 58 ± 10 | 22 | - | - | 44 ± 6 | - | 100 | 0 |
| *Verma (2015)* | 263 | 60 ± 9 | 19 | - | - | 44 ± 6 | - | 100 | 0 |
| *Verma (2015)* | 259 | 61 ± 9 | 24 | - | - | 46 ± 6 | - | 100 | 0 |
| *Wang (2013)* | 70 | 62 ± 10 | 37 | | | 47 ± 7 | - | 0 | 100 |
| *Wang (2013)* | 70 | 63 ± 9 | 38 | | | 45 ± 5 | - | 0 | 100 |
| *Wang (2013)* | 70 | 64 ± 8 | 38 | - | - | 47 ± 5 | - | 0 | 100 |
| *Wong (2015)* | 65 | 61 ± 9 | 26 | 2 [<1–8] | - | 46 ± 7 | - | 54 | 46 |
| *Wong (2015)* | 65 | 61 ± 11 | 23 | 2 [<1–6] | - | 45 ± 6 | - | 63 | 37 |
| *Yang (2017)* | 114 | 57 ± 10 | 19 | - | 19 ± 29 | 41 ± 5 | - | 100 | |
| *Yang (2017)* | 115 | 58 ± 8 | 26 | - | 16 ± 33 | 41 ± 5 | - | 100 | |

AF=atrial fibrillation; IQR=interquartile range; LA=left atrial; LSPAF=longstanding persistent AF; n=number; persAF=persistent AF; SD=standard deviation.

**Table S3.** Perioperative data.

| Study | Lesions | LAA management (%) and Method | Single/staged | Ablation energy Source | Surgical Approach | Epicardial Device | Endocardial Device |
|---|---|---|---|---|---|---|---|
| **Hybrid** | | | | | | | |
| *Bisleri (2013)* | Box lesion + lines | 0 | Staged | Unipolar RF | Thoracoscopic right-sided | Cobra Adhere XL (Estech) | NaviStar Thermocool (Biosense Webster) |
| *Budera (2017)* | Box lesion | 32 - AtriClip | Staged | Uni and bipolar RF | Thoracoscopic right-sided | Cobra Fusion (Estech) | Thermocool Smarttouch (Biosense Webster) |
| *Bulava (2017)* | Box lesion + lines | 89 - AtriClip | Staged | Bipolar RF | Thoracoscopic bilateral | Synergy clamp, isolator pen (AtriCure) | Thermocool Smarttouch (Biosense Webster) |
| *de Asmundis (2017)* | Box lesion | 73 - AtriClip | Single | Bipolar RF | Thoracoscopic bilateral | Synergy clamp, isolator pen, coolrail (AtriCure) | NaviStar Thermocool (Biosense Webster) |
| *Edgerton (2016)* | Box lesion + lines | 100 - Electrical isolation | Single | Unipolar RF | Subxiphoidal | Visitrax, nContact (AtriCure) | Biosense Webster |
| *Gehi (2013)* | PVI + CFAE + lines | 0 | Single | Unipolar RF | Subxiphoidal | Visitrax, nContact (AtriCure) | NaviStar ThermoCool (Biosense Webster) |
| *Gersak (2012)* | PVI + lines | 0 | Staged = 32% Single = 68% | Unipolar RF | Subxiphoidal | nContact (AtriCure) | Thermocool Smarttouch (Biosense Webster) |
| *Krul (2011)* | PVI + lines | 94 - Stapler | Single | Bipolar RF | Thoracoscopic bilateral | Isolator pen, synergy clamp (AtriCure) | NS |
| *La Meir (2012)* | Box lesion + lines | 0 | Single | Unipolar RF | Thoracoscopic right-sided | Cobra Adhere XL (Estech) | Thermocool (Biosense Webster) |
| *Mahapatra (2011)* | PVI + lines | 100 - Stapler | Single | Bipolar RF | Thoracoscopic right-sided | Synergy clamp, isolator pen (AtriCure) | Irrigated and 5 mm tip (Biosense Webster) |
| *Pison (2014)* | Box lesion | 45 - Stapler or AtriClip | Single | Bipolar RF | Thoracoscopic bilateral | Synergy clamp, isolator pen, coolrail (AtriCure) | Thermocool (Biosense Webster) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Richardson (2016)* | PVI + lines | 96 - Stapler or AtriClip | Single = 63% Staged = 37% | Bipolar RF | Thoracoscopic bilateral | Synergy clamp, isolator pen (AtriCure) | Thermocool (Biosense Webster) |
| *Zembala (2012)* | Box lesion + lines | 4 - Resection | Single | Unipolar RF | Subxiphoidal bilateral | Visitrax, nContact (AtriCure) | Thermocool (Biosense Webster) |
| **Catheter** | | | | | | | |
| *Bassiouny (2016)* | PVI + CFAE | 0 | - | Unipolar RF | - | - | Irrigated tip (NS) |
| *Boersma (2012)* | PVI + lines | 0 | - | Unipolar RF | - | - | Single tip and irrigated tip (Biosense Webster) |
| *Di Biase (2016)* | PVI + lines | 100 - Electrical isolation | - | Unipolar RF | - | - | Irrigated tip (NS) |
| *Di Biase (2016)* | PVI + lines | 0 | - | Unipolar RF | - | - | Irrigated tip (NS) |
| *Dixit (2012)* | PVI + non-PV triggers (standard approach) | 0 | - | Unipolar RF | - | - | Navistar and Navistar Thermocool (Biosense Webster) |
| *Dixit (2012)* | PVI + lines | 0 | - | Unipolar RF | - | - | Navistar and Navistar Thermocool (Biosense Webster) |
| *Dixit (2012)* | PVI + CFAE | 0 | - | Unipolar RF | - | - | Navistar and Navistar Thermocool (Biosense Webster) |
| *Dong (2015)* | PVI + lines (fixed approach) | 0 | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Dong (2015)* | PVI + lines + CFAE (stepwise approach) | 0 | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Elayi (2008)* | CPVI | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |
| *Elayi (2008)* | PVI | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |
| *Elayi (2008)* | PVI + CFAE | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Elayi (2011)* | PVI | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |
| *Elayi (2011)* | PVI + CFAE | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |
| *Fink (2017)* | PVI | 0 | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Fink (2017)* | PVI + lines | 0 | - | Unipolar RF | - | | NaviStar Thermocool (Biosense Webster) |
| *Gaita (2008)* | PVI | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |
| *Kim (2015)* | PVI + lines | 0 | - | Unipolar RF | - | - | Celsius (Biosense Webster) |
| *Kim (2017)* | PVI + lines (SR) | 0 | - | Unipolar RF | - | - | Coolflex (St Jude Medical) |
| *Kim (2017)* | PVI + lines (AF) | 0 | - | Unipolar RF | - | - | Coolflex (St Jude Medical) |
| *Kim (2017)* | PVI + CFAE (AF) | 0 | - | Unipolar RF | - | - | Coolflex (St Jude Medical) |
| *Mont (2014)* | PVI + CFAE + lines | 0 | - | Unipolar RF | - | - | Cooled-tip (NS) |
| *Pokushalov (2013)* | PVI + GP | 0 | - | Unipolar RF | - | - | NS |
| *Pokushalov (2013)* | PVI + lines | 0 | - | Unipolar RF | - | - | NS |
| *Rostock (2011)* | PVI + lines | 0 | - | Unipolar RF | - | - | Irrigated-tip (Biosense Webster) |
| *Schmidt (2017)* | PVI | 0 | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Schmidt (2017)* | PVI | 0 | - | Laser energy | - | - | Laser balloon (CardioFocus) |
| *Singh (2016)* | PVI | 0 | - | Unipolar RF | - | - | Irrigated tip (NS) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Tilz (2012)* | PVI + CFAE + lines | 10 - Electrical isolation | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Verma (2015)* | PVI | 0 | - | Unipolar RF | - | - | Irrigated tip (NS) |
| *Verma (2015)* | PVI + CFAE | 0 | - | Unipolar RF | - | - | Irrigated tip (NS) |
| *Verma (2015)* | PVI + lines | 0 | - | Unipolar RF | - | - | Irrigated tip (NS) |
| *Wang (2013)* | PVI + lines + CFAE | 0 | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Wang (2013)* | PVI + lines + CFAE | 0 | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Wang (2013)* | PVI + CFAE | 0 | - | Unipolar RF | - | - | NaviStar Thermocool (Biosense Webster) |
| *Wong (2015)* | PVI + lines | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |
| *Wong (2015)* | PVI + lines + CFAE | 0 | - | Unipolar RF | - | - | Thermocool (Biosense Webster) |
| *Yang (2017)* | PVI + lines | 0 | - | Unipolar RF | - | - | NS |
| *Yang (2017)* | PVI + lines + CFAE | 0 | - | Unipolar RF | - | - | NS |

LAA=left atrial appendage, box-lesion=pulmonary vein isolation, roof line and inferior line. PVI=pulmonary vein isolation, CFAE=complex fractionated atrial electrograms, CPVI=circumferential PVI, GP=ganglionated plexus, RF=radiofrequency; NS=not specified.

**Table S4.** Reported complications.

| Study | Stroke/TIA | Tamponade | Conversion to sternotomy | Pacemaker implantation | Bleeding requiring reoperation or transfusion | Bleeding requiring reoperation | Pneumothorax | Pulmonary vein narrowing requiring stenting | Insignificant pulmonary vein narrowing | Phrenic nerve damage | Groin hematoma requiring therapy | Hospital mortality | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hybrid** | | | | | | | | | | | | | |
| *Bisleri (2013)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Budera (2017)* | n=1 2.6% | 0 | 0 | 0 | n=6 15.8% | 0 | n=2 5.3% | 0 | 0 | n=1 2.6% | 0 | 0 | Post-pericardiotomy Syndrome n=1; 2.6% |
| *Bulava (2017)* | 0 | n=1 1.4% | n=2 2.9% | 0 | 0 | 0 | 0 | n=1 1.4% | n=7 10.0% | n=7 10.0% | n=1 1.4% | 0 | Arteriovenous fistula n=1; 1.4% Sternal wound infection n=2; 2.9% |
| *De Asmundis (2017)* | 0 | n=2 3.1% | n=1 1.6% | 0 | 0 | 0 | n=1 1.6% | 0 | 0 | 0 | 0 | 0 | Left atrial perforation, minimally invasive thoracotomy and sepsis n=2; 3.1% (Pleuro-) pericarditis n=4; 6.3% Pneumonia n=3; 4.7% |
| *Edgerton (2016)* | n=2 8.3% | n=1 4.2% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n=1 4.2% | 0 | n=3 12.5% | Arteriovenous fistula n=1; 4.2% |
| *Gehi (2013)* | 0 | n=2 2.4% | 0 | 0 | n=2 2.4% | 0 | 0 | 0 | 0 | 0 | 0 | n=2 2.4% | Arteriovenous fistula n=1; 1.2% |
| *Gersak (2012)* | n=1 2.1% | n=1 2.1% | 0 | 0 | n=1 2.1% | 0 | 0 | 0 | 0 | 0 | 0 | n=2 4.3% | 0 |
| *Krul (2011)* | 0 | 0 | n=3 20.0% | 0 | 0 | 0 | n=1 6.7% | 0 | 0 | 0 | 0 | 0 | Pneumonia n=2; 13.3% Hemothorax n=1; 6.7% |
| *La Meir (2012)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Mahapatra (2011)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Pison (2014)* | 0 | 0 | 0 | n=2; 4.1% | n=2 4.1% | n=1 2.0% | 0 | 0 | 0 | 0 | 0 | 0 | Pneumonia n=2; 4.1% |
| *Richardson (2016)* | 0 | n=1 1.2% | 0 | n=1; 1.2% | n=7 8.5% | 0 | 0 | 0 | 0 | n=1 1.2% | 0 | 0 | 0 |
| *Zembala (2012)* | 0 | n=1 3.7% | n=1 3.7% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Left atrial perforation n=1; 3.7% |
| ***Total patients (n=574)*** | n=4 0.7% | n=9 1.6% | n=7 1.2% | n=3 0.5% | n=18 3.1% | n=1 0.2% | n=4 0.7% | n=1 0.2% | n=7 1.2% | n=10 1.7% | n=1 0.2% | n=7 1.2% | |
| **Catheter** | | | | | | | | | | | | | |
| *Bassiouny (2016)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Boersma (2012)* | n=1 3.8% | n=1 3.8% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n=4 15.4% | 0 | 0 |
| *Di Biase (2016)* | n=4 2.3% | n=2 1.2% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Abdominal bleeding n=1; 0.6% |
| *Dixit (2012)* | n=2 1.3% | n=1 0.6% | 0 | 0 | 0 | 0 | 0 | n=1 0.6% | 0 | 0 | n=1 0.6% | 0 | Arteriovenous fistula n=1; 0.6% Pseudo aneurysm n=1; 0.6% |
| *Dong (2015)* | n=1 0.7% | n=1 0.7% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Elayi (2008)* | 0 | n=2 1.4% | 0 | 0 | 0 | 0 | 0 | 0 | n=2 1.4% | 0 | 0 | 0 | 0 |
| *Elayi (2011)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n=2 2.0% | 0 | 0 | 0 | 0 |
| *Fink (2017)* | n=3 2.5% | n=2 1.7% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n=5 4.2% | 0 | 0 |
| *Gaita (2008)* | n=2 2.5% | n=2 2.5% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Atrio-esophageal fistula n=1; 1.3% |
| *Kim (2015)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Kim (2017)* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Transient respiratory arrest related to anesthesia n=1; 0.7%<br>Transient sick sinus node syndrome not requiring pacemaker n=5; 3.6%<br>Atrioesophageal fistula n=1; 0.7% |
| *Mont (2014)* | 0 | n=1 1.0% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Pericarditis n=2; 2.0% |
| *Pokushalov (2013)* | n=4 1.5% | n=3 1.1% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Rostock (2011)* | n=1 1.2% | n=4 4.9% | 0 | n=2 2.5% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Schmidt (2017)* | n=3 2.0% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n=1 0.7% | 0 | 0 | Myocardial infarct n=2; 1.3%<br>False aneurysm n=3; 2.0% |
| *Singh (2016)* | 0 | NS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Symptomatic congestive heart failure requiring diuretics or hospitalization n=10; 10.5%<br>Pericarditis or pericardial effusion n=7; 7.4% |
| *Tilz (2012)* | n=3 1.5% | n=1 0.5% | 0 | 0 | 0 | 0 | n=1 0.5% | 0 | 0 | 0 | n=11 5.4% | 0 | Pneumonia n=1; 0.5%<br>Transient pulmonary oedema n=1; 0.5% |
| *Verma (2015)* | n=3 0.5% | n=3 0.5% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n=5 0.8% | n=1 0.2% | Pericarditis n=3; 0.5%<br>Arteriovenous fistula n=6; 1.1%<br>Anesthesia-related complication n=8; 1.4%<br>Fluid overload n=4; 0.7% |
| *Wang (2013)* | 0 | n=1 0.5% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n=2 1.0% | n=9 4.3% | 0 | 0 |
| *Wong (2015)* | 0 | n=1 0.8% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Femoral artery pseudo aneurysm n=4; 3.1%<br>Deep vein thrombosis n=1; 0.8% |
| *Yang (2017)* | 0 | n=7 3.1% | 0 | n=1 0.4% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Vasovagal syncope n=1; 0.4% |
| ***Total patients (n=3291)*** | n=27 0.8% | n=32 1.0% | n=0 | n=3 0.1% | n=0 | n=0 | n=1 <0.1% | n=1 <0.1% | n=4 0.1% | n=3 0.1% | n=35 1.1% | n=1 <0.1% | |

TIA=Transient Ischemic Attack, PV=Pulmonary Vein.



82

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# CHAPTER 4

## Hybrid Ablation Versus Repeated Catheter Ablation in Persistent Atrial Fibrillation: A Randomized Controlled Trial

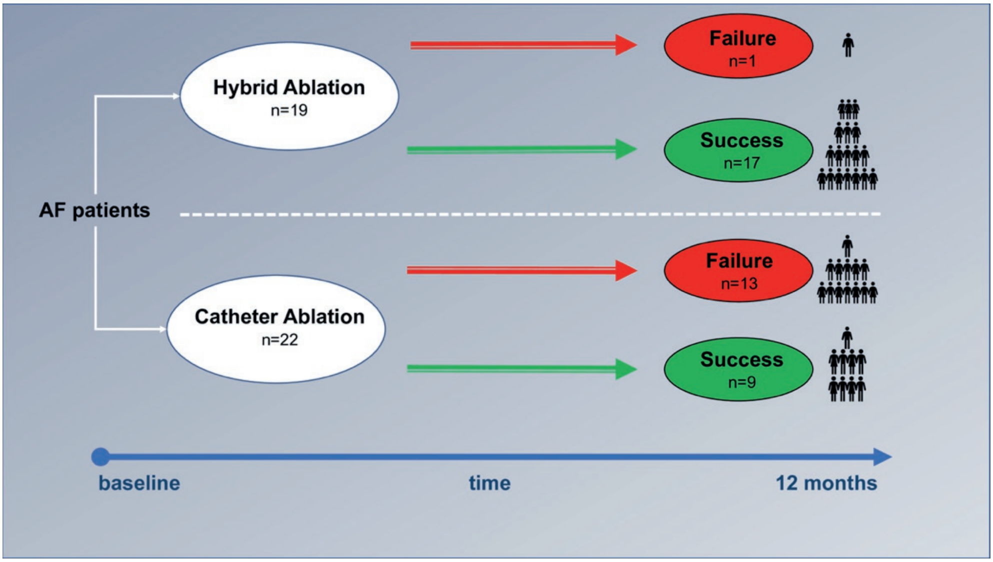
**Short Title: HARTCAP-AF**

**Claudia A.J. van der Heijden*,** Vanessa Weberndörfer*, Mindy Vroomen, Justin G.L.M. Luermans, Sevasti-Maria Chaldoupi, Elham Bidar, Kevin Vernooy, J.G. Maessen, Laurent Pison, Sander M. J. van Kuijk, Mark La Meir, Harry J. Crijns, Bart Maesen

*Both authors contributed equally

*JACC: clinical electrophysiology, January 2023.*

**Central Illustration.** Efficacy results after hybrid and catheter ablation.




Patients with AF were randomized between hybrid and catheter ablation and success rates (freedom from supraventricular tachyarrhythmia off anti-arrhythmic drugs) were determined until 12 months of follow-up. AF=atrial fibrillation.

**Abstract**

**Background** Although catheter ablation (CA) is successful for the treatment of paroxysmal atrial fibrillation (AF), results are less satisfactory in persistent AF (persAF). Hybrid ablation (HA) results in better outcomes in patients with persAF as it combines a thoracoscopic epicardial and transvenous endocardial approach in a single procedure.

**Objectives** To compare the effectiveness and safety of HA with CA in a prospective, superiority, unblinded, randomized controlled trial.

**Methods** Forty-one ablation-naive patients with (longstanding)-persAF were randomized to HA (n=19) or CA (n=22) and received pulmonary vein isolation, posterior left atrial wall isolation and if needed a cavotricuspid isthmus ablation. The primary efficacy endpoint was freedom from any atrial tachyarrhythmia >5 minutes off antiarrhythmic drugs (AADs) after 12-months. The primary and secondary safety endpoints included major and minor complications and the total number of serious adverse events (SAEs).

**Results** After 12 months, the freedom of atrial tachyarrhythmias off AADs was higher in the hybrid ablation group compared to the catheter ablation group (89% vs. 41%, *P*=0.002). There was one pericarditis requiring pericardiocentesis and one femoral arteriovenous-fistula in the HA group. In the CA arm, one bleeding from the femoral artery occurred. There were no deaths, strokes, need for pacemaker implantation or conversions to sternotomy and the number of (S)AEs was comparable between groups (21% vs. 14%, *P*=0.685).

**Conclusions** Hybrid AF ablation is an efficacious and safe procedure and results in better outcomes than catheter ablation for the treatment of patients with persistent AF. (Clinicaltrials.gov, NCT 02441738).

**Keywords** Atrial fibrillation • Hybrid ablation • Catheter ablation • Randomized controlled trial

## Condensed abstract

We compared the effectiveness and safety of hybrid ablation (HA) with catheter ablation (CA) in a difficult to treat patient population ((longstanding)-persistent AF, ablation naïve, LAVI 51±12 ml/$m^2$) in a prospective randomized controlled trial (n=41). After 12 months, freedom of atrial tachyarrhythmias off anti-arrhythmic drugs was significantly higher after HA compared to CA (89% vs. 41%, *P*=0.002), without leading to more complications (*P*=0.685). Based on these results, hybrid AF ablation combining a thoracoscopic epicardial and transvenous endocardial approach should be considered as a first-choice treatment for this patient category when performed by an experienced team.

## Glossary of Abbreviations

| | |
|---|---|
| AADs | Antiarrhythmic drugs |
| AF | Atrial fibrillation |
| AT | Atrial tachycardia |
| CA | Catheter ablation |
| CTI | Cavotricuspid isthmus |
| EP | Electrophysiologic |
| HA | Hybrid ablation |
| LA | Left atrium |
| LAA | LA appendage |
| LAVI | LA volume index |
| LVEF | Left ventricle ejection fraction |
| PAF | Paroxysmal AF |
| PV | Pulmonary vein |
| PVI | PV isolation |
| RCT | Randomized controlled trial |
| RF | Radio frequency |
| SAE | Serious adverse event |

## Introduction

Transvenous catheter ablation (CA) is an effective treatment strategy for paroxysmal atrial fibrillation (AF), with success rates >80%.[1] However, its effectiveness in (longstanding)-persistent AF is limited and results are rather disappointing, independent of the ablation strategy applied.[2] Hybrid ablation (HA), combining a thoracoscopic epicardial and transvenous endocardial approach, has been reported to be more effective in treating persistent AF (persAF).[3,4] Also a recent meta-analysis showed that HA is more effective than CA in persAF in restoring sinus rhythm (SR) and comes with a slightly higher complication rate.[1] To date no direct comparison has been performed to determine whether HA via a thoracoscopic approach is superior to CA in persAF.

We hypothesized that a single-stage HA leads to a higher freedom of atrial tachyarrhythmias at 12 months compared to CA (even when allowing repeat catheter ablations within 6 months), without increasing the number of major and minor complications. Therefore, we aimed to directly compare the efficacy and safety of both procedures on AF recurrence in patients with (longstanding)-persistent AF in a randomized controlled trial.

## Patients and Methods

Study design and participants

This randomized controlled trial is reported according to the CONSORT statement. In this open-label, unblinded, superiority randomized controlled trial, we compared the effectiveness and safety of a HA with (optional) repeated CA within six months in patients with a history of symptomatic (long-standing)-persistent AF in the Maastricht University Medical Centre between October 2016 and December 2018. Inclusion criteria were age >18 years, symptomatic (longstanding-)persistent AF refractory to one or more Vaughan-Williams class I or III antiarrhythmic drugs and no prior (catheter) ablation. Exclusion criteria were LA diameter >60 mm, contraindications for ablation or prior ablation, BMI >40 kg/m$^2$, history of cardiac surgery, life expectancy <12 months and pregnancy (Figure 1. CONSORT Flowchart). After obtaining written informed consent, 1:1 block randomization stratified on AF type was performed by the Clinical Trial Centre Maastricht using the ALEA software program 8 (FormsVision BV, Abcoude, The Netherlands). For every patient that withdrew consent before the ablation, an additional patient was included and randomized. All patients gave their written informed consent for the use of their data for scientific purposes and the prospective analysis of patient data was approved by the Institutional Review Board (METC 162011/NCT 02441738).

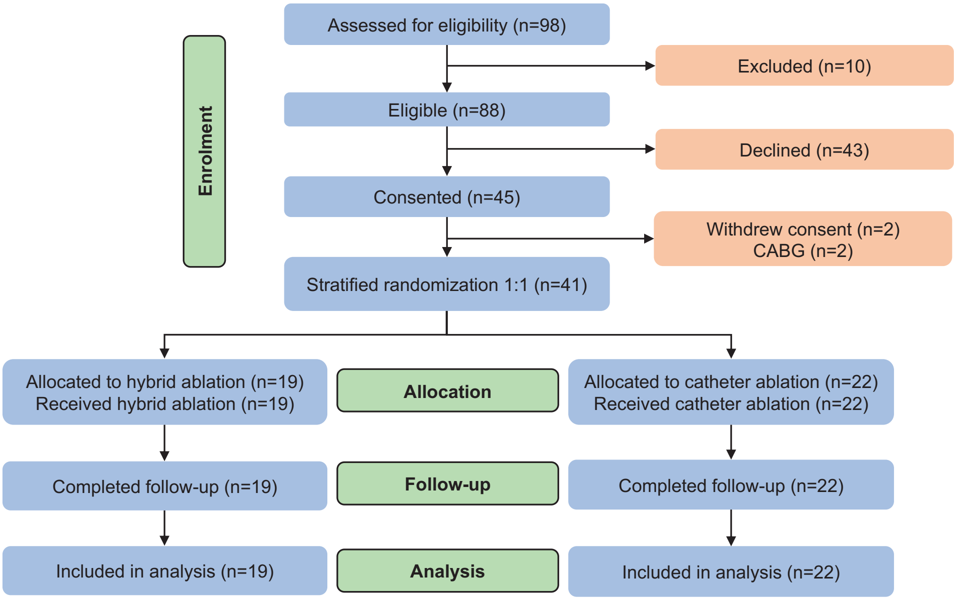



**Figure 1.** CONSORT flowchart describing enrolment, allocation, follow-up and analysis of all participants.

Hybrid procedure

All procedures were performed by a dedicated team of an experienced surgeon and electrophysiologist. A single staged HA was performed under general anesthesia using double-lumen endotracheal intubation for selective lung ventilation. Intracardiac thrombi were excluded by trans-esophageal echocardiography. Video-assisted thoracoscopic surgical ablation was performed using a three-port access introduced in the 3$^{rd}$, 5$^{th}$ and 7$^{th}$ intercostal space. The pericardium was opened posterior to the phrenic nerve. The pericardial reflections around both caval veins were exposed. Once access to the transverse and oblique sinus were obtained, isolation of the left pulmonary veins (PV) was performed with a bipolar radiofrequency (RF)-clamp (Synergy System, AtriCure, Cincinnati, OH, USA). A box lesion connecting the superior and inferior pulmonary veins with each other by creating a roof and inferior line was performed using a unidirectional bipolar RF pen (Coolrail, AtriCure, Cincinnati, OH, USA). Thereafter, PV isolation was performed on the right side. If the right veins could be safely ablated from the left side, right-sided thoracoscopic access was omitted (n=14). In all patients the left atrial appendage (LAA) was excluded using an epicardial clipping device (AtriClip Pro or Atriclip Pro 2, AtriCure, Cincinnati, OH, USA) or an LAA closure device (Lariat, SentreHEART, Pleasanton, CA). Once the surgical ablation was completed, transvenous endocardial validation was performed. After trans-septal puncture, exit and entrance block of all PVs and the box lesion on the posterior left atrium were evaluated using a 3.5-mm tip ablation catheter (Thermocool Smarttouch, Biosense Webster, Diamond Bar, CA, USA). If needed, endocardial touch-up ablation was performed. In case of previously documented left or right-sided flutter or atrial tachycardia, these were also ablated.

Catheter ablation

The endocardial procedure was routinely performed under sedation. After placing a coronary sinus catheter under fluoroscopic guidance, echo-guided double trans-septal puncture was performed. Heparin was administered adjusted to the bodyweight of the patient and an ACT >300ms was maintained with continuous heparin infusion. After creation of an electro-anatomical 3D map of the left atrium, endocardial ablation was performed with an irrigated tip contact force mapping catheter (ThermoCool Smarttouch, Biosense Webster, Diamond Bar, California, USA). Automated lesion tagging (VisiTag, Biosense Webster, Diamond Bar, California, USA) was used to mark each ablation lesion.

Power setting for the anterior and posterior wall were 30-35 Watt with an ablation index of 500 versus 25-30 Watt with an ablation index of 400, respectively. The minimal lesion set performed by endocardial catheter ablation was bilateral PVI and a box lesion excluding the posterior left atrium. In case of previously clinically documented arrhythmias from the atria, such as a left or right-sided flutter or ATs, additional ablation was performed conform standard-care. Before the end of the procedure, bilateral PVI and the box lesion were checked in SR for entrance and exit block and touch-up ablation was administered where needed.

Primary and secondary effectiveness endpoints

The primary effectiveness endpoint was defined as freedom from any recurrent supraventricular tachyarrhythmia off AADs, lasting ≥5 minutes as recorded on a 12-lead ECG and 7-day Holter after the three months blanking period until 12 months after the last procedure. In the catheter arm, re-ablation until 6 months after the initial ablation procedure did not count as a failure. In the hybrid arm, any re-intervention after the three-months blanking period was counted as a failure.

Secondary effectiveness endpoints included freedom from any recurrent supraventricular tachyarrhythmia lasting ≥30 seconds as recorded on a 12-lead ECG and 7-day Holter after the three months blanking period until 12 months of follow-up, off AADs. Other secondary endpoints were freedom from AAD use, the number of arrhythmia-related re-hospitalizations and reinterventions such as cardioversions and redo catheter ablations. Changes in quality of life (QOL), quantified by the (European Heart Rhythm Association (EHRA) overall symptom score) and EQ-5D-5L crosswalk index (representing 1 as perfect health and 0 dead), were evaluated as well.

Safety endpoints

The primary safety endpoint was a composite of major adverse events and complications occurring within 12 months of follow-up. Any of the following endpoints counted as major adverse event: death, stroke, bleeding requiring transfusion and/or reoperation, cardiac tamponade or pericardial effusion requiring intervention, empyema, myocardial infarction, pericarditis requiring pericardiocentesis or (prolongation of) (re)hospitalization, pneumothorax requiring intervention (after removal of chest tubes), gastroparesis, symptomatic PV stenosis>70% or (persistent) diaphragmatic paresis. Secondary safety endpoints were the total number of serious adverse events, pacemaker implantation, minor complications such as superficial wound infections and vascular access complications, but also cumulative procedural radiation exposure time, -dosage and cumulative procedure time.

Follow-up

Rhythm follow-up was performed with a 12-lead ECG and 24h-Holter monitoring at 3 and 6 months after the procedure, or in case of symptoms. It was recommended to stop AADs at the end of the blanking period, but the final decision was left at the discretion of the treating cardiologist. A 7d-Holter was obtained after 12 months and analyzed by the treating cardiologist. QOL was measured using the EQ-5D-5L questionnaire, reported using the EQ-5D-5L crosswalk index (higher values indicate an improved QOL (range 0-1, representing 1 as perfect health and 0 death). Furthermore, the EHRA questionnaire was used to report the modified EHRA index (representing 1 as no symptoms affecting daily life and 5 as normal daily activity discontinued). Scores were measured at baseline and after 12 months and compared between groups.

Sample size calculation

The estimated success rate (freedom from any supraventricular arrhythmia lasting >5 minutes without class I or III AADs) until 12 months of follow-up was estimated to be 83% after a single hybrid ablation and 35% after a single catheter ablation procedure.[3,6] With a significance level $\alpha=0.05$ and a power of 90%, 20 patients needed to be included in each arm.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) if they were normally distributed, or median [interquartile range] if they were not normally distributed. Categorical variables were reported as absolute number and percentage. For the primary and principle secondary efficacy outcomes, Kaplan-Meier survival curves were plotted to estimate the probability of being free from recurrences over the course of one year. Consequently, the log-rank test was used to test for differences between groups. Other secondary efficacy outcomes and safety outcomes were tested using the independent-samples t-test or the Mann-Whitney U test for continuous variables, and Pearson's chi-square test or Fisher's exact test for categorical variables. Data were analyzed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) and R version 4.0.4. All analyses were performed according to an intention-to-treat principle using a two-sided α of 5%.

Ethics

Eligible candidates from our outpatient clinic were screened considering in- and exclusion criteria. Extensive oral and written information was provided to all patients. If the patient agreed to participate in the study, written informed consent was obtained, followed by randomization to either the hybrid ablation arm or the catheter ablation arm. The study was conducted in accordance with the Declaration of Helsinki for the ethical principles for the conduction of medical research in human subjects. The study was approved by the Institutional Review Board of Maastricht University Medical Centre and Maastricht University (AZM/UM, Maastricht, The Netherlands) (METC 162011/NCT 02441738). A data safety monitoring board was involved to regularly advise the steering committee on continuation of the study based on efficacy, adverse- and serious adverse events. A clinical research monitor of the Clinical Trial Centre Maastricht regularly monitored the conduct of the study.

## Results

Study sample

Of the 98 patients that were assessed for eligibility for the study, 10 patients were excluded based on the in- and exclusion criteria. Furthermore, 43 patients declined participation in the study and 2 withdrew informed consent. Two more patients were excluded because they were referred for concomitant cardiac surgery. In total, 41 patients were included in this study, which were randomly allocated to the HA arm (n=19) and CA (n=22) arm and all received the allocated treatment (Figure 1. CONSORT Flowchart).

Patients in the HA and CA arm were on average 64±9 and 64±8 years old, most had persAF rather than longstanding persAF (90% and 91% persAF) and fewer patients were female (5% and 18%). $CHA_2DS_2$-VASc scores >3 (53% and 23%) and severe LA dilatation (LAVI = 54 and 49 ml/m$^2$) seemed more common in the HA arm. Also, more patients with COPD and OSAS were randomized to the HA arm, while more patients with congestive heart failure were randomized to the CA arm (Table 1).

**Table 1**. Baseline characteristics and comorbidities comparing hybrid versus catheter ablation.

| | Hybrid ablation (n=19) | Catheter ablation (n=22) |
|---|---|---|
| **Demographics (n=41)** | | |
| Age (years) | 64 ± 9 | 64 ± 8 |
| Female | 1 (5%) | 4 (18%) |
| BMI (kg/m$^2$) | 28.4 ± 4 | 29.2 ± 4 |
| $CHA_2DS_2VASC$ > 3 | 10 (53%) | 6 (27%) |
| Congestive heart failure | 1 (5%) | 6 (27%) |
| COPD | 2 (10%) | 0 (0%) |
| Coronary artery disease | 1 (5%) | 2 (9%) |
| Diabetes mellitus | 4 (21%) | 3 (14%) |
| Hypertension | 10 (53%) | 15 (68%) |
| Kidney dysfunction (eGFR<50ml/min) | 1 (5%) | 1 (5%) |
| OSAS | 5 (26%) | 3 (14%) |
| PAOD | 1 (5%) | 2 (9%) |
| **AF history** | | |
| AAD use | 10 (53%) | 8 (36%) |
| Class I | 8 (42%) | 7 (32%) |
| Class III | 2 (11%) | 2 (9%) |
| AF duration (months) | 22 [6 – 455] | 33 [12 – 221] |
| Persistent AF | 17 (90%) | 20 (91%) |
| Longstanding AF | 2 (11%) | 2 (9%) |
| Previous ECV | 18 (95%) | 20 (91%) |
| **Echocardiographic parameters** | | |
| LVEF (%) | 55 ± 7 | 54 ± 8 |
| LA volume (ml) | 114 ± 35 | 101 ± 18 |
| LAVI (ml/m2) | 54 ± 16 | 49 ± 8 |
| MI = I° (%) | 6 (32%) | 7 (32%) |

Data are presented as mean ± standard deviation, median [interquartile range] or frequencies: n (%). AF=atrial fibrillation; AAD=anti-arrhythmic drugs; BMI=body mass index; COPD=chronic obstructive pulmonary disease; OSAS=obstructive sleep apnea syndrome; ECV=electrical cardioversion; LVEF=left ventricular ejection fraction; LA=left atrial; LAVI=left atrial volume index; MI=mitral valve insufficiency; POAD=peripheral obstructive artery disease.

## Procedural data

All patients of both groups were treated according to the protocol. In the HA group, 14 (74%) received a left-sided approach, only 5 (26%) received a bilateral approach. Epicardial check-up was performed in 14 patients to validate entry and exit block of the PVs and the box lesion set, whereafter additional ablation was performed if necessary. Additional ablation of ganglionated plexus ablation was performed in five patients. All patients received closure of the LAA either using AtriClip (n=17) or the Lariat closure device (n=2). After the epicardial ablation, 8 (42%) patients needed endocardial touch-up ablation. Gaps were located in the roof line (n=5), inferior line (n=1), around the RSPV (n=2) and the left and right carina (n=1) and after endocardial touch-up all patients had entry and exit block of the PVs and box. Additional ablation lines consisted of a CTI-line (n=14) or a mitral isthmus line (n=1) for isthmus-dependent flutter.

In the CA group, transvenous PVI and the box lesion were created in all patients. Endocardial validation showed complete PVI in all patients and entry/exit block of the box was confirmed in all but two patients (91%). Successful additional CTI ablation was performed in 46% (n=10). For both procedures, an ECV was performed to convert to SR if the patient was still in AF or AFL at the end of the ablation. Furthermore, median procedure time and length of hospital stay were significantly longer in the HA group, while the exposure to radiation dose and -time were significantly higher in the CA group (Table 2).

**Table 2**. Procedural characteristics comparing a hybrid procedure with a catheter ablation procedure.

| | **Hybrid ablation (n=19)** | **Catheter ablation (n=22)** | ***P*-value** |
|---|---|---|---|
| Radiation dose ($cGycm^2$) | 31 [8 – 69] | 67 [8 – 153] | 0.004 |
| Total radiation exposure time (hours:min) | 00:23 [0 – 1:59] | 1:54 [1:05 – 2:34] | <0.001 |
| Total procedure time (hours:min) | 4:16 [3:03 – 5:55] | 2:53 [2:05 – 3:34] | <0.001 |
| Length of hospital stay (days) | 4 [3 – 7] | 2 [1 – 7] | <0.001 |

Data are presented as median [interquartile range].

Primary and secondary outcomes

*Efficacy*

All included patients reached 12 months follow-up. The primary efficacy endpoint, i.e., freedom from any supraventricular tachyarrhythmia lasting >5 minutes off AADs at 12 months, was significantly higher in the HA group compared to the CA group (89% vs. 41%, *P*=0.002) (Table 3). The secondary effectiveness outcome, i.e., freedom from any supraventricular tachyarrhythmia lasting >30 seconds off AADs at 12 months, was also significantly higher in the HA arm (89% vs. 36%, *P*<0.001). When allowing the use of AADs, the freedom from documented atrial tachyarrhythmias within 12 months was 95% in the HA group and 41% in the CA arm (*P*<0.001) (Figure 2A-B).

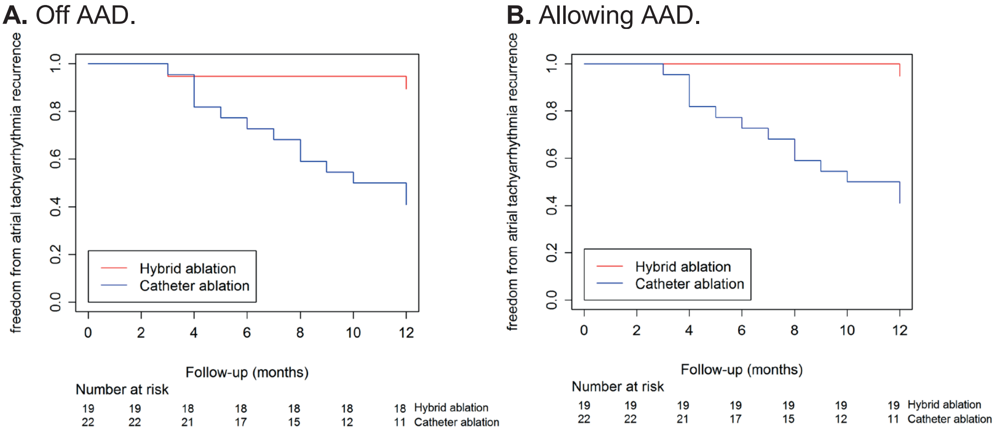



**Figure 2.** Kaplan-Meier curve depicting recurrence-free survival comparing hybrid with catheter ablation, until one year after the index procedure **(A)** off AAD and **(B)** allowing AAD. AAD=anti arrhythmic drug.

While it was more likely for the HA group compared to the CA group to receive AADs until 3 months after the procedure, more patients in the HA were off AADs after one year (95% compared to 36% off AADs, *P*=0.005) (Figure 3). Furthermore, the number of cardioversions after the blanking period did not significantly differ between both arms, nor did the number of redo-ablations (*P*=0.191). Although permitted for the primary efficacy endpoint, there were no redo ablations performed within 6 months in the CA arm. Furthermore, there was no difference in the frequency of arrhythmia related hospitalizations through 12 months (*P*=1.000) (Table 3).

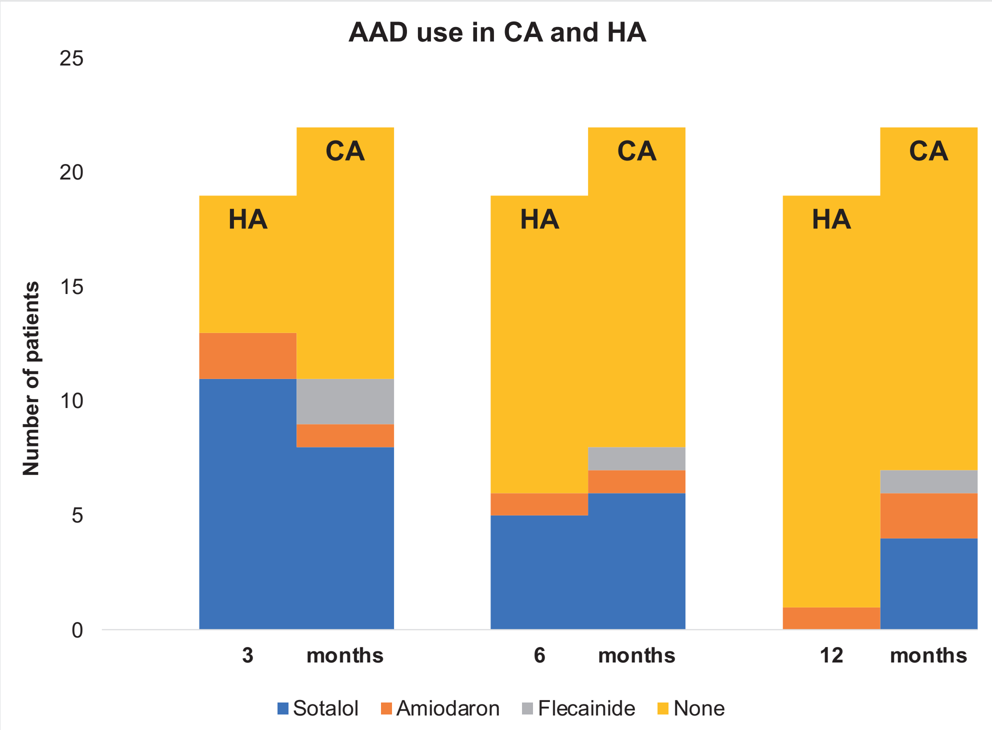



**Figure 3.** Bar chart depicting the number of patients on AAD at 3, 6 and 12 months after a hybrid or catheter ablation procedure. Data are presented as a graphical view of the number of patients per AAD in each ablation arm. AAD=anti arrhythmic drug.

In the HA group, only one patient received an electrical cardioversion and a redo catheter ablation due to atrial tachycardia and atrial flutter (AFL). During the redo procedure, isolation of the box, PVs and the CTI-line was confirmed. RF ablation of a (micro-re-entry) atrial tachycardia at the anterior wall of the LA was performed from the right superior pulmonary vein to the mitral valve annulus, with bidirectional block and consequently also successful conversion to SR. In the CA group, 13 patients experienced a recurrence (pAF n=8, AFL+AT n=1, AT n=1, AFL n=1, persAF n=1, persAF+AFL n=1). In five of them, a redo catheter ablation was performed and four underwent an ECV (with or without adding AAD therapy), after which these patients converted to SR (Table 3, Table S1).

**Table 3.** Primary and secondary efficacy outcomes following hybrid and catheter ablation until 12 months of follow-up.

| Effectiveness outcomes | Hybrid ablation (n=19) | Catheter ablation (n=22) | *P*-value |
|---|---|---|---|
| **Primary efficacy** | | | |
| Freedom from any SVT arrhythmia >5 min off AAD | 17 (89%) | 9 (41%) | 0.002 |
| **Secondary efficacy** | | | |
| Freedom from any SVT arrhythmia >30 sec off AAD | 17 (89%) | 8 (36%) | <0.001 |
| Freedom from AAD I/III | 18 (95%) | 15 (68%) | 0.050 |
| Number of cardioversions | 1 (5%) | 5 (23%) | 0.350 |
| Redo catheter ablations | | | |
| <6 months | 0 | 0 | - |
| >6 months | 1 (5%) | 5 (23%) | 0.191 |
| Number of arrhythmia related hospital admissions | 1 (5%) | 1 (5%) | 1.000 |

Data are presented as absolute numbers and frequencies (%). AF=atrial fibrillation; AAD=anti-arrhythmic drugs; SVT=supraventricular tachy-arrhythmia.

*Safety*

The primary safety outcome, i.e., the number of major adverse events and complications, was low in both groups and there was no mortality. In the HA arm, one patient had a pericarditis requiring pericardiocentesis. In the CA arm, one patient had a bleeding from the femoral artery which required surgical intervention. There were no other major complications such as cardiac tamponade, conversion to sternotomy or strokes for both groups (Table 4). With regards to the secondary safety outcome, minor complications were low. In the hybrid group, vascular access complication consisting of a femoral arteriovenous fistula occurred in one patient. In both patients who received closure of the LAA using the Lariat device, adequate closure of the LAA was confirmed on the postoperative transthoracic echocardiography. Another patient in the HA group underwent a staged epi/endocardial procedure due to malfunction of the equipment for the endocardial ablation. In the CA group there was one patient where the ablation was postponed due to hematuria when inserting the urinary bladder catheter until further analysis of the urologist. No patients needed a pacemaker implantation (Table 4).

**Table 4.** Primary and secondary safety outcomes including major and minor complications and total serious adverse events until 12 months of follow-up.

| Safety outcomes | Hybrid ablation (n=19) | Catheter ablation (n=22) | *P*-value |
|---|---|---|---|
| **Primary safety: major adverse events and complications** | | | |
| Bleeding | 0 | 1 | - |
| Cardiac tamponade | 0 | 0 | - |
| Conversion to sternotomy | 0 | 0 | - |
| Diaphragmatic paresis | 0 | 0 | - |
| Empyema | 0 | 0 | - |
| Gastroparesis | 0 | 0 | - |
| Mortality | 0 | 0 | - |
| Myocardial infarction | 0 | 0 | - |
| Pericarditis | 1 | 0 | - |
| Pneumothorax | 0 | 0 | - |
| Stroke | 0 | 0 | - |
| Symptomatic PV stenosis | 0 | 0 | - |
| Total | 1 (5%) | 1 (5%) | 1.000 |
| **Secondary safety** | | | |
| Minor complications | 1 | 0 | - |
| Vascular access | 1 | 0 | - |
| Pacemaker implantation | 0 | 0 | - |
| Number of SAE's | 4 (21%) | 3 (14%) | 0.685 |
| Radiation dose (cGycm$^2$) | 31 [8 – 69] | 67 [8 – 153] | 0.004 |
| Total radiation exposure time (hours:min) | 00:23 [0 – 1:59] | 1:54 [1:05 – 2:34] | <0.001 |
| Total procedure time (hours:min) | 4:16 [3:03 – 5:55] | 2:53 [2:05 – 3:34] | <0.001 |

Data are presented as absolute numbers and frequencies (%). PV=pulmonary vein stenosis; SAE=serious adverse event.

## Quality of Life

One year following both HA and CA, patient-reported QOL measured by the EQ-5D-5L questionnaire did not improve compared to baseline scores (HA baseline: 0.86 [0.72-0.94] and after 1 year 0.89 [0.79-1.00], *P*=0.211 and CA baseline: 0.84 [0.72-0.92] and after 1 year 0.88 [0.73-1.00], *P*=0.349). After 12 months, QOL scores did not differ between HA and CA groups (*P*=0.491). Furthermore, EHRA symptom scores did not significantly differ either between HA and CA groups after 1 year. In the HA group, one patient (5.6%) had a high EHRA score of 3 or more, compared to 3 patients (13.6%) in the CA arm (*P*=0.613).

## Discussion

This study describes a randomized trial comparing hybrid with catheter ablation in patients with symptomatic (longstanding)-persistent AF. We found that in patients with symptomatic, drug-refractory, ablation-naïve, (longstanding)-persAF, HA resulted in significantly fewer patients experiencing recurrences from supraventricular tachy-arrhythmias compared to CA until 12 months. The uniqueness of our study is underlined by the fact that we excluded patients with prior ablations. Hence our study overcomes a bias frequently found in to-date published studies on hybrid ablation or surgical ablation as we know that multiple catheter ablations in the same patient establish SR.[7,8] Overall, mortality was zero and morbidity was low in both groups with no significant difference in (serious) adverse events between HA and CA until one year of follow-up.

Primary outcome: efficacy

While CA for PVI shows excellent results in patients with pAF and is recommended for rhythm control after one failed or intolerant class I or III AAD,[9] success percentages in patients with persistent and long-standing persistent AF are far less satisfactory.[7] Even when adding linear ablation lines or CFAE ablation in addition to PVI, success rates of CA in persAF do not exceed 48% after a single procedure off AADs.[2] Additional ablation lines can even be pro-arrhythmogenic and lead to increased numbers of atypical flutter, if lesions fail to be transmural.[2] Also adding posterior wall box isolation to circumferential PVI only did not improve rhythm outcome for CA.[10]

Over the past years, several studies have evaluated the efficacy and safety of a single-stage HA procedure, off AADs, without a redo procedure. After one year, Zembala et al. reported a success percentage of 62% of patients in SR.[11] Similar to our study, patients had a long history of AF duration, but prior CA was allowed. Pison et al. reported a higher one-year success percentage of 90% in persAF after a bilateral approach,[3] which is comparable to our efficacy outcome. Also, Maesen et al.[4] reported on freedom from any supraventricular arrhythmia recurrence following a single HA procedure in patients with persAF after one, two and three years being 82%, 79% and 79% respectively.

One of the advantages of a hybrid over a catheter procedure is the use of biparietal bipolar RF clamps for the PVI, instead of unipolar devices used in CA. Bipolar clamps are thought to be more effective than unipolar devices in creating durable transmural lesions, as the

RF energy is applied to both sides of the tissue while the tissue is in between the jaws of the clamp.[12] Still, even bipolar RF energy does not always guarantee transmural lesions.[13] The advantage of HA is that epicardial ablation is succeeded by endocardial validation. As such, conduction gaps that are not identified during epicardial ablation can immediately be detected during the endocardial procedure and treated accordingly to achieve bidirectional block.[3] Moreover, anatomical structures that are easily accessible from the endocardium, such as the mitral or cavo-tricuspid isthmus, can still be ablated during HA without increasing the risk of pacemaker implantation.[14] While PV ablation represents the cornerstone of AF ablation[15], other non-PV triggers originating from the LA posterior wall, the ligament of Marshall and the LA septum play an important role in maintaining AF, especially in (longstanding)-persAF.[16] Accordingly, we added the roof and inferior lines between both isolated PV pairs to create the box lesion and posterior wall isolation. In the HA arm, the PVI and box lesions were probably more transmural due to both the use of a bipolar clamp as well as the combination of epicardial and endocardial approach, which may explain why fewer patients experienced recurrent arrhythmias compared to the CA arm during follow-up.

In addition to a meticulously isolated posterior wall, most patients undergoing HA underwent LAA closure and therefore also LAA isolation. In the BELIEF-trial, adding empirical electrical isolation of the LAA to standard ablation of the PVs by CA increased clinical success in persAF until 12 months (56% SR vs. 28%, $P$=0.001).[17] Although potentially effective, a major concern due to mechanical dissociation of the LAA was the possible increased risk of stroke on the long-term. By clipping the LAA, we did not only electrically isolate the LAA, but also mechanically occluded the LAA. In the LAAOS-III trial, concomitant LAA occlusion reduced the risk of ischemic stroke or systemic thromboembolism by 33% in patients with AF undergoing cardiac surgery. In our study, the effectiveness of maintaining SR was higher following HA compared to CA and there was no stroke in both groups.

The CONVERGE trial randomized patients with non-paroxysmal AF to the convergent procedure or endocardial catheter ablation.[18] Although the lesion set is comparable, the technique is quite different. Posterior wall isolation is performed with unipolar RF and endocardial PVI by CA is needed to complete the lesion set. The hybrid convergent arm had significant better freedom from AF than the catheter arm, but the arrhythmia-free survival at 1 year off AAD, 53.5% vs. 32%, is low compared to our study. In the FAST trial, surgical AF ablation was also superior to CA in terms of rhythm outcome until 12 months, but was associated with significantly more (procedural) complications (34% vs. 16%, *P*=0.027) due to pneumothorax and permanent pacemaker implantation.[19] Over the past decade, minimally invasive surgical ablation techniques and tools have improved, along with the experience of the operating team. In our study, periprocedural and postoperative complication rate for the surgical ablation as a part of HA was low and comparable with complications in the CA arm. Surprisingly, the CASA-AF trial showed no significant difference between the CA arm and the surgical ablation arm using continuous monitoring in patients with longstanding-persAF.[20] However, more extensive lesion sets were applied in the CA arm compared to the surgical arm, limited experience was requested in the surgical arm and it was a non-hybrid approach.

Quality of life

Although recovery time after a surgical procedure takes longer than after a percutaneous procedure, QOL measured by the EQ5D-5L score did not differ 12 months after a HA or CA. It is interesting to see that despite this longer revalidation trajectory, quality of life is equal between both interventions. This finding suggests that the beneficial effect of HA on the arrhythmia burden compensates for the longer postprocedural recovery time. Neither did the EHRA score differ between both groups. However, one could question if the EHRA score, that should evaluate the burden of AF complaints at that timepoint, is able to discriminate between symptoms solely attributable to AF and reduced wellbeing following the longer revalidation period after hybrid AF ablation.

Safety

A recent meta-analysis comparing efficacy and safety endpoints between HA with CA showed that HA resulted in a slightly higher complication rate compared to CA.[5] Although minimally-invasive, any surgical procedure comes with a higher risk of complications. In our study, however, this was not the case. Overall, major and minor complications were low in both groups and did not statistically differ between HA and CA (*P*=0.685). In the HA arm, only one major complication occurred (5%) and 1 major complication was noted in the CA arm (5%). The low complication rates following HA and CA compared to current literature may be explained by the fact that all procedures were carried out by a dedicated team with years of experience, whereas other studies are still undergoing the effect of the learning curve.

**Limitations**

All procedures were conducted in a single, highly-specialized center with a dedicated team consisting of cardiac surgeons and electrophysiologists with substantial experience in performing HA, which decreases the generalizability and external validity of our results. As such, more centers of excellence with extensive collaboration between cardiac surgeons and electrophysiologists to perform HA should be encouraged. Furthermore, this study is not double-blinded as this would not be feasible, given the nature of interventions and operators required to perform them. Moreover, the rate of patients in SR at one-year might be overrated as discontinuous rhythm-monitoring for follow-up was used for both groups. Therefore, future studies should include multicenter experiences comparing both techniques and preferentially use continuous rhythm monitoring during follow-up. Finally, although the initial study protocol permitted redo CA within the first 6 months after the initial procedure in the CA arm, the protocol did not prescribe strict indications to perform redo CA. As such, patients presenting with SVT recurrences after the 3 months blanking period were kept on AADs and were planned for an ECV. If necessary, a redo procedure was scheduled after further rhythm assessment after 6 months. As such, we learned that in daily practice it is logistically difficult to perform a redo catheter ablation within 6 months and we advise future trials to extend the allowance for redo ablations. As such, our study shows us the results of a single HA compared to a single CA procedure, rather than repeated CA.

**Conclusion**

Here we present our results from a superiority, randomized controlled trial comparing hybrid with catheter ablation in patients with symptomatic, ablation-naïve, drug-refractory, (longstanding)-persistent AF. We found that HA resulted in significantly more patients in SR off AADs until 12 months of follow-up compared to CA (89% vs. 41%, $P$=0.002), without increasing the number of serious adverse events (21% vs 14%, $P$=0.685). Based on our results, we recommend to consider HA as a first-choice treatment for this patient category when performed by an experienced team.

## Conflict of Interest

Bart Maesen and Mark La Meir are a consultant to AtriCure, Bart Maesen is consultant to Medtronic.

## Study Protocol

Vroomen, M., La Meir, M., Maesen, B., Luermans, J. G., Vernooy, K., Essers, B., ... & Pison, L. (2019). Hybrid thoracoscopic surgical and transvenous catheter ablation versus transvenous catheter ablation in persistent and longstanding persistent atrial fibrillation (HARTCAP-AF): study protocol for a randomized trial. *Trials*, *20*(1), 1-11.

## Funding

No sources of funding were used.

## Perspectives

<u>Competency in Medical Knowledge</u>

In the treatment of more persistent forms of atrial fibrillation, hybrid ablation is as safe, but more efficacious than catheter ablation. As such, patients with persistent or longstanding persistent AF should be made aware by their treating physician of the possibility to undergo a hybrid AF ablation.

<u>Translational Outlook</u>

Up until now, translation of basic research on the underlying pathophysiological AF mechanisms -including high resolution mapping studies- into an individualized patient treatment strategy has not yet been successful. Hybrid AF ablation facilitates a patient-tailored approach by combining the best of two worlds. Within this hybrid setting, further investigation of the underlying mechanisms and implementation of those findings into patient-tailored treatment approaches may even further improve its efficacy.

## Acknowledgements

None.

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## Supplementary Materials

### Tables

**Table S1.** Overview of all patients with a recurrence of any supraventricular arrhythmia (>5 minutes) after the index procedure, management and rhythm outcome.

| Randomized group | Type of SVT recurrence | On/off AAD I/III | Management of recurrence | Rhythm outcome after additional therapy |
|---|---|---|---|---|
| HA | AT + AFL | off | ECV + redo CA | SR |
| CA | pAF | sotalol | redo CA | AF |
| CA | pAF | sotalol | redo CA | persAF |
| CA | AFL + AT | off | AAD + redo CA | SR |
| CA | AT | off | - | - |
| CA | AFL | off | AAD + ECV | SR |
| CA | persAF | amiodaron | ECV + redo CA | SR |
| CA | pAF | off | redo CA | SR |
| CA | pAF | off | AAD + ECV | SR |
| CA | pAF | sotalol | ECV | SR |
| CA | persAF + AFL | sotalol | - | - |
| CA | pAF | off | rate control | AF/AFL |
| CA | pAF | flecainide | - | - |
| CA | pAF | off | - | - |

Data are presented as the type of arrhythmia documented per treatment group, AAD use, management and rhythm outcome. AAD=anti-arrhythmic drug; AF=atrial fibrillation; AFL=atrial flutter; AT=atrial tachycardia; CA=catheter ablation; ECV=electrical cardioversion; HA=hybrid ablation; pAF=paroxysmal AF; persAF=persistent AF; SR=sinus rhythm; SVT=supraventricular tachyarrhythmia.

## Clinical perspectives

Hybrid ablation for AF is the preferred therapy for restoring sinus rhythm in drug-resistant, ablation naïve, patients with (longstanding)-persistent AF. Patients with difficult to treat AF and enlarged atria who have an indication for surgical intervention should be made aware by their cardiologist of the option of a hybrid ablation. As the follow-up period of this study is relatively short (12 months), longer term follow-up of rhythm monitoring, quality of life and cost-effectiveness will lead to a better understanding of the potential comparative benefit of hybrid ablation over a catheter ablation procedure.

## Appendix

<u>Data safety monitoring board</u>
Dr. M.H. Prins, Statistician, The Netherlands.
Prof. F. Wellens, Cardiothoracic surgeon, Belgium.
Prof. T. Gorgels, Cardiologist, The Netherlands.

These members do not have conflict of interest with the sponsor in the study.

<u>Steering committee</u>
Prof. Dr. M. La Meir, MD, PhD, Brussels, Belgium.
Dr. J. Luermans, MD, PhD, Maastricht, The Netherlands.

<u>Writing committee</u>
Drs. C.A.J. van der Heijden, MD, PhD candidate, Maastricht, The Netherlands.
Drs. V. Weberndörfer, MD, PhD candidate, Maastricht, The Netherlands.
Dr. B. Maesen, MD, PhD, Maastricht, The Netherlands.
Dr. S.M.J. van Kuijk, PhD, Clinical epidemiologist, Maastricht, The Netherlands.
Prof Emer. H. Crijns, MD, PhD, Maastricht, The Netherlands.

# CHAPTER 5

## Hybrid Ablation of Atrial Fibrillation: A Unilateral Left-sided Thoracoscopic Approach

**Short Title: Unilateral Left-sided Thoracoscopic Hybrid Ablation**

**Claudia A.J. van der Heijden*,** Vanessa Weberndörfer*,
Justin G.L.M. Luermans, Sevasti-Marisevi Chaldoupi,
Sander M.J. van Kuijk, Mindy Vroomen, Elham Bidar,
Jos G. Maessen, Laurent Pison, Mark La Meir, Bart Maesen

*Both authors contributed equally

*Journal of Cardiac Surgery, October 2022.*

## Abstract

**Background** Hybrid ablation (HA) of atrial fibrillation (AF) combines minimally invasive thoracoscopic epicardial ablation with transvenous endocardial electrophysiologic validation and touch-up of incomplete epicardial lesions if needed. While studies have reported on a bilateral thoracoscopic HA approach, data on a unilateral left-sided approach are scarce. We aimed to evaluate the efficacy and safety of a unilateral left-sided thoracoscopic approach.

**Methods** Retrospective analysis of a prospectively gathered cohort of all consecutive patients undergoing a unilateral left-sided HA for AF between 2015 and 2018 in the Maastricht University Medical Centre.

**Results** One-hundred nineteen patients were analyzed (mean age 64±8, 28% female, mean BMI 28±4 kg/m$^2$, median $CHA_2DS_2$-VASc Score 2 [1-3], (longstanding)-persistent AF 71%, previous catheter ablation 44%). In all patients, a unilateral left-sided HA consisting of pulmonary vein (PV) isolation, posterior left atrial (LA) wall isolation and LA appendage exclusion was attempted. Epicardial (n=59) and/or endocardial validation (n=81) was performed and endocardial touch-up was performed in 33 patients. Major peri-operative complications occurred in 5% of all patients. After 12 and 24 months, the probability of being free from supraventricular tachyarrhythmia recurrence was 80% [73-87] and 67% [58-76] respectively, when allowing anti-arrhythmic drugs.

**Conclusion** Unilateral left-sided hybrid AF ablation is an efficacious and safe approach to treat patients with paroxysmal and more persistent AF. Future studies should compare a unilateral with a bilateral approach to determine whether a left-sided approach is as efficacious as a bilateral approach and allows for less complications.


**Keywords** Atrial fibrillation • Hybrid ablation • Unilateral left-sided approach

## Glossary of Abbreviations

| | |
|---|---|
| AAD | Antiarrhythmic drug |
| AF | Atrial fibrillation |
| AT | Atrial tachycardia |
| HA | Hybrid ablation |
| LA | Left atrium |
| LAA | LA appendage |
| pAF | Paroxysmal AF |
| persAF | Persistent AF |
| PV | Pulmonary vein |
| PVI | PV isolation |
| SR | Sinus rhythm |

## Introduction

Thoracoscopic ablation for atrial fibrillation (AF), including hybrid AF ablation, is recognized as a valid treatment option for patients with symptomatic, drug-refractory paroxysmal or persistent AF.[1] The standard hybrid ablation (HA) procedure combines minimally invasive bilateral thoracoscopic epicardial ablation with transvenous endocardial electrophysiologic validation and touch-up of incomplete epicardial lesions if needed.[2] The results of HA are promising when performed by an experienced team, with high success percentages even after three years of follow-up (freedom from atrial arrhythmia recurrence of 80% for paroxysmal AF and 79% for more persistent forms).[3] Furthermore, when comparing HA with catheter ablation (CA) in a meta-analysis, the outcome following HA is superior to CA for persistent and long-standing persistent AF until 12 months (70.7% vs 49.9%, $P<0.001$).[4]

More recently, we have changed our surgical technique to a unilateral left-sided thoracoscopic approach.[5] The possible advantage of a unilateral approach is the reduced risk of complications on the contralateral side, while still performing the same lesion set as in a bilateral approach. Although studies have reported on the bilateral HA approach[2], cohort data on a unilateral left-sided approach are scarce. Therefore, we aimed to evaluate the efficacy and safety of a unilateral left-sided thoracoscopic approach in all consecutive patients referred for HA in our center.

## Patients and Methods

Study population and design

In this retrospective analysis of a prospectively gathered cohort, we analyzed all patients who underwent a unilateral left-sided thoracoscopic HA between January 2015 and December 2018 at the Maastricht University Medical Centre. The study was approved by the Institutional Review Board (IRB) and Ethics Committee (METC 2019-1430) in accordance with IRB guidelines and patient informed consent was waived. The study complies with the ethical principles of the Helsinki Declaration.

Hybrid ablation procedure

All HA procedures were performed by an experienced team consisting of two surgeons (B.M. and M.L.M) and two electrophysiologists (J.L. and L.P.). The technique of the unilateral left-sided HA has been described previously.[5] In brief, left-sided thoracoscopic ablation consisting of left and right pulmonary vein (PV) isolation using a biparietal bipolar radiofrequency clamp (Isolator, AtriCure) was performed, followed by ablation of roof and inferior lines (Coolrail, AtriCure) to create the box lesion. In all patients, closure of the left atrial appendage (LAA) was attempted. Finally, epicardial and/or endocardial electrophysiological validation of entrance and exit block of the PVs and the box was attempted and if necessary, additional touch-up of unintended gaps was performed. For patients with a left atrial (LA) flutter or -tachycardia, additional ablation thereof was performed endocardially, if inducible. A left isthmus line was made in patients developing a mitral isthmus-dependent atrial flutter during the procedure and a cavo-tricuspid isthmus (CTI) line if the patient presented with right atrial (RA) dilatation or a typical atrial flutter.

Outcomes and follow-up

The primary outcome was defined as freedom from any supraventricular tachyarrhythmia ≥30 seconds until 24 months of follow-up, allowing AADs, after three months blanking period.[1] Discontinuation of AADs after the blanking period was encouraged if the patient appeared to be arrhythmia free, though the final decision was left to the discretion of the referring cardiologist. Secondary outcomes included peri- and postoperative complications until 24 months: bleeding, cardiac tamponade, conversion to sternotomy, haematothorax or pleural effusion requiring drainage, myocardial infarction[6], mortality, pacemaker implantation, pericarditis (either stable hemodynamics requiring optimal medication therapy or unstable hemodynamics requiring pericardiocentesis), phrenic nerve injury, pneumothorax (after removal of chest tubes) and stroke.

All patients were encouraged to visit the outpatient clinic at 3, 12 and 24 months. Rhythm follow-up consisted of 24-h, 48-h or 7-days Holter monitoring (dependent on the preference of the physician), read-out of implanted devices or by 12-lead ECG monitoring, conform our standard of care. In case of AF recurrence, patient tailored treatment followed conform routine care.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range, while categorical variables as count and relative frequencies. A Pearson's $\chi^2$ test or Fisher's exact test was performed to compare categorical variables between both groups, whereas a Student's T-test or Mann-Whitney-*U* test (dependent on data distribution) was used for the comparison of continuous variables. One-way ANOVA was used for the comparison of continuous variables between multiple groups. Next, a Kaplan-Meier curve was plotted to estimate the probability of being free from any supraventricular recurrence within the course of 24 months. The log-rank test was used to test for differences in efficacy outcome throughout the whole follow-up period between patients undergoing endocardial or epicardial validation only for the whole group, paroxysmal AF only and persistent AF only. A *P*-value <0.05 was considered statistically significant and all analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) and R version 4.1.2.

## Results

Study population

In total, 119 patients were analyzed. Patients were on average 64±8 years old, 28% was female, the mean BMI was 28±4 kg/$m^2$ with a median $CHA_2DS_2$-VASc Score of 2 [1-3] (Table 1). Four percent had a history of a hemorrhage, 13% had obstructive sleep apnea and 8% had vascular disease. More patients had (longstanding)-persistent AF (71%) than paroxysmal AF (29%) and the median history of AF duration was 61 [25-125] months. Forty-five patients (38%) were also known with an AFL and/or AT and 53 patients (44%) underwent previous CA for AF or AFL. The mean LVEF and LA volume index were 54±9%

and 50±16ml/m$^2$ respectively. The mean RA volume index was 38±14 ml/m$^2$. When comparing baseline characteristics of the patients who underwent epicardial validation only (n=33) with those who underwent (at least) endocardial validation (n=81), patients were older (66±7 vs. 62±8, *P*=0.014), mean BMI was lower (26±3 vs. 28±4kg/m$^2$, *P*=0.019) and more patients had a previous hemorrhage (12% vs. 0%, *P*=0.002). All other characteristics were comparable between both groups (Table 1).

**Table 1**. Baseline characteristics of the total population compared to patients who received epicardial validation only versus at least endocardial validation.

| Patient characteristics | All patients (n=119) | Epicardial validation only (n=33) | Endocardial validation (n=81) | *P*-value |
|---|---|---|---|---|
| Age (years) | 64 ± 8 | 66 ± 7 | 62 ± 8 | 0.014 |
| BMI (kg/m$^2$) | 28 ± 4 | 26 ± 3 | 28 ± 4 | 0.019 |
| Female (%) | 33 (28%) | 11 (33%) | 20 (25%) | 0.524 |
| $CHA_2DS_2$-VASc | 2 [1 – 3] | 2 [1 – 3] | 2 [0 – 3] | 0.345 |
| COPD | 13 (11%) | 4 (12%) | 8 (10%) | 0.543 |
| Hemorrhage | 5 (4%) | 4 (12%) | 0 (0%) | 0.002 |
| OSAS | 15 (13%) | 2 (6%) | 12 (15%) | 0.314 |
| Vascular disease | 10 (8%) | 3 (9%) | 7 (9%) | 0.999 |
| **AF characteristics** | | | | |
| pAF | 34 (29%) | 12 (36%) | 19 (24%) | 0.091 |
| (longstanding)-persAF | 85 (71%) | 21 (64%) | 62 (77%) | 0.091 |
| AF duration (months) | 61 [25 – 125] | 66 [23 – 128] | 45 [26 – 119] | 0.533 |
| AFL and/or AT | 45 (38%) | 7 (21%) | 36 (44%) | 0.051 |
| Previous CA ablation | 53 (44%) | 13 (39%) | 39 (48%) | 0.669 |
| Use of AAD I/III | 70 (58%) | 17 (52%) | 44 (54%) | 0.115 |
| **Echocardiographic measurements** | | | | |
| LVEF (%) | 54 ± 9 | 53 ± 10 | 54 ± 9 | 0.860 |
| LA (mm) | 44 ± 7 | 45 ± 6 | 45 ± 7 | 0.908 |
| LAVI (ml/m$^2$) | 50 ± 16 | 51 ± 17 | 51 ± 15 | 0.788 |
| pAF | 45 ± 14 | 45 ± 12 | 47 ± 17 | 0.778 |
| non-pAF | 52 ± 16 | 55 ± 19 | 52 ± 15 | 0.438 |
| RAVI (ml/m$^2$) | 38 ± 14 | 40 [22 – 49] | 38 [28 – 46] | 0.121 |

AF=atrial fibrillation; AFL=atrial flutter; AT=atrial tachycardia; AAD=anti-arrhythmic drug; BMI=body mass index; CA=catheter ablation; COPD=chronic obstructive pulmonary disease; (D)OAC=(direct)oral anticoagulant; LA=left atrial; LAV=LA volume; LVEF=left ventricular ejection fraction; MI=mitral valve insufficiency; OSAS=obstructive sleep apnea syndrome; RAV=right atrial volume; SVT=supraventricular tachycardia.

Procedural data

All 119 patients underwent unilateral left-sided HA. In 10 patients (8%), epicardial ablation of the right PVs was incomplete due to a too short clamp (n=6), no good visualization (n=3) or bleeding of the RA (n=1). Isolation of the PVs was attempted in all patients (n=119) and the box in all but two (n=117) that were known with pAF. Furthermore, the LAA was occluded in 96% (n=115) of all patients, either by AtriClip (90%, n=103), Lariat (4%, n=4), stapler (2%, n=2) or a Watchman device (5%, n=6). In the remaining 5 patients (4%), the LAA was not closed due to bleeding at its base (n=1), $CHA_2DS_2$-VASc Score of zero (n=1), typical Wind-sock configuration with a high risk of creating a rest pouch (n=1), the inability of exposing the LAA due to adhesions after a previous CABG surgery (n=1) and AT ablation, not necessitating LAA closure (n=1).

For logistical and/or safety reasons, 81 of the 119 patients underwent an endocardial EP validation, 33 patients received epicardial EP validation only and 5 patients received no EP validation. Of all patients undergoing endocardial validation, touch-up of unintentional gaps was performed in 41% (n=33/81) (Figure 1). Overall, 82% (27/33) of all touch-up ablations concerned the box region, mainly in the roof line followed by the right PVs. To evaluate a possible influence of a 'learning curve' on the number of endocardial touch-up ablation needed, 6 cohorts of 20 consecutive patients were created (Figure 2). Over time, there was no significant difference in the number of unintended gaps between the cohorts ($P$=0.728). In 48% of all patients (n=58), additional endocardial ablation including a CTI line (n=39), complex fractionated atrial electrograms (n=15) and/or a mitral isthmus line (n=8) with bidirectional block was performed. In 10 patients, a CTI line was created in a previous CA procedure and bidirectional block was still present during the HA procedure.

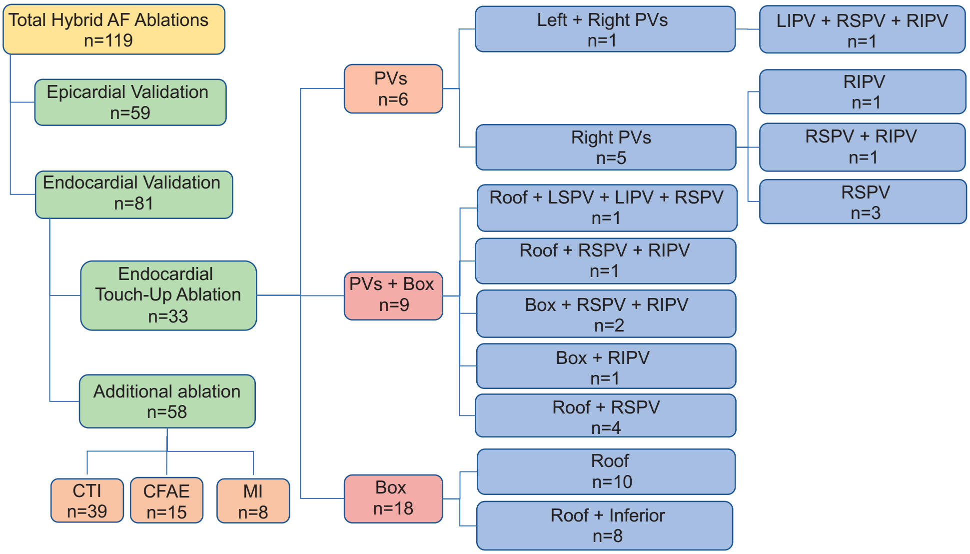


**Figure 1.** Overview of the number of patients undergoing endocardial touch-up per region after epicardial ablation. AF=atrial fibrillation; LSPV=left superior PV; PV=pulmonary vein; RIPV=right inferior PV; RSPV=right superior PV.

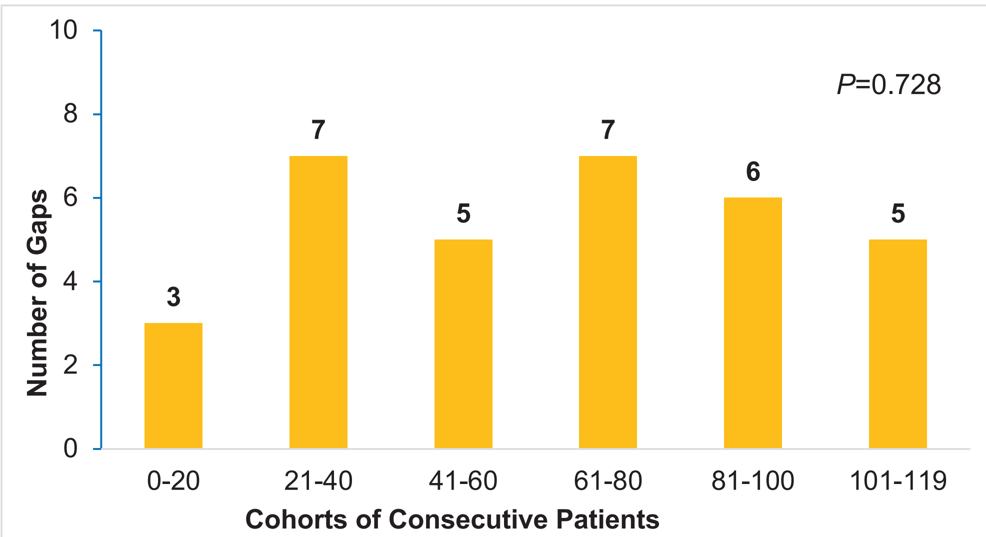


**Figure 2.** The number of unintended gaps over time per cohort of 20 consecutive patients following epicardial ablation for AF does not decrease over time. AF=atrial fibrillation.

Complications

Perioperative major complications consisted of: bleeding requiring reoperation (n=1, 0.8%), cardiac tamponade (n=1, 0.8%), myocardial infarction requiring percutaneous coronary intervention and stenting of the left anterior descending artery (n=1, 0.8%), pacemaker implantation due to conversion pauses (n=1, 0.8%) and pneumothorax (n=1, 0.8%). Minor complications were: bleeding requiring transfusion or drainage (n=4, 3.4%), hemodynamically stable pericarditis requiring medication (n=1, 0.8%) and pneumonia (n=1, 0.8%). There were no incidences of stroke, conversion to sternotomy or mortality. Postoperative complications until 24 months of follow-up were: late cardiac tamponade (n=2, 1.7%), diaphragm paresis (n=1, 0.8%), haematothorax (n=1, 0.8%), pacemaker or ICD-implantation (n=3, 2.5%), pericarditis requiring medication (n=4, 3.4%) or pericardiocentesis (n=2, 1.7%), hospital readmission due to heart failure due to recurrent AF (n=2, 1.7%), pleural effusion (n=2, 1.7%) and pneumonia (n=1, 0.8%) (Table 2).

**Table 2**. Peri-operative complications and complications until 24 months of follow-up.

| **Peri-operative** | **All patients n=119** |
|---|---|
| Bleeding requiring transfusion or drainage | 4 (3%) |
| Bleeding reoperation | 1 (1%) |
| Cardiac tamponade | 1 (1%) |
| Myocardial infarction with PCI+DES LAD | 1 (1%) |
| Pacemaker implantation | 1 (1%) |
| Pericarditis (HD stable) | 4 (3%) |
| Pneumonia | 1 (1%) |
| Pneumothorax | 1 (1%) |
| Total | 14 (12%) |
| **Until 24 months** | |
| Cardiac rehospitalization | 17 (14%) |
| Late cardiac tamponade ≤30 days | 2 (2%) |
| Decompensatio cordis due to AF | 2 (2%) |
| Pericarditis OMT | 4 (3%) |
| Pericarditis drainage | 2 (2%) |
| Haematothorax | 1 (1%) |
| Pacemaker or ICD implantation | 3 (3%) |
| Pleural effusion | 2 (2%) |
| Pneumonia | 1 (1%) |
| Diaphragm paresis | 1 (1%) |
| Total | 18 (15%) |

AF=atrial fibrillation; DES=drug eluting stent; ICD=implantable cardioverter-defibrillator; LAD=left descending artery; PCI=percutaneous coronary intervention.

Follow-up

One and two-year follow-up was reached by 112 (94%) and 105 (88%) patients respectively. Patients were lost to follow-up as they had moved abroad or did not wish to receive further rhythm follow-up. The primary outcome until 12 months was reached by 82% (allowing AADs) and 62% (off AADs) for pAF and 78% (allowing AADs) and 76% (off AADs) for (longstanding)-persistent AF. After two years, the efficacy rates were 71% (allowing AADs) and 50% (off AADs) for pAF compared to 65% (allowing AADs) and 61% (off AADs) for (longstanding)-persistent AF (Figure 3, Table 3). When comparing the efficacy outcome between patients undergoing epicardial validation only and endocardial validation, no significant difference was found (all patients *P*=0.584, pAF *P*=0.920, persistent AF *P*=0.385) (Table S1). Furthermore, discontinuation of AADs of all patients who were in SR after 12 months did not differ between pAF (83%) and non-pAF (78%) (*P*=0.574) nor after 24 months (pAF 86%, non-pAF 88% *P*=1.000) (Figure S1).

**Table 3.** Efficacy results until 12 and 24 months after unilateral left-sided hybrid ablation.

| **Efficacy outcomes** | | **SR allowing AADs** | **SR off AADs** |
|---|---|---|---|
| **12 months** | All patients | 80% (73 – 87) | 72% (64 – 81) |
| | pAF | 82% (71 – 96) | 62% (47 – 81) |
| | non-pAF | 78% (70 – 88) | 76% (67 – 86) |
| **24 months** | All patients | 67% (58 – 76) | 58% (49 – 68) |
| | pAF | 71% (57 – 88) | 50% (36 – 70) |
| | non-pAF | 65% (55 – 77) | 61% (51 – 73) |

Efficacy rates of a unilateral left-sided hybrid ablation. Groups were made based on preoperative rhythm. pAF=paroxysmal AF.

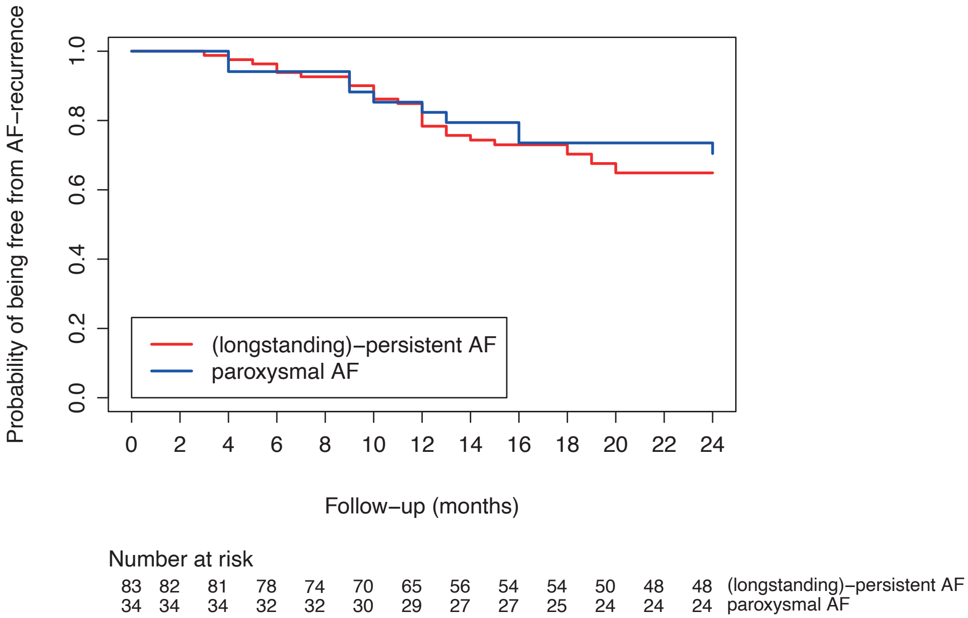


**Figure 3.** Arrhythmia-free survival after unilateral left-sided thoracoscopic hybrid AF ablation. Kaplan-Meier curve depicting the probability of being free from AF recurrence following unilateral left-sided hybrid AF ablation until 24 months of follow-up based on pre-operative rhythm (Blue=pAF, Red=non-pAF). AF=atrial fibrillation; pAF=paroxysmal AF.

## Discussion

In this study, we describe the efficacy and safety of a unilateral left-sided thoracoscopic hybrid AF ablation approach in a cohort study of 119 patients. After 12 and 24 months, freedom from supraventricular arrhythmia recurrence was 80% and 67% respectively, when allowing AADs. Major and minor complications during hospital stay and after discharge until 24 months were low.

### Efficacy

While unilateral thoracoscopic beating-heart approaches with microwave or unipolar RF have previously been reported,[7] thoracoscopic AF ablation using a bipolar RF clamp is usually performed via a bilateral approach.[2,8] More recently, two unilateral techniques have been introduced: a left-sided technique, either as a stand-alone procedure[5, 9] or concomitant to minimally invasive bypass grafting of the left anterior descending artery,[10] and a right-sided epicardial approach.[11] The quest for unilateral thoracoscopic approaches is driven by the conceivably advantages such as reduced surgical trauma and less complications on the contralateral side.

In our study, freedom from atrial tachyarrhythmia recurrence after 12 months was 88% in pAF and 73% in non-pAF, when allowing AADs. Compared to Asmundis et al.[12], who reported on 51 patients undergoing unilateral left-sided HA ablation with 69% of patients in SR off AADs after 24 months, our study showed a comparable overall efficacy rate of 65%, but on AADs. Moreover, Pison et al. reported on one-year efficacy rates following a bilateral approach of 93% in SR for pAF vs. 90% in SR for non-pAF, when allowing AADs.[2] Maesen et al. even reported on efficacy results 3 years after a bilateral HA approach, with success ratios of 80% and 79% of patients in SR for pAF and non-pAF respectively, both with and without the use of AADs.[3] Both our 1- and 2-year results seem lower than the results published by Pison and Maesen et al. There are several explanations for this difference. First, our patient population was probably more difficult to treat, as they had higher $CHA_2DS_2$-VASc scores, larger LA and more patients had (longstanding)-persistent AF. Second, discontinuation of AADs was left to discretion of the referring cardiologists and AADs were often continued for unknown reasons.

Within the hybrid concept, several surgical techniques have been described to improve outcomes.[13] In the CONVERGE trial[14], non-pAF patients were randomized between the hybrid convergent technique (posterior LA wall isolation with a vacuum assisted unipolar RF catheter and endocardial PVI to complete the box lesion set) or a catheter ablation approach. Although the efficacy outcome in the hybrid convergent arm was significantly higher compared to the catheter arm, the arrhythmia-free survival at 1 year was low compared to our study (67.7% vs. 50.0% when allowing the use of AAD). The advantage of the convergent technique is that is allows access via a minimally invasive subxiphoidal approach, while its disadvantage is that is offers poor efficacy results (53% off AAD after 1 year). This may be explained by the fact that unilateral RF is used and due to the absence of LAA occlusion.

Another mono-lateral technique as part of a two-stage hybrid approach uses a flexible RF device (COBRA Fusion, AtriCure Inc., Cincinnati, OH, US) to encircle the 4 PVs and perform posterior LA isolation via right-sided thoracoscopy, followed by an endocardial validation after 3 months.[7] Efficacy outcomes following the epicardial ablation were poor, as only 50.6% presented in sinus rhythm before the second stage catheter ablation. After the endocardial touch-up, efficacy rates improved to 63% off AAD, which again highlights the importance of a hybrid approach.[15] Although the technique uses a combination of unipolar and bipolar RF, its success is strongly dependent on suction-dependent tissue contact and therefore less effective that the bipolar biparietal RF application.[16] Recently, the technique of a totally thoracoscopic right-sided AF approach using a bipolar RF clamp was described in 13 patients.[11] As the authors did not report on efficacy and safety outcomes after 3 months follow-up, we cannot compare both unilateral approaches after 1 and 2 years. Nevertheless, a left-sided approach has several potential advantages over a right-sided approach: larger lung capacity during single right lung ventilation, dissection of the pericardial folds away from the heart, adequate visualization of the LAA during exclusion and PVI with the convex side of the bipolar clamp towards the heart, resulting in antral isolation and minimal risk of PV stenosis. The right-sided approach, on the other hand, has the advantage of adding RA lines. However, it remains to be determined if these RA lesions are beneficial without its key lesion (the lesion towards the tricuspid annulus). From an electrophysiological point of view, only a circular lesion to isolate the superior caval vein has been proven to increase success rate, especially in patients with (longstanding)-paroxysmal AF who present with trigger-initiated AF rather than substrate perpetuation of AF.[17]

While the use of a biparietal bipolar RF clamp for PVI is thought to be very effective in creating transmural lesions,[18] even bipolar RF energy cannot always prevent conduction gaps.[19] As such, the natural strength of a HA is that epicardial ablation is succeeded by endocardial validation of bidirectional conduction block and the possibility of precise touch-up of unintentional gaps.[2] Especially for a unilateral (left-sided) thoracoscopic procedure, establishing bidirectional conduction block is of paramount importance, as it can be challenging to reach and completely isolate the right PVs. While epicardial conduction block of the PVs and box corresponds well with endocardial conduction block, completeness of RSPV isolations and linear lesions is often misjudged.[20] This may be due to tissue edema, an antral location of the conduction gap or misplacement of the mapping catheter due to limited visualization in a unilateral approach.[20] Therefore, the added value of the endocardial ablation and -validation to prevent false negative results following epicardial ablation and -validation should not be underestimated. Furthermore, RSPV ablation specifically can be challenging because of anatomy or adhesions and could explain that the majority of endocardial touch-up ablation were in the region of RSPV and the adjacent superior part of the box lesion. This can be partly overcome by verifying the position of the RF-clamp on the RSPV via the transverse sinus during isolation of the right veins. Conduction gaps at the junction of the roof line and RSPV, potentially associated with this unilateral approach, can easily be addressed from the endocardium within the hybrid setting. As such, the need for a right thoracoscopy can be avoided, thereby reinforcing the need for endocardial EP validation following a unilateral left-sided HA. In our study, patients were pre-selected based on logistical and/or safety reasons to either undergo epicardial and/or endocardial EP validation. For example, patients with a previous hemorrhage underwent epicardial validation to prevent the need for full heparinization, whereas patients with a high chance of failure due to a higher substrate, e.g., obesity and higher BMI, underwent endocardial validation. In a subset of patients, no EP validation was performed at all due to safety reasons such as procedural bleeding.

While PVI is believed to be the cornerstone in AF ablation[21], PV isolation alone is insufficient to achieve satisfactory results in more persistent forms of AF. Other non-PV sources of arrhythmias of the LA include the appendage. Not only did the LAAOS-III trial indicate that concomitant LAA occlusion significantly reduces the risk of stroke in patients with AF undergoing cardiac surgery[22], the BELIEF trial showed that electrical isolation of the LAA also improves long-term freedom from supraventricular tachyarrhythmias.[23] Other LA anatomical structures that are often involved in re-entry leading to atrial tachyarrhythmias, which may therefore represent important targets for AF substrate ablation, include Bachman's bundle[24], the Ligament of Marshall and the coronary sinus.[25]

Complications

Inherently, although minimally invasive, surgical techniques come with higher complication rates than truly minimally invasive catheter ablation (CA) techniques. In our study, major and minor complications during hospitalization occurred in 12% of patients, although the severity of a pneumothorax after thoracoscopic surgery remains semantic. Not unimportantly, pericarditis without hemodynamic instability and bleeding requiring transfusion or drainage represented half of all complications. Major complications occurred in 4% of all patients and there were no incidences of conversion to sternotomy, atrio-esophageal fistula, stroke or mortality. Compared to the incidence of major complications after percutaneous approaches, which are also around 5%,[26] our complication rate was similar. After discharge, complications occurred in 18 patients (15%) until a long-term follow-up of 24 months. In a safety analysis of thoracoscopic surgical ablation only, the 30-day complication rate including peri-operative complications was already 12%.[27] As such, although perhaps technically more challenging, the shift to a left-sided only approach may even reduce the rate of major and minor complications until long-term follow-up. Importantly, not only acute complications must be taken into account, but also the added risk of complications for every additional ablation in repeat procedures to establish freedom from AF recurrence.[28] Therefore, unilateral left-sided thoracoscopic HA may not only reduce major complications compared to a bilateral approach, but also to percutaneous approaches on the long-term. Furthermore, as surgical ablation for AF improves quality of life (QOL), especially in patients where SR is established,[29] QOL may even further improve when complications and postoperative pain are reduced by limiting surgery to one side only.

## Limitations

Our data is derived from a single-center observational study, where all procedures were performed by an experienced team, thereby reducing the generalizability of the study. Secondly, not all patients underwent endocardial validation and some patients received no EP validation at all. According to the definition of a HA, it is questionable whether these patients received a 'true' HA procedure. Further limitations are the lack of structural rhythm follow-up until 24 months and a protocol mandating discontinuation of AADs, which affects efficacy results off AAD.

## Conclusion

Within the concept of a single staged hybrid ablation for AF, a unilateral left-sided thoracoscopic approach for patients with pAF or persAF is efficacious and safe. A randomized controlled trial comparing the unilateral left-sided hybrid approach with bilateral approaches or with stand-alone percutaneous and/or epicardial approaches should be performed to validate our results.

## Acknowledgments

This research did not receive any financial support.

## Disclosures

BM, JL, MLM are consultants for AtriCure and/or Medtronic.

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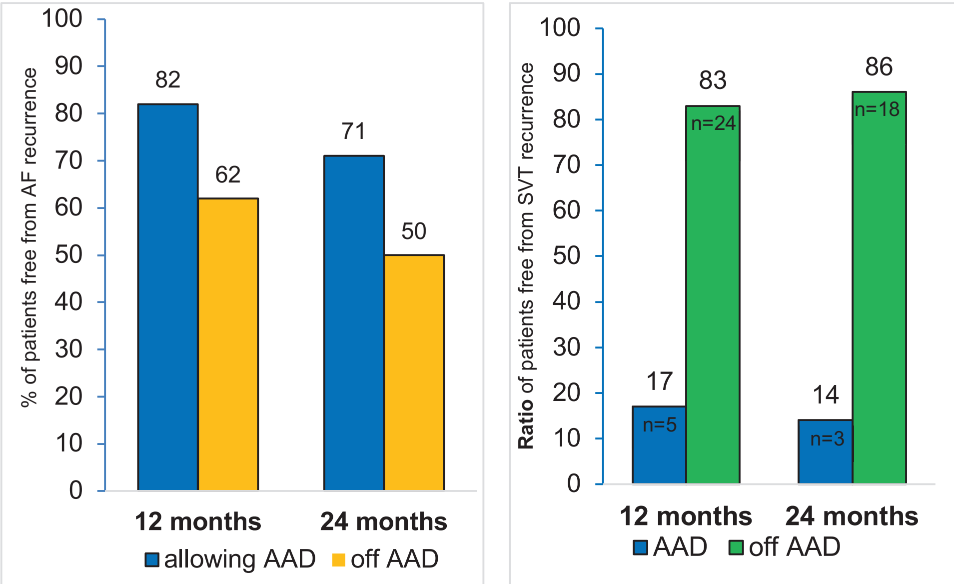
## Supplementary Materials

### Figures

**A.** paroxysmal AF.




**B.** (longstanding)-persistent AF.

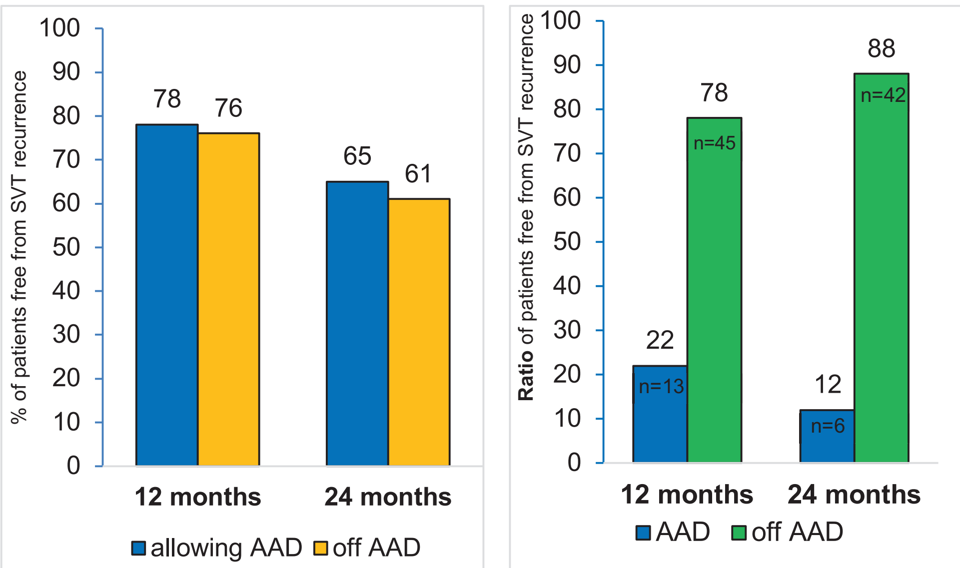



**Figure S1.** Overview of AAD use in patients who were free from AF recurrence at 12 and 24 months after a unilateral left-sided hybrid ablation. **(A)** Patients with pre-operative paroxysmal AF. **(B)** Patients with pre-operative (longstanding)-persistent AF. AAD=antiarrhythmic drugs; AF=atrial fibrillation.

## Tables

**Table S1.** Efficacy results until 12 and 24 months after unilateral left-sided hybrid ablation.

| SR allowing AADs | | Epicardial validation | Endocardial validation |
|---|---|---|---|
| **12 months** | All patients | 87% (77 – 100) | 75% (66 – 86) |
| | pAF | 84% (70 – 100) | 74% (64 – 86) |
| | non-pAF | 92% (77 – 100) | 79% (63 – 77) |
| **24 months** | All patients | 70% (56 – 89) | 65% (55 – 76) |
| | pAF | 62% (43 – 89) | 63% (52 – 77) |
| | non-pAF | 83% (65 – 100) | 68% (50 – 93) |

Groups were made based on electrophysiologic validation strategy and pre-operative AF type.
pAF=paroxysmal AF.

# CHAPTER 6

## Unilateral Left-sided Thoracoscopic Ablation of Atrial Fibrillation Concomitant to Minimally Invasive Bypass Grafting of the Left Anterior Descending Artery

**Claudia A.J. van der Heijden,** Patrique Segers, Anna Masud, Vanessa Weberndörfer, Sevasti-Marisevi Chaldoupi, Justin G.L.M. Luermans, Geertruida P. Bijvoet, Bas L.J.H. Kietselaer, Sander M.J. van Kuijk, Paul J.C. Barenbrug, Jos G. Maessen, Elham Bidar, Bart Maesen

*European Journal of Cardio-Thoracic Surgery. July 2022.*

## Visual abstract

**Key question**

Is a minimally invasive all-in-one approach for patients with AF and LAD disease feasible?

↓

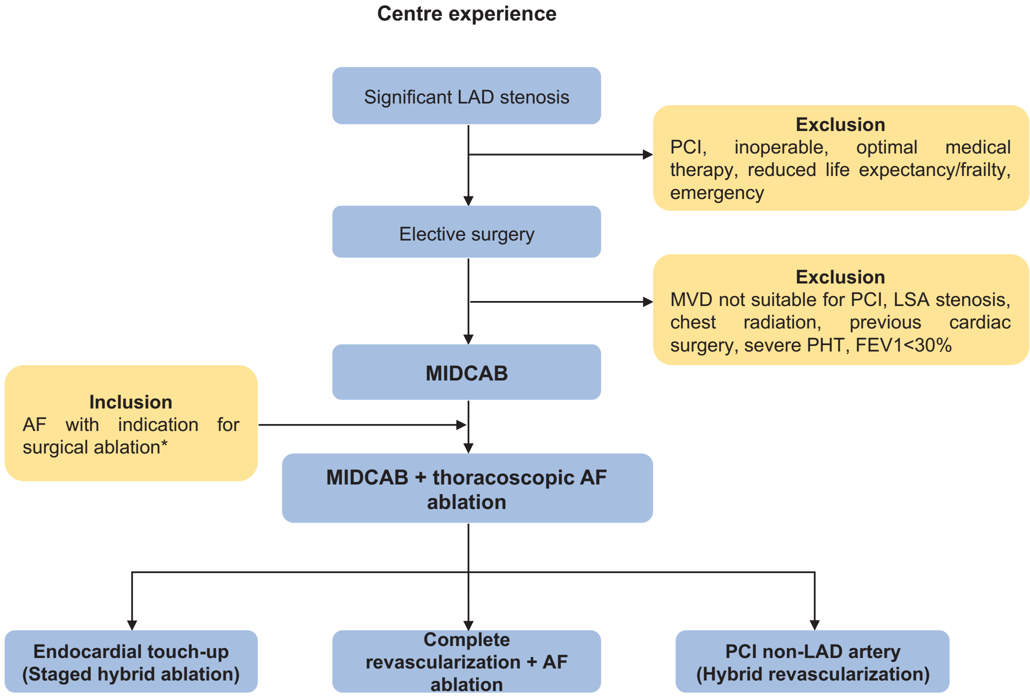
**Key finding**

Unilateral left-sided thoracoscopic AF ablation and concomitant minimally invasive MIDCAB surgery is feasible, safe and efficacious.

↓

**Take-home message**

We recommend to consider unilateral left-sided thoracoscopic ablation and concomitant MIDCAB for patients with AF and a critical LAD stenosis.




*ESC AF Guidelines 2020

AF=atrial fibrillation; FEV1=forced expiratory volume; LAD=left anterior descending artery; LSA=left subclavian artery; MVD=multivessel disease; PCI=percutaneous coronary intervention; PHT=pulmonary hypertension

**Central Image.** Center experience illustrating a patient tailored treatment approach.

## Abstract

**Objectives** Thoracoscopic ablation for atrial fibrillation (AF) and minimally invasive direct coronary artery bypass (MIDCAB) with robot-assisted left internal mammary artery (LIMA) harvesting may represent a safe and effective alternative to more invasive surgical approaches via sternotomy. The aim of our study was to describe the feasibility, safety and efficacy of a unilateral left-sided thoracoscopic AF ablation and concomitant MIDCAB surgery.

**Methods** Retrospective analysis of a prospectively gathered cohort was performed of all consecutive patients with AF and at least a critical left anterior descending artery (LAD) stenosis that underwent unilateral left-sided thoracoscopic AF ablation and concomitant off-pump MIDCAB surgery in the Maastricht University Medical Centre between 2017 and 2021.

**Results** Twenty-three patients were included (age 69 years (standard deviation=8), paroxysmal AF 61%, left atrial volume index 42 ml/m$^2$ (standard deviation=11)). Unilateral left-sided thoracoscopic isolation of the left (n=23) and right (n=22) pulmonary veins and box (n=21) by radiofrequency ablation was succeeded by epicardial validation of exit- and entrance block (n=22). All patients received robot-assisted LIMA harvesting and off-pump LIMA-LAD anastomosis through a left mini-thoracotomy. Perioperative complications consisted of one bleeding of the thoracotomy wound and one aborted myocardial infarction not requiring intervention. Mean duration of hospital stay was 6 days (standard deviation=2). After discharge, cardiac hospital readmission occurred in four patients (AF n=1; pleural- and pericardial effusion n=2, myocardial infarction requiring percutaneous intervention of the LIMA-LAD n=1) within one year. After 12 months, 17/21 (81%) patients were in sinus rhythm when allowing anti-arrhythmic drugs. Finally, the left atrial ejection fraction improved postoperatively (26% (standard deviation=11) to 38% (standard deviation=7), $P$=0.01).

**Conclusion** In this initial feasibility and early safety study, unilateral left-sided thoracoscopic AF ablation and concomitant MIDCAB for LIMA-LAD grafting is a feasible, safe and efficacious for patients with AF and a critical LAD stenosis.


**Keywords** Minimally invasive • Thoracoscopic ablation • Atrial fibrillation • Minimally invasive direct coronary bypass grafting • MIDCAB

## Glossary of Abbreviations

| | |
|---|---|
| AF | Atrial fibrillation |
| AAD | Anti-arrhythmic drug |
| CTI | Cavotricuspid isthmus |
| INR | International normalized ratio |
| LA | Left atrial |
| LAA | LA appendage |
| LAD | Left anterior descending |
| LAEF | LA ejection fraction |
| LAVI | Left atrial volume index |
| LIMA | Left internal mammary artery |
| LMWH | Low molecular weight heparin |
| LVEF | Left ventricle ejection fraction |
| MIDCAB | Minimally invasive direct coronary artery bypass graft |
| OAC | Oral anticoagulants |
| pAF | Paroxysmal AF |
| persAF | Persistent AF |
| PCI | Percutaneous coronary intervention |
| PV | Pulmonary vein |
| PVI | PV isolation |
| RDP | Right descending posterior |
| RSPV | Right superior pulmonary vein |
| SR | Sinus rhythm |

## Introduction

Over the past years, complex cardiac procedures have evolved into minimally invasive alternatives. In the treatment of atrial fibrillation (AF), minimally invasive thoracoscopic AF ablation has been recommended as a successful strategy for patients with symptomatic and drug-refractory AF to lower the burden of AF symptoms.[1] In coronary artery bypass surgery, minimally invasive direct coronary artery bypass (MIDCAB) grafting with left internal mammary artery (LIMA) harvesting for single-vessel revascularization via a small left thoracotomy is a well-established alternative to a standard sternotomy approach, resulting in a shorter hospital stay due to fast recovery.[2]

While both stand-alone thoracoscopic AF ablation and MIDCAB have been shown to be safe and effective as separate procedures[3], cohort data on unilateral left-sided thoracoscopic AF ablation and concomitant MIDCAB have never been reported. Here we describe our experience with additional unilateral left-sided thoracoscopic AF ablation during MIDCAB procedures.

## Patients and Methods

<u>Patients and study design</u>

In this single-center cohort study, retrospective analysis of a prospectively gathered cohort was performed. All consecutive patients with AF and at least a critical left anterior descending artery (LAD), and possibly also a diagonal artery stenosis and multivessel disease, that underwent a unilateral left-sided thoracoscopic AF ablation and concomitant off-pump MIDCAB surgery between September 2017 and June 2021 in the Maastricht University Medical Centre were analyzed. Clinical data were collected from the electronic patients records of the hospital.

<u>Ethics statement</u>

This study was approved by the Institutional Review Board (IRB) and Ethics Committee (METC 2019-1430) and analyzed in accordance with IRB guidelines. Informed consent was waved due to the retrospective character of the study. The study complies with the ethical principles of the Helsinki Declaration.

<u>Surgical procedure</u>

Absence of thrombus in the left atrial appendage (LAA) was confirmed by trans-esophageal echocardiogram and a double lumen endotracheal tube was inserted, allowing selective right lung ventilation. The unilateral left-sided thoracoscopic ablation procedure has been described elsewhere in detail.[4] In brief, 3x5mm trocars were introduced in the second, fourth and sixth left intercostal space in the midaxillary line. Left and right pulmonary vein (PV) isolation was performed using a biparietal bipolar radiofrequency clamp (Isolator, AtriCure) and ablation of a roof and inferior line was performed (Coolrail, AtriCure) to create the box lesion. Next, epicardial exclusion of the LAA (Atriclip Pro, AtriCure) was performed. Finally, epicardial entrance and exit block of the PVs and the box was evaluated. Patients who were still in AF after epicardial ablation were electrically converted to sinus rhythm (SR). Hereafter, exit and entrance block was validated on the PVs and box by sensing and pacing at 20 mA at least 20 beats/s above the heart rate using the Isolator Transpolar Pen (MAX 5, AtriCure Inc., Cincinnati, OH, USA). The right superior PV was only tested if adequately reachable.

Subsequently, thoracoscopic trocars were exchanged for robotic trocars and LIMA harvesting was performed using the Da Vinci Robot (Intuitive Surgical). A soft tissue retractor (Alexis, Applied Medical) was inserted through an anterior small thoracotomy of approximately 5-7 centimeter in the 4-5th intercostal space for the exposure of the LAD and if necessary, the diagonal artery. A rib spreader was mainly used to mount the minimally invasive stabilizer (Octopus Evolution, Medtronic, MN, USA) for local immobilization of the LAD and if necessary, the diagonal artery. Consequently, the LIMA-LAD anastomosis was performed manually on the beating heart. To assess the patency and the quality of the graft, intra-operative transit-time flow measurement was used.

<u>Outcomes</u>

The primary outcome was the procedural feasibility and safety up and until 12 months of follow-up. Feasibility was assessed by the number of patients where complete isolation of both PVs and the box, confirmed by epicardial entrance and exit block, and a successful LIMA-(D)-LAD anastomosis could be performed as planned. As described in the image, all patients underwent MIDCAB and unilateral left-sided thoracoscopic AF ablation. In patients with unintentional incomplete AF ablation, a staged endocardial touch-up was performed (staged hybrid AF ablation). Patients in the hybrid revascularization group underwent a percutaneous coronary intervention (PCI) of a non-

LAD artery after the surgical procedure, as planned. Safety was evaluated by the incidence of peri-operative complications including conversion to sternotomy; bleeding requiring transfusion, drainage or reoperation; cardiac tamponade; infection requiring prolongation of hospitalization; mortality; myocardial infarction; pacemaker implantation; pericarditis requiring drainage; phrenic nerve injury; pneumothorax or pleural effusion requiring intervention (after removal of chest tubes); readmission to the intensive care unit; respiratory insufficiency requiring re-intubation, stroke and cardiac rehospitalization.

The secondary outcome was the efficacy of both procedures, defined as freedom from AF and freedom from myocardial infarction and/or percutaneous interventions until 12 months of follow-up. AF recurrence was defined as an (a)symptomatic episode of any supraventricular arrhythmia ≥30 seconds, detected by continuous rhythm monitoring (24-hours, 48-hours or 7-days Holter) or a 12-lead ECG according to the ESC AF 2020 Guidelines[1], and the number of unscheduled AF reinterventions including electrical cardioversion or endocardial touch-up via catheter ablation, after a 3 months blanking period. Myocardial infarction was defined conform the definition used in the Netherlands Heart Registration[5] as an increase or decrease in cardiac biomarkers with at least one of the following: symptoms suspicious for ischemia; new significant ST-segment, T-wave alterations or a new bundle branch block; pathological Q-waves; loss of viable myocardial tissue or new regional wall motion dysfunction based on imaging; identification of intra-coronary thrombus during angiography or autopsy.

Left atrial contractility

Minimal and maximal LA volumes were calculated by tracing the endocardial border of the LA, with exclusion of the LAA and the pulmonary veins, by 2D echocardiography in both the apical two-chamber and four-chamber views in end-systole and end-diastole. Consequently, the left atrial ejection fraction (LAEF) was calculated, blinded for preoperative AF type, using the biplane modified Simpson method.

Peri-operative management

Direct oral anticoagulants (OAC) were discontinued two days prior to surgery. After surgery, the patient received low molecular weight heparin (LMWH). At the day of discharge, LMWH was discontinued and DOAC was restarted. In patients using a vitamin-

K antagonist, OAC was discontinued at least 3 days before surgery until an International Normalized Ratio (INR) of <1.5 was reached. Postoperatively, the vitamin-K antagonist was restarted on the 3rd postoperative day and the patient received LMWH until an adequate INR was obtained. For all patients, pre-operatively discontinued OAC therapy was only bridged with LMWH in case of a $CHA_2DS_2$-VASc Score of ≥8 or with a high risk of thrombo-embolic events. After discharge, all patients were invited to the outpatient clinic after 3 and 12 months for regular check-up using a 12-lead ECG and 24-hour Holter monitoring. In case of AF recurrence, patient tailored treatment followed conform routine care. Monitoring for cardiac ischemia due to myocardial infarction was performed by a 12-lead ECG and routine determination of cardiac enzymes after 6, 9 hours and the next morning. Further control of enzymes took place after 72 hours or when indicated, as part of standard care. In case of symptoms suspicious for cardiac ischemia, further diagnostics to evaluate myocardial ischemia by ECG and, if necessary, a coronary angiography was performed and treated conform standard care. Furthermore, all data, including late myocardial infarction and/or coronary intervention, was prospectively entered in the Netherlands Heart Registration (NHR) for prospective analyses.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) if normally distributed or median and interquartile range (not-normally distributed), while categorical variables as count and relative frequencies. A paired T-test was used to compare continuous variables (such as LAEF) at two different time points for the same subject, while a student's T-test was used to compare continuous variables between groups. A Kaplan-Meier survival curve was plotted to estimate the probability of being free from AF recurrences over the course of one year. Analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) and R version 4.1.2.

## Results

Study population

Between September 2017 and June 2021, 23 patients underwent unilateral left-sided thoracoscopic AF ablation and concomitant MIDCAB surgery. Patients were on average 69 years old (SD=8), 22% was female, the mean body mass index was 29kg/m$^2$ (SD=4) with a median $CHA_2DS_2$-VASc Score of 3 [2–4] (Table 1). Furthermore, 5 patients (17%) were known with chronic obstructive pulmonary disease (COPD) and/or obstructive sleep apnea, one (4%) had ischemic cardiomyopathy and one (4%) was diagnosed with polycythemia vera. The mean preoperative EuroSCORE-II was 2.5 (SD= 2.0). Moreover, sixty-one percent of all patients had paroxysmal AF (pAF) and 39% had (longstanding)-persistent (pers) AF. Two (9%) underwent previous catheter pulmonary vein isolation (PVI) and 10 (43%) underwent one or more electrical cardioversions. Mean duration of AF history was 59 months (SD=78). Furthermore, 5 patients (22%) had a previous myocardial infarction of which 2 (9%) had a previous percutaneous coronary intervention (PCI) with stenting of the right coronary artery (n=1) or circumflex artery (n=1). More patients were known with single-vessel disease (83%) compared to multi-vessel disease (17%). Overall, left ventricle ejection fraction was preserved (mean LVEF=57%, SD=7) and the left atrial volume was severely enlarged (mean LAVI=42ml/m$^2$, SD=11) (Table 1).

**Table 1.** Baseline characteristics.

| Clinical characteristics and risk profile | All patients (n=23) |
|---|---|
| Age (years) | 69 (8) |
| BMI kg/$m^2$ | 29 (4) |
| $CHA_2DS_2$-VASc Score | 3 [2 – 4] |
| COPD | 4 (17%) |
| Diabetes mellitus (%) | 4 (17%) |
| EuroSCORE-II | 2.5 (2.0) |
| Female (%) | 5 (22%) |
| Hypertension (%) | 22 (96%) |
| Ischemic cardiomyopathy | 1 (4%) |
| OSAS | 5 (22%) |
| Polycythemia vera | 1 (4%) |
| Stroke | 2 (9%) |
| **AF** | |
| Duration (months) | 59 (78) |
| Previous ECV | 10 (43%) |
| Previous endocardial PVI | 2 (9%) |
| Type | |
| Paroxysmal | 14 (61%) |
| (longstanding) persistent | 9 (39%) |
| **Coronary artery disease** | |
| Previous myocardial infarction | 5 (22%) |
| Previous PCI | 2 (9%) |
| Stenting of the RCA | 1 (4%) |
| Stenting of the RCx | 1 (4%) |
| Single vessel disease | 19 (83%) |
| Multivessel disease | 4 (17%) |
| **Echocardiographic measurements** | |
| LA diameter (mm) | 39 (5) |
| LA volume (ml) | 84 (21) |
| LAVI (ml/$m^2$) | 42 (11) |
| LVEF (%) | 57 (7) |

Data are presented as mean (standard deviation), median (interquartile range) or frequencies: n (%). AF=atrial fibrillation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; LA=left atrial; LAVI=left atrial volume index; LVEF=left ventricular ejection fraction.

Primary outcome

*Feasibility*

All procedures were carried out by 2 experienced cardiac surgeons (B.M, P.S). Mean surgical procedure operation time was 224 minutes (SD=38) and the duration of hospital stay was 6 days (SD=2) (Supplementary Table S1). Of all patients with pAF (n=14), 12 (86%) had single vessel disease of which 10 (71%) received isolation of the PVs and box (Figure 1). In 9 of them (64%), epicardial mapping was performed which confirmed entrance and exit block, but in one patient (7%) a very antral PVI was performed and therefore epicardial validation of the box was impossible. Furthermore, in one patient (7%) only a left PVI could be performed due to abundant epicardial adipose tissue. For safety reasons, and considered the fact that this patient was only recently diagnosed with pAF, no bilateral approach was performed. As such, the patient was referred for an endocardial touch-up procedure as part of a staged hybrid procedure within the 3 months blanking period. Consequently, endocardial validation demonstrated transmural isolation of the left PVs, whereafter a wide antral circumferential ablation of the right PVs was performed along with successful CTI ablation. The last patient in this group of single vessel disease and pAF (7%) presented with a very small LA, had only recently diagnosed pAF and therefore received left and right PVI only. Of the patients with pAF and multivessel disease (n=2), all received a complete isolation of the PVs and box, confirmed by epicardial mapping (100%). One patient (50%) underwent an elective PCI of the right coronary artery and one (50%) patient was referred for PCI of a (small) obtuse marginal artery in the case of symptoms during follow-up.

Of all patients with (longstanding)-pers AF (n=9), 7 (78%) had single vessel disease whom all received PVI and box isolation, thus a full AF ablation. The box could not successfully be isolated in 1 patient (11%) due to too much epicardial adipose tissue, where a staged hybrid ablation was only opted in case of symptoms. Isolation of the RSPV could not be evaluated in 2 patients (22%) and 1 of them experienced AF recurrence. A redo catheter ablation was performed where endocardial mapping confirmed isolated left PVs but no isolation of the right PVs. Subsequently, a successful wide area circumferential ablation of the right PVs was achieved. As the voltage map still showed a low voltage area in the LA, combined with a registered atypical flutter, an anterior mitral isthmus line with bidirectional block was created. The patients with (longstanding)-persAF and multivessel disease (n=2) all received PVI and box isolation and LIMA-LAD anastomosis. Considered the fact that in both patients a stenosis of a small RDP was present with a dominant left system, no intervention of the RDP was performed. An epicardial left ventricle lead was placed in one patient who suffered from ischemic cardiomyopathy and this patient was referred for an elective cardiac resynchronization therapy device implantation, as the LVEF did not restore. This was also the only patient who received grafting of the diagonal artery (Supplementary Table S1, Figure 1).

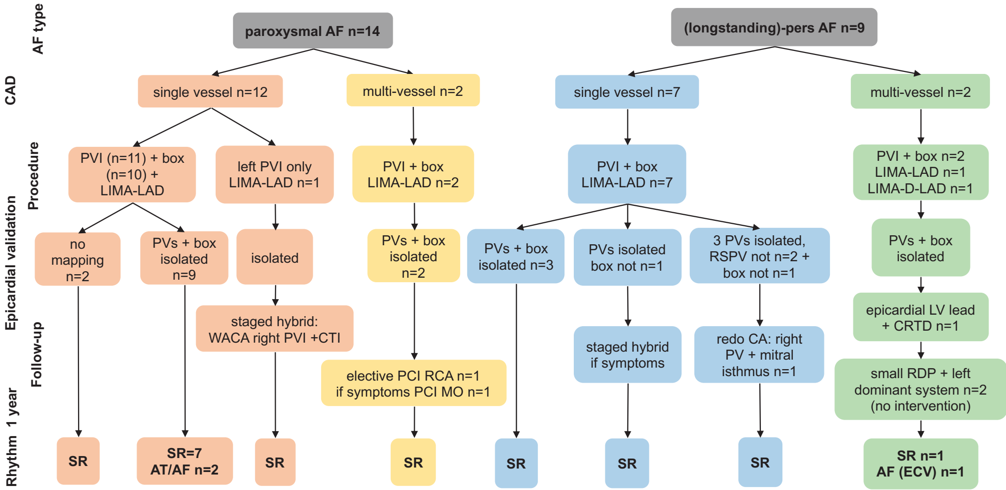



**Figure 1.** Patient specific treatment flowchart representing individualized treatment strategies and outcome. AF=atrial fibrillation; AFL=atrial flutter; AT=atrial tachycardia; CA=catheter ablation; CAD=coronary artery disease; iCMP=ischemic cardiomyopathy; CRT-D=cardiac resynchronization therapy-defibrillator; CTI=cavo-triscupid isthmus; ECV=electrical cardioversion; LIMA-LAD=left internal mammary artery–left anterior descending artery; LV=left ventricle; NSTEMI=non-ST elevated myocardial infarction; PCI=percutaneous coronary intervention; PV=pulmonary vein; PVI=PV isolation; RCA=right coronary artery; RSPV=right superior pulmonary vein; SR=sinus rhythm; WACA=wide antral circumferential ablation.

*Safety*

Perioperative complications were: bleeding from the thoracotomy wound (requiring drainage, transfusion and re-thoracotomy) (n=1) and myocardial infarction based on increased cardiac biomarkers with new significant ST-segment elevation (n=1). In the latter patient, the coronary angiography showed a patent LIMA-LAD anastomosis and no intervention was required. Within 30 days after discharge, one patient was readmitted due to recurrent AF treated with digoxin, one patient with polycythemia vera had a myocardial infarction requiring PCI of the LIMA-LAD and two patients with pleural- and pericardial effusion requiring drainage. There was no conversion to sternotomy, cardiac tamponade, pericarditis, respiratory insufficiency, stroke, phrenic nerve injury or mortality (Supplementary Table S1 and Table 2).

<u>Secondary outcome</u>

*Efficacy*

The secondary outcome was to evaluate the efficacy of both procedures up to 12 months of follow-up. Until now, 21 (87%) patients completed one-year follow-up, as two patients only reached 6 months follow-up (Table 2). Freedom from any supraventricular tachyarrhythmia ≥30 seconds occurred in 17/21 patients (81%), of which 8 were off AAD (Figure 2). For logistical reasons, their AADs were not discontinued after the ablation, even though there were no AF-related complaints and Holter monitoring showed SR. As mentioned earlier, one patient unintentionally received an incomplete AF ablation and therefore underwent a staged hybrid procedure within 3 months. This patient was in SR after 12 months of follow-up. In total, 4 patients experienced a recurrence of a supraventricular tachyarrhythmia after the 3 months blanking period, of which 2 patients underwent a successful electrical cardioversion, one received a redo-catheter ablation and one patient preferred to receive no additional therapy due to being asymptomatic. Concerning the revascularization efficacy outcome, all patients received a full revascularization, of which one patient underwent a staged hybrid revascularization with a planned PCI of the right coronary artery. Furthermore, 2 patients experienced a myocardial infarction; one during hospitalization and one within 30 days postoperative as described earlier.

**Table 2.** Follow-up.

| 12 months of follow-up | All patients (n=23) |
|---|---|
| **Complications after discharge** | |
| Cardiac hospital readmission | 4 (17%) |
| AF | 1 (4%) |
| Myocardial infarction requiring PCI LIMA-LAD | 1 (4%) |
| Pleural and pericardial effusion | 2 (9%) |
| Staged hybrid ablation >30 days, <3 months | 1 (4%) |
| Wound infection | 0 (0%) |
| **12 months follow-up reached** | 21 (91%) |
| Recurrence of AF/AT >3 months | 4 (19%) |
| Electrical cardioversion | 2 (9%) |
| Expectative | 1 (4%) |
| Redo catheter ablation | 1 (4%) |
| Mortality | 0 (0%) |
| Stroke | 0 (0%) |
| **Rhythm outcome until 12 months** | |
| SR allowing AADs | 17 (81.3%; 95% CI [66.3 - 99.7%]) |
| SR off AADs | 9 (43%) |

Data are presented as frequencies: n (%). AADs=anti-arrhythmic drugs; CI=confidence interval; SR=sinus rhythm.

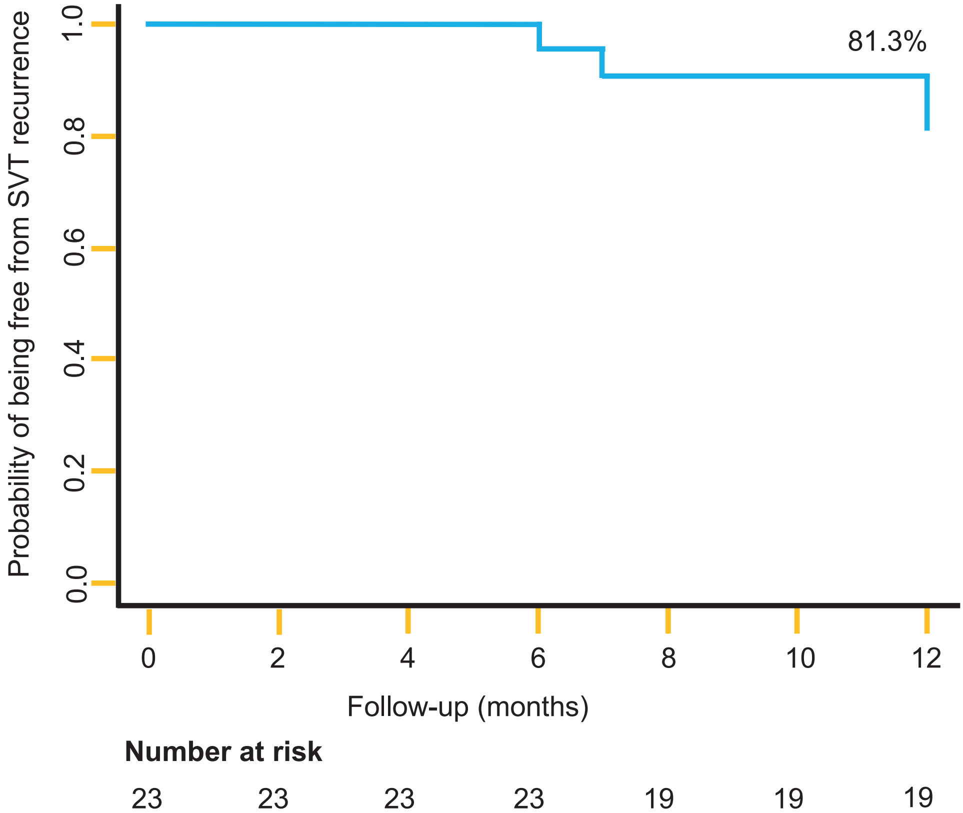



**Figure 2.** Kaplan meier survival curve representing the probability of being free from any SVT recurrence. SVT=supraventricular tachyarrhythmia.

Left atrial contractility

Of all 23 patients, 13 patients (5 persAF, 8 pAF) had a postoperative TTE in SR (median time of postoperative TT was 11 months [6-21]). Mean postoperative LAEF was 38% (7). Of those 13 patients, 11 (3 persAF, 8 pAF) patients also had a pre-operative TTE in SR. After analysis of pre- and postoperative TTE in those 11 patients, mean LAEF increased (26% (11) to 38% (7), *P*=0.01, see Figure 3). Furthermore, postoperative mean LAEF was significantly higher in patients with paroxysmal AF (n=8) compared to patients with persAF (n=5; 40% (6) vs. 31% (4) respectively, *P*=0.05). Although we did not have echocardiographic data in all patients, our analysis clearly shows that postoperative electrical freedom of AF also results in restoration (in patients in AF during pre-operative TTE) or improvement (in patients in SR during pre-operative TTE) of atrial contractility.

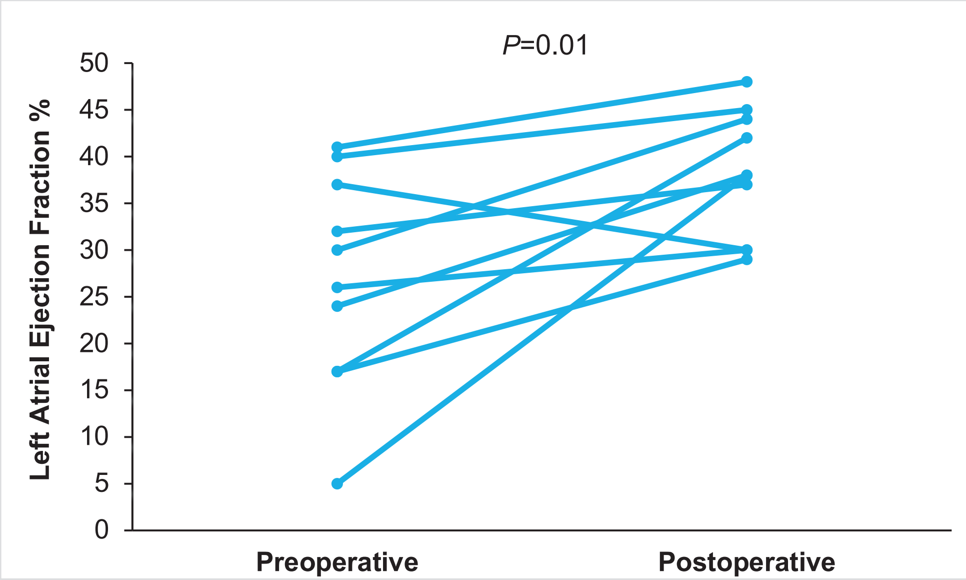



**Figure 3.** Left atrial contractility, measured as left atrial ejection fraction, restoration after unilateral left-sided AF ablation concomitant to MIDCAB surgery.

## Discussion

To the best of our knowledge, this is the first study that describes the feasibility, safety and efficacy of patients undergoing a unilateral left-sided thoracoscopic AF ablation and concomitant robot-assisted minimally invasive direct coronary artery bypass grafting (MIDCAB) procedure for a critical LAD (and if necessary, the diagonal artery) stenosis. We found that this all-in one minimally invasive approach is safe, feasible and efficacious with satisfactory results at 12 months follow-up.

<u>Minimally invasive AF ablation</u>

Thoracoscopic AF ablation targeting the PVs, LA posterior wall and exclusion of the LAA, with or without endocardial touch-up, is an effective and safe treatment for patients with pAF or persAF and has been associated with better rhythm outcomes than non-surgical treatments options such as catheter ablation.[6-8] Although a minimally invasive procedure, thoracoscopic AF ablation is still more invasive with higher risks for complications and longer hospitalization than percutaneous alternatives.[7] According to the ESC 2020 AF Guidelines, a stand-alone thoracoscopic approach should therefore be considered preferentially in patients with previously failed catheter ablation or when a high chance of success following surgical ablation is expected.[1] This is especially true for patients with persAF, as success rates in more persistent forms of AF are higher following surgical ablation than catheter ablation.[9] In our population, where patients with pAF as well as persAF were included, the heart team could have opted for conservative alternatives including catheter ablation. However, for concomitant cardiac procedures, surgical AF ablation should be considered in symptomatic and asymptomatic patients when the benefits of freedom from AF and the risk of recurrence (LA dilatation, comorbidities) outweigh the minimal additional risk of the ablation,[1-10] as was the case in our patients. While concomitant AF ablation has a class IIA recommendation,[1] surgical AF ablation is associated with an improvement in quality of life after both stand-alone and concomitant procedures.[11] Moreover, thoracoscopic AF ablation is still feasible after MIDCAB, but comes with a higher risk of complications due to pericardial adhesions. Furthermore, the LAAOS-III trial demonstrated that concomitant LAA closure in patients with AF who also undergo cardiac surgery is a safe therapy to reduce ischemic strokes (4.8% stroke after LAA occlusion vs. 7.0% without LAA occlusion, $P<1.000$).[12] All of our patients received clipping of the LAA, which may attribute to the fact that no strokes were reported during follow-up.

Minimally invasive coronary bypass grafting

In patients with a critical LAD stenosis, several treatment strategies including PCI, on- or off-pump CABG and MIDCAB have been reported. Minimally invasive surgery is associated with less coronary re-interventions than PCI to achieve revascularization of the anterior wall of the left ventricle[13,14] and surgical intervention of the proximal LAD has a class IA recommendation.[15] Moreover, MIDCAB surgery with LIMA harvesting via a small thoracotomy, either video or robot assisted, has shown to be a safe and effective treatment compared to conventional on- and off-pump procedures through sternotomy for single vessel disease.[16] The potential advantages of a minimally invasive approach compared to on/off-pump approaches via sternotomy are less bleeding, fewer wound infections and faster recovery.[17] In our study, we experienced one bleeding and no wound infection.

In certain patients with multivessel disease, a staged hybrid coronary revascularization strategy combining minimally invasive LIMA-LAD anastomosis with PCI of non-LAD vessels can represent a good alternative to CABG.[15,18] In our study, one patient with multivessel disease was referred for a successful staged hybrid revascularization approach and for one patient the staged hybrid revascularization was opted, but the patient remained asymptomatic. A potential restriction of minimally invasive revascularization through a small thoracotomy is the inability of single lung ventilation in patients with very severe COPD, the risk of incomplete identification of the LIMA (due to pleural adhesions) or the LAD (due to a large amount of epicardial adipose tissue) possibly necessitating sternotomy.[18] In our study, all patients received a LIMA-LAD anastomosis without conversion to sternotomy, which may be attributed partly to the careful patient selection in a dedicated heart team.

<u>Combining minimally invasive MIDCAB with thoracoscopic AF ablation in one procedure</u>

In regular practice, the surgical options for a patient with LAD disease and AF are limited to either a minimally invasive procedure without surgical AF treatment (MIDCAB), or a concomitant procedure via sternotomy. In an earlier report, we presented an all-in-one minimally invasive approach that overcomes these shortcomings.[19] In the current cohort study, we confirm the feasibility, safety and efficacy of adding a unilateral left-sided thoracoscopic AF ablation to MIDCAB in a small patient population.

In terms of feasibility and efficacy, as mentioned earlier, a LIMA-LAD through a small left thoracotomy could be performed in all patients. Due to our existing center experience in robotic and video assisted surgery for MIDCAB and AF surgery, all patients received robot assisted MIDCAB surgery and video assisted thoracoscopy for the AF ablation. Adding thoracoscopic ablation for AF to the MIDCAB procedure was not only feasible but also effective, as almost all patients received a complete PVI and box lesion set with good one-year rhythm outcomes (81% allowing AADs). These results are comparable with previously reported results following stand-alone thoracoscopic ablation for pAF and persAF.[20] Importantly, left atrial contractility was regained or even improved after the procedure (Figure 3). Patients with persAF are believed to have an AF substrate that is far more complex than in patients with pAF. Accordingly, we found that the postoperative LAEF was higher in patients with pAF compared to persAF. Be that as it may, patients with pAF did show a significant improvement in post-operative LAEF compared to baseline. This can be explained by reversed contractility remodeling in this group.[21] These results are in line with the results of La Meir et al.[22], where the LAEF improved significantly after surgical AF ablation.

Totsugawa et al.[23] described in a case report a technique combining surgical AF ablation and LAD revascularization. There are two important differences between their technique and the technique described in the current manuscript: surgical AF ablation was performed via unilateral thoracoscopy compared to bilateral anterolateral thoracotomy and LIMA harvesting was robot-assisted compared to under direct vision. Furthermore, Totsugawa et al. did not report on outcomes. To date, there are no other reports to compare our results to. The possible advantage of a unilateral left-sided approach is that it avoids right-sided complications, such as bleeding, right phrenic nerve injury and right sided postoperative pain. In terms of safety, the complication rate perioperatively and after discharge was low. Mean surgical procedure time for both the MIDCAB and the thoracoscopic ablation was 224 minutes (SD=38), which may be longer than a LIMA-LAD and concomitant AF ablation through sternotomy, but is still less than a CABG and full Cox-Maze IV procedure and does not require the need for cardiopulmonary bypass.

**Limitations**

First, our results are based on a single-center experience in a small patient population. Secondly, all surgeries were performed by a skilled team in a center of excellence with high volume of stand-alone MIDCAB procedures and stand-alone thoracoscopic AF ablation. As these procedures require advanced skills and training in robot-assisted surgery and thoracoscopy, the generalizability and external validity of our results may be reduced. Moreover, calculating LA volumes on 2D echocardiography might under- or overestimate LAEF and postoperative echocardiography data was not available in all patients. Finally, 24-hours Holter monitoring may be a potential study limitation, as well as the absence of a control group.

## Conclusion

In this initial feasibility and early safety study, combining unilateral left-sided thoracoscopic AF ablation and concomitant robot-assisted MIDCAB surgery for LIMA- (diagonal artery)-LAD grafting is feasible, safe and efficacious and improves left atrial contractility post-procedure. In patients with an incomplete thoracoscopic AF ablation or revascularization, a staged hybrid ablation or revascularization can be considered to deliver a patient oriented and personalized treatment. Future studies should compare the efficacy and safety of this minimally invasive approach with CABG and concomitant AF ablation via sternotomy. Given the success of the current combination, future perspectives could be to combine more cardiac minimally invasive procedures, that each have proven their efficacy and safety as a standalone procedure, and study their added value in patients.

## Acknowledgements

None.

## Funding statement

None.

## Conflict of interest

Bart Maesen is consultant for Atricure and Medtronic.

## Author contribution statement

All authors contributed significantly to this work.

## Data availability statement

Data available on request.

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## Supplemental Materials

### Tables

**Table S1.** Surgical characteristics.

| Procedural characteristics | All patients (n=23) |
|---|---|
| **AF ablation** | |
| Left PVI | 23 (100%) |
| Right PVI | 22 (96%) |
| Box (roof and inferior lines) | 21 (91%) |
| LAA occlusion | 23 (100%) |
| Epicardial check-up | 21 (91%) |
| Left PVs | 21 (91%) |
| Entrance/exit block confirmed | 21 (100%) |
| Right PVs | 18 (78%) |
| Entrance/exit block confirmed | 18 (100%) |
| Box (roof and inferior lines) | 20 (86%) |
| Entrance/exit block confirmed | 18 (86%) |
| **MIDCAB procedure** | |
| Off-pump LIMA-LAD | 22 (96%) |
| Off-pump LIMA-diagonal artery-LAD | 1 (4%) |
| **Total surgical time** (minutes) | 224 (38) |
| **Peri-operative complications** | |
| Bleeding | 1 (4%) |
| Cardiac tamponade | 0 (0%) |
| Conversion to sternotomy | 0 (0%) |
| Infection | 0 (0%) |
| Myocardial infarction | 1 (4%) |
| Mortality | 0 (0%) |
| Pacemaker implantation | 0 (0%) |
| Pericarditis | 0 (0%) |
| Phrenic nerve injury | 0 (0%) |
| Readmission to ICU | 0 (0%) |
| Respiratory insufficiency | 0 (0%) |
| Stroke | 0 (0%) |
| Duration of hospital admission (days) | 6 (2) |

Data are presented as mean (standard deviation) or frequencies: n (%). AF=atrial fibrillation; LAA=left atrial appendage; LIMA-LAD=left internal mammary artery–left anterior descending artery; MIDCAB=minimally invasive direct coronary artery bypass; PVI=pulmonary vein isolation.

# CHAPTER 7

## Left Atrial Function after Thoracoscopic Hybrid Ablation for Atrial Fibrillation

**Claudia A.J. van der Heijden,** Bouke P. Adriaans, Sander M.J. van Kuijk, Justin G.L.M. Luermans, Sevasti-Marisevi Chaldoupi, Jos G. Maessen, Elham Bidar, Bart Maesen

*Submitted to European Journal of Cardio-Thoracic Surgery. August 2023.*

# CHAPTER 8

## Patient-Reported Quality of Life After Stand-Alone and Concomitant Arrhythmia Surgery: A Systematic Review and Meta-Analysis

**Claudia A.J. van der Heijden*,** Bart Maesen*, Elham Bidar, Rein Vos, Thanos Athanasiou, Jos G. Maessen

*Both authors contributed equally

*Interactive CardioVascular and Thoracic Surgery. September 2021.*

*Book chapter Patient Reported Outcomes and Quality of Life in Cardiovascular Interventions by Springer et al. 2022.*

## Visual Abstract

**Key question**

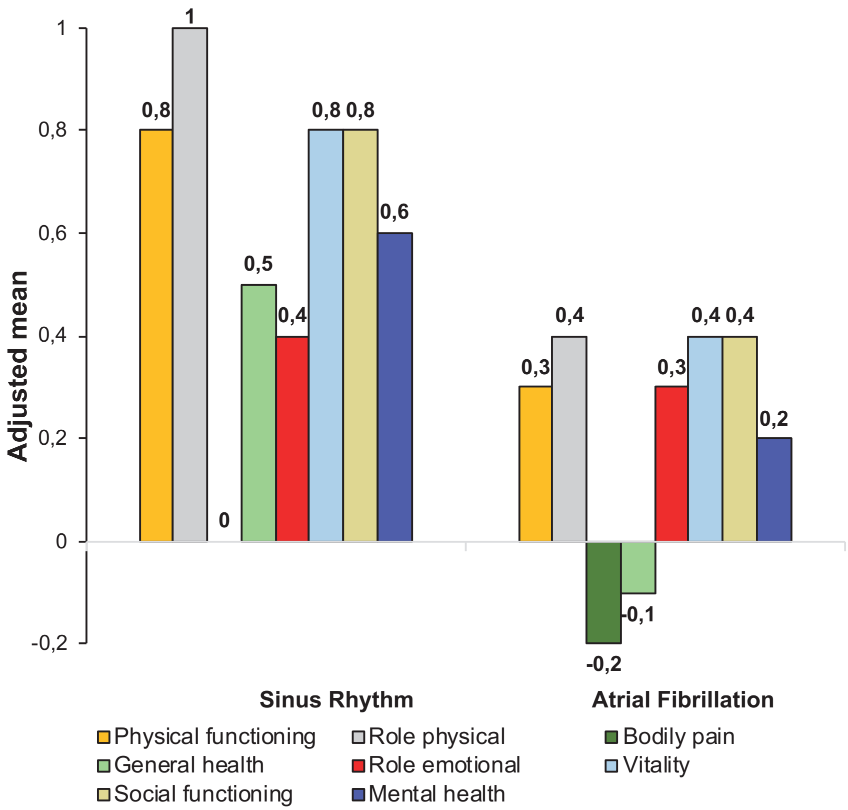
Should we perform surgical ablation for atrial fibrillation (AF) to improve quality of life (QOL)?

**Key finding**

QOL measured by the SF-36 improves after both stand-alone and concomitant surgical ablation for AF.

**Take-home message**

The improvement of QOL is related to the effectiveness of the procedure to maintain sinus rhythm.



**Abstract**

**Objectives** Patient-reported quality of life (QOL) has become an important endpoint for arrhythmia surgery for atrial fibrillation (AF). While studies specifically evaluating the effect of arrhythmia surgery on QOL are scarce, we aimed to summarize current evidence of QOL following concomitant and stand-alone arrhythmia surgery for AF.

**Methods** All studies reporting on QOL using questionnaires from patients undergoing arrhythmia surgery for AF, both stand-alone and concomitant, were included in this systematic review. A meta-analysis was performed on inter-study heterogeneity of changes in QOL on 9 of 12 included studies who used the Short-Form (SF) 36 tool and meta-regression based on rhythm outcome after one year was executed. Finally, differences in QOL following stand-alone arrhythmia surgery and concomitant procedures were evaluated.

**Results** Overall, QOL scores improved one year after surgical ablation for AF evaluated by several questionnaires. In standalone arrhythmia procedures, meta-regression showed significant improvements in those who were in sinus rhythm compared to those in AF after one year. This association between an improved QOL and the procedural effectiveness was also suggested in concomitant procedures. However, when comparing QOL of patients undergoing cardiac surgery with and without add-on surgical ablation for AF, only the variable 'physical role' demonstrated a significant improvement.

**Conclusions** In patients with AF, QOL improves after both stand-alone and concomitant arrhythmia surgery. In the concomitant group, this improvement can be attributed to both the cardiac procedure itself as well as the add-on arrhythmia surgery. However, both in standalone and concomitant procedures, the improvement in QOL seems to be related to the effectiveness of the procedure to maintain sinus rhythm after 12 months.

**Keywords** Quality of life • Surgical arrhythmia ablation • Atrial fibrillation • Systematic review and meta-Analysis

## Glossary of Abbreviations

| | |
|---|---|
| AF | Atrial fibrillation |
| AV | Aortic valve |
| CABG | Coronary artery bypass graft |
| CFAE | Complex fractionated atrial electrograms |
| CTI | Cavotricuspid isthmus |
| CVA | Cardiovascular accident |
| GP | Ganglionated plexi |
| LA | Left atrial |
| LAA | LA appendage |
| MV | Mitral valve |
| PVI | Pulmonary vein isolation |
| QOL | Quality of life |
| RCT | Randomized controlled trial |
| RF | Radiofrequency |
| SCV | Superior caval vein |
| SF-36 | Short Form 36 |
| SE | Standard error |
| SMD | Standardized mean difference |
| SR | Sinus rhythm |
| TV | Tricuspid valve |

## Introduction

Historically, the emergence of a surgical treatment for heart rhythm disorders was mainly triggered by ventricular arrhythmias and with the first successful surgical interruption of the bundle of Kent in a patient with the Wolff-Parkinson-White syndrome,[1] arrhythmia surgery got off to a great start. Notwithstanding the above, today most surgical arrhythmia procedures are focused on the management of supraventricular arrhythmias.[2] Surgical ablation of atrial fibrillation (AF) can be either done in conjunction with other cardiac procedures as a concomitant procedure or on itself as a standalone procedure. Concomitant AF surgery is often performed with cardiopulmonary bypass via sternotomy or right anterolateral mini-thoracotomy, but recently also left thoracoscopic ablation in combination with minimal invasive direct coronary artery bypassing on the beating heart has been reported.[3,4] Although standalone procedures are often performed via bilateral thoracoscopy, unilateral thoracoscopic and subxiphoid techniques have been successfully introduced.[5-7] This progression in minimally invasiveness of surgical ablation approaches is important as it can be expected that the reduction in complications and postoperative pain by limiting surgery to one side will lead to further improvement in QOL.

Although one-year success of arrhythmia surgery for AF has long been defined as freedom from any supraventricular tachyarrhythmia, the evaluation of other endpoints, such as patient-reported quality of life (QOL), have become increasingly important in recent years.[8] Despite the fact that the measurement of QOL is potentially limited by a treatment expectancy bias, it represents an important endpoint for ablation studies.[9] Be that as it may, studies specifically evaluating the effect of standalone or add-on arrhythmia surgery on QOL are scarce. Moreover, the reported outcomes are often heterogeneous as not all studies use the same ablation strategy to treat the arrhythmia.

In this systematic review and meta-analysis, we summarized current evidence on QOL at baseline and one year after both stand-alone and concomitant arrhythmia surgery for AF. Since the guidelines for AF define success of rhythm outcome after surgical ablation for AF after one year, we chose to evaluate the improvement in QOL as well after one year, along with the rhythm outcome.

## Patients and Methods

Literature search

This systematic review and meta-analysis was written according to PRISMA standards.[10] A systematic literature search was conducted with free terms in the PubMed and Cochrane databases (see Online Supplement). Forwards and backwards search were also performed to screen for further eligible papers.

Study selection and risk of bias

All identified studies were screened based on their title and abstract, and full text, when necessary, by two independent reviewers (C.H. and B.M.). All English articles reporting on QOL using the Short-Form 36 (SF-36) questionnaire for measuring QOL after arrhythmia surgery in patients with AF, both stand-alone and concomitant, were found eligible. In all observational studies and non-randomized clinical trials, the methodological quality was assessed with use of the ROBINS-I tool.[11] In articles reporting on randomized controlled trials (RCTs), the risk of bias was assessed using the Cochrane Checklist.[12]

Outcomes

The primary outcome was defined as the standardized mean difference (SMD) in QOL variables assessed one year after arrhythmia surgery compared to baseline scores, using the Short-Form 36 (SF-36) QOL questionnaire. As secondary endpoints, differences in the improvement of QOL between patients who were in sinus rhythm (SR) or in AF after 12 months of follow-up were determined for standalone procedures and differences between patients who did and did not receive add-on ablation for concomitant procedures.

Statistical analysis

The metric 'standardized mean difference (μ)' (rho=0) was used to analyze continuous QOL changes, comparing one-year outcomes with baseline scores, per variable of the SF-36 QOL questionnaire.[13] Additional meta-regression was performed using rhythm outcome and add-on arrhythmia surgery after 12 months of follow up as covariate. All statistical values were computed with a 95% confidence interval in a random-effects model and the two-tailed *P*-value threshold for statistical significance was set at 0.05. Weighted means (μ) of continuous baseline characteristics were computed using the

metric 'TX Mean', whereas 'Untransformed Proportions', defined as the count of successes in the sample divided by the size of that sample, were used for mean frequencies.[14] The latter metric was also used to analyze the percentage of patients that was in SR after 12 months of follow-up. Due to the relatively low complication rate, the metric 'Freeman–Tukey Double Arcsine Proportion' was used to analyze the incidence of peri-operative complications following arrhythmia surgery.
Inter-study heterogeneity was tested and visualized in forest plots per variable of the SF-36 QOL questionnaire. A statistical $P$ value <0.10 and/or $I^2$>50% was used as cut-off point for significant heterogeneity. All statistical analyses were performed using Meta-Analyst for Mac software (2009)[14] (version Beta 1.0). Furthermore, publication bias was tested using funnel plots made in Excel, where the SMD was plotted against the standard error (SE) of that study. The variance was calculated after transforming Cohen's d to Hedges' g by correcting for sample size and standard deviation per study.[15]

## Results

<u>Study selection</u>

After exclusion based on title, abstract and full text reading, 9 out of 2.142 studies from the literature search were included in our systematic review and meta-analysis (Supplementary Material, Figure S1 and Table S1).

<u>Risk of bias</u>

The risk of bias in most of the RCT's was estimated to be medium to low, mostly due to unclear reporting of blinding of patients and/or researchers during follow-up.[16,17] For the observational studies and nonrandomized trials, risk of bias was estimated to be medium high. Confounding due to missing baseline characteristics or marked differences in important predictors of the procedure's success (e.g., type and duration of AF) between groups could not be ruled out in the studies by Joshibayev et al.[18] and Lundberg et al.[19]. Selection bias based on the inclusion of patients with serious comorbidities was present in the study of Joshibayev et al.[18]. Other factors contributing to the increased risk of bias were missing QOL data due to substantial loss of follow-up in the study by Bagge et al.[20] and the lack of continuous heart rhythm monitoring in the studies by Joshibayev et al.[18] and Lonnerholm et al.[21]. Furthermore, funnel plots where the SMD was plotted against the SE of Hedges'g of that study showed that publication bias cannot be ruled out in this review. Due to marked variance of the included studies, scattering of results unequally along the x-axis occurred. Moreover, the forest plots illustrated that statistical heterogeneity, and thus inter-study variance, per QOL variable measured by the SF-36 was marked.

Study population

Most studies reported on arrhythmia surgery performed in the Netherlands[16,17,22,23], followed by Sweden[19,21], the United Kingdom[24] and Kazakhstan.[18] In total, 545 patients were included in the analysis (Table 1). Most patients were men (69.4%), mean age was 60 years, mean duration of AF was 53 months, 8.0% had a history with cerebrovascular accident (CVA) and the mean left atrial (LA) diameter was 49.2mm. Most patients had longstanding-persistent AF (41.9%), followed by persistent (29.8%) and paroxysmal AF (27.6%).

**Table 1**. Baseline characteristics of studies reporting on cardiac arrhythmia surgery and quality of life using the Short-Form-36 questionnaire.

| Characteristics (n=545) | Number of patients: n (%) | Adjusted mean (95% CI) |
|---|---|---|
| Age (years) | 453 (83) | 59.8 (56.5 – 63.0) |
| AF duration (months) | 316 (58) | 53.0 (5.0 – 101.0) |
| CVA (%) | 466 (86) | 8.0% (5.6 – 10.5) |
| Female (%) | 545 (100) | 30.6% (23.6 – 37.6) |
| Hypertension (%) | 491 (90) | 32.7% (22.1 – 43.2) |
| LA diameter (mm) | 369 (68) | 49.2 (43.8 – 54.6) |
| LVEF (%) | 395 (72) | 52.3% (50.0 – 54.5) |
| **Type of AF** | | |
| Paroxysmal (%) | 520 (95) | 27.6% (12.5 – 42.8) |
| Persistent (%) | 520 (95) | 29.8% (11.8 – 47.9) |
| Longstanding-persistent (%) | 520 (95) | 41.9% (4.6 – 79.3) |

Data are presented as number of patients (n) and the percentage (%) of the total group at baseline. The adjusted means or proportions followed by the 95% confidence interval were calculated using the metric 'TX Mean' or 'Untransformed Proportion' respectively in a binary random-effects model. AF=atrial fibrillation; CVA=cerebrovascular accident; LA=left atrial; LVEF=left ventricular ejection fraction.

Arrhythmia surgery

The technique by which arrhythmia surgery was performed differed between the twelve studies (Table 2). In most of the studies, the LAA was addressed, either by surgically excision, clipping or stapling. Furthermore, there were three studies that reported on thoracoscopic beating-heart AF ablation.[16,17,20] One study reported on single-stage hybrid ablation.[22] Of the remaining studies, five reported on concomitant AF ablation, in most of them a Cox-Maze-III or –IV procedure was performed, and one study used an alternative overlapping PVI technique. While different techniques were used, all studies performed PVI with or without extra lesions (Supplementary Materials, Table S2). Five studies ablated the roof and inferior lines as well to create the so called 'box lesion', while van Breugel only added a roof line.[23] Four studies ablated the RA free wall, a line to the mitral annulus and 3 ablated the posterior LA wall. Three studies ablated the connection between the superior and inferior caval vein and two ablated the coronary sinus and the tricuspid valve. Six studies ablated either an additional cavotricuspid isthmus line, CFAE, ganglionated plexi or the ligament of Marshall, or performed a bi-atrial maze or LA reduction. These marked differences in techniques and lesion sets have led to marked clinical heterogeneity in this review and meta-analysis.

**Table 2.** Surgical characteristics per study including type of cardiac surgery performed, left atrial appendage procedure, energy source, concomitant surgery.

| Study | Arrhythmia Surgery | | | LAA | Energy Source | Concomitant Surgery |
|---|---|---|---|---|---|---|
| | Minimally Invasive (Off-pump) | Hybrid | Cox-Maze III/IV | | | |
| **Al-Jazairi et al.** [2] | - | Single Stage | - | Occlusion (Atriclip 30%) | Bipolar RF | - |
| **Bagge et al.** [3] | Thoracoscopic | - | - | Excised (stapler 76%) | Bipolar RF | - |
| **Buist et al.** [4] | Thoracoscopic | - | - | Ligation (endoloop 100%) | Bipolar RF | - |
| **Driessen et al.** [5] | Thoracoscopic | - | - | Excised (stapler 100%) | Bipolar RF | - |
| **Joshibayev et al.** [6] | - | - | Cox-Maze IV | LA sealing (55%) | Unipolar RF | MV repair n=12<br>MV replacement n=42 |
| **Lonnerholm et al.** [7] | - | - | Cox-Maze III | 100% | Cut and sew | Atrial septum defect closure n=1<br>CABG n=3<br>Septal myectomy n=1<br>TV repair n=1 |
| **Lundberg et al.** [8] | - | - | Cox-Maze III | 100% | Cut and sew | CABG n=2<br>Atrial septal defect closure n=1<br>MV repair n=5 |
| **van Breugel et al.** [9] | - | - | - | Resection (100%) | Bipolar RF | CABG n=18<br>Valve replacement n=32<br>CABG + valve replacement n=10<br>Other n=5 |
| **von Oppell et al.** [10] | - | - | Cox-Maze IV | Excised (100%) | Bipolar RF | AV replacement n=7<br>CABG n=10<br>MV repair n=8<br>MV replacement n=16<br>TV repair n=13 |

AV=aortic valve; CABG=coronary artery bypass graft; LAA=left atrial appendage; MV=mitral valve; NS=non specified; RF=radiofrequency; TV=tricuspid valve.

Primary outcome: QOL following stand-alone arrhythmia surgery

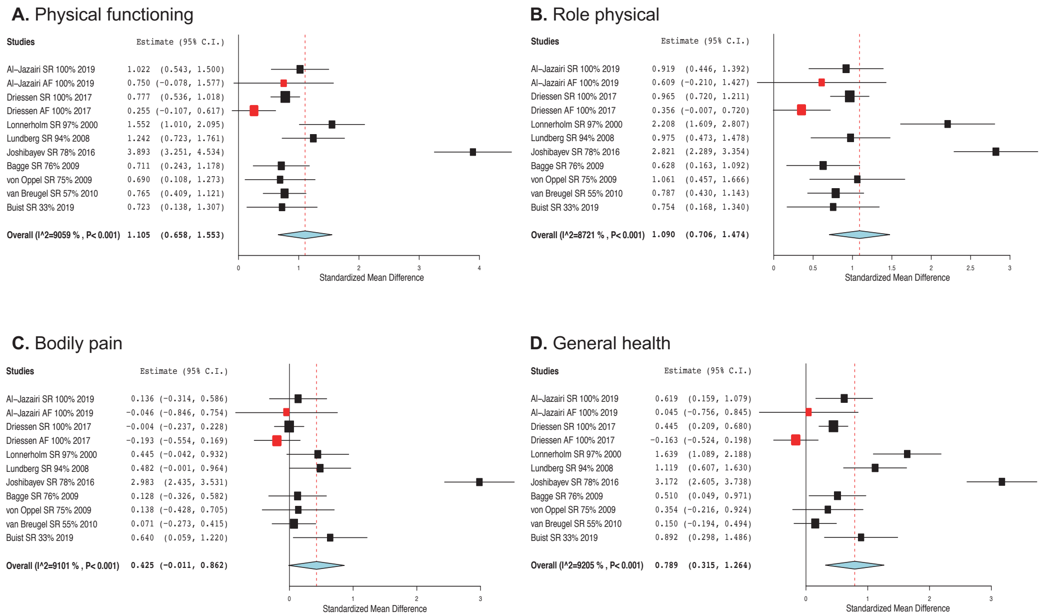
Overall, QOL improved across all variables incorporated in the SF-36 tool (e.g., physical functioning, bodily pain, role physical, general health, role emotional, vitality, social functioning and mental health). Moreover, the incidence of perioperative complications was low for all studies (Supplementary Materials, Tables S3 and S4).

Interestingly, studies with higher success percentages in terms of rhythm outcome (SR after one year) also showed greater QOL improvements across all variables (Figure 1, 2). Moreover, meta-regression based on rhythm outcome in the two studies by Al-Jazairi et al. and Driessen et al., who divided outcomes into two groups based on rhythm outcome, showed that following cardiac surgery the QOL scores of both SR and AF patients improved. Moreover, patients who were in SR showed significantly greater improvements in QOL compared to baseline concerning physical functioning, physical role, general health and social functioning, than those who remained in AF.[17,22] The other variables, including bodily pain, role emotional, vitality and mental health, also showed better outcomes for those in SR compared to those in AF, however non-significant (Table 3).

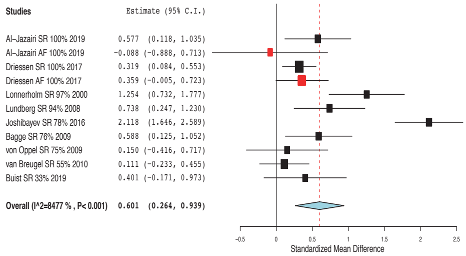
**Table 3**. Changes in SF-36 quality of life variables based on rhythm outcome after 12 months' follow-up.

| **SF-36 variable** | **SR 12 months** | | **AF 12 months** | | ***P*-value** |
|---|---|---|---|---|---|
| | Adjusted mean | 95% CI | Adjusted mean | 95% CI | |
| **Physical functioning** | 0.8 | (0.6 – 1.0) | 0.3 | (0.0 – 0.7) | 0.015 |
| **Role physical** | 1.0 | (0.7 – 1.2) | 0.4 | (0.1 – 0.7) | 0.006 |
| **Bodily pain** | 0.0 | (-0.2 – 0.2) | -0.2 | (-0.5 – 0.2) | 0.331 |
| **General health** | 0.5 | (0.3 – 0.7) | -0.1 | (-0.5 – 0.2) | 0.002 |
| **Role emotional** | 0.4 | (0.2– 0.6) | 0.3 | (0.0 – 0.6) | 0.654 |
| **Vitality** | 0.8 | (0.5 – 1.0) | 0.4 | (0.1 – 0.8) | 0.096 |
| **Social functioning** | 0.8 | (0.5 – 1.0) | 0.4 | (0.0 – 0.7) | 0.043 |
| **Mental health** | 0.6 | (0.3 – 0.8) | 0.2 | (-0.1 – 0.6) | 0.123 |

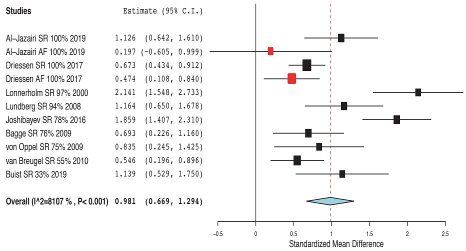
Data are presented as adjusted mean between QOL scores after 12 months versus baseline scores, followed by the 95% CI. P-value of the meta-regression was computed using the metric 'Standardized mean difference' in a binary random-effects model using rhythm outcome after 12 months of follow-up as covariate factor. AF=atrial fibrillation; CI=confidence interval; SF=Short-Form 36; SR=sinus rhythm.


A. Physical functioning
Studies
Estimate (95% C.I.)
Al–Jazairi SR 100% 2019 1.022 (0.543, 1.500)
Al–Jazairi AF 100% 2019 0.750 (−0.078, 1.577)
Driessen SR 100% 2017 0.777 (0.536, 1.018)
Driessen AF 100% 2017 0.255 (−0.107, 0.617)
Lonnerholm SR 97% 2000 1.552 (1.010, 2.095)
Lundberg SR 94% 2008 1.242 (0.723, 1.761)
Joshibayev SR 78% 2016 3.893 (3.251, 4.534)
Bagge SR 76% 2009 0.711 (0.243, 1.178)
von Oppel SR 75% 2009 0.690 (0.108, 1.273)
van Breugel SR 57% 2010 0.765 (0.409, 1.121)
Buist SR 33% 2019 0.723 (0.138, 1.307)
Overall (I^2=9059 % , P< 0.001) 1.105 (0.658, 1.553)
0 1 2 3 4
Standardized Mean Difference
B. Role physical
Studies
Estimate (95% C.I.)
Al–Jazairi SR 100% 2019 0.919 (0.446, 1.392)
Al–Jazairi AF 100% 2019 0.609 (−0.210, 1.427)
Driessen SR 100% 2017 0.965 (0.720, 1.211)
Driessen AF 100% 2017 0.356 (−0.007, 0.720)
Lonnerholm SR 97% 2000 2.208 (1.609, 2.807)
Lundberg SR 94% 2008 0.975 (0.473, 1.478)
Joshibayev SR 78% 2016 2.821 (2.289, 3.354)
Bagge SR 76% 2009 0.628 (0.163, 1.092)
von Oppel SR 75% 2009 1.061 (0.457, 1.666)
van Breugel SR 55% 2010 0.787 (0.430, 1.143)
Buist SR 33% 2019 0.754 (0.168, 1.340)
Overall (I^2=8721 % , P< 0.001) 1.090 (0.706, 1.474)
0 0.5 1 1.5 2 2.5 3
Standardized Mean Difference
C. Bodily pain
Studies
Estimate (95% C.I.)
Al–Jazairi SR 100% 2019 0.136 (−0.314, 0.586)
Al–Jazairi AF 100% 2019 −0.046 (−0.846, 0.754)
Driessen SR 100% 2017 −0.004 (−0.237, 0.228)
Driessen AF 100% 2017 −0.193 (−0.554, 0.169)
Lonnerholm SR 97% 2000 0.445 (−0.042, 0.932)
Lundberg SR 94% 2008 0.482 (−0.001, 0.964)
Joshibayev SR 78% 2016 2.983 (2.435, 3.531)
Bagge SR 76% 2009 0.128 (−0.326, 0.582)
von Oppel SR 75% 2009 0.138 (−0.428, 0.705)
van Breugel SR 55% 2010 0.071 (−0.273, 0.415)
Buist SR 33% 2019 0.640 (0.059, 1.220)
Overall (I^2=9101 % , P< 0.001) 0.425 (−0.011, 0.862)
0 1 2 3
Standardized Mean Difference
D. General health
Studies
Estimate (95% C.I.)
Al–Jazairi SR 100% 2019 0.619 (0.159, 1.079)
Al–Jazairi AF 100% 2019 0.045 (−0.756, 0.845)
Driessen SR 100% 2017 0.445 (0.209, 0.680)
Driessen AF 100% 2017 −0.163 (−0.524, 0.198)
Lonnerholm SR 97% 2000 1.639 (1.089, 2.188)
Lundberg SR 94% 2008 1.119 (0.607, 1.630)
Joshibayev SR 78% 2016 3.172 (2.605, 3.738)
Bagge SR 76% 2009 0.510 (0.049, 0.971)
von Oppel SR 75% 2009 0.354 (−0.216, 0.924)
van Breugel SR 55% 2010 0.150 (−0.194, 0.494)
Buist SR 33% 2019 0.892 (0.298, 1.486)
Overall (I^2=9205 % , P< 0.001) 0.789 (0.315, 1.264)
0 1 2 3
Standardized Mean Difference

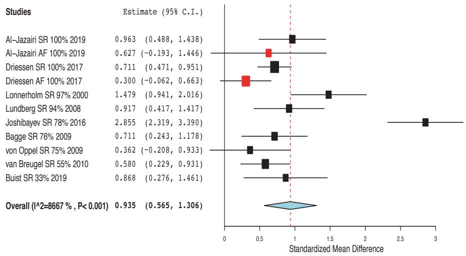
**E.** Role emotional



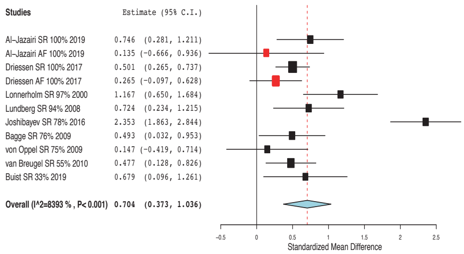

**F.** Vitality




**G.** Social functioning



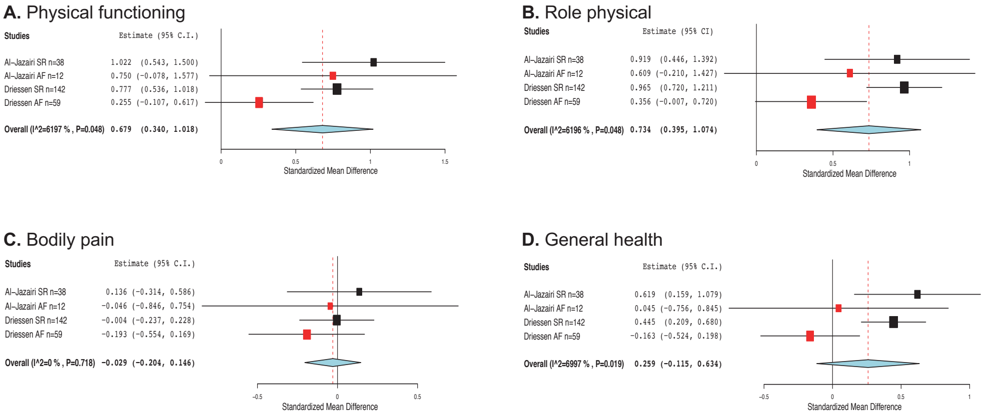

**H.** Mental health






195

**Figure 1**. Forest plots showing the changes per Short-Form 36 quality of life variable after 12 months' follow-up, expressed by the standardized mean difference. The weight given to each study is illustrated by the size of the square box, the point effect estimate by its mid-point and the degree of variance per study by the horizontal line through the box. A greater horizontal line indicates a greater 95% confidence interval for the effect estimates. Red boxes are studies where all patients were still in AF after 12 months. The overall effect estimate is represented by the diamante shape. (**A**). Physical functioning. Heterogeneity: $\tau^2$=0.503, Q(df = 10) = 106.286, *P*<0.001, $I^2$ = 90.6%. (**B**). Role physical. Heterogeneity: $\tau^2$=0.354, Q(df=10) = 78.169, *P*<0.001, $I^2$ = 87.2%. (**C**). Bodily pain. Heterogeneity: $\tau^2$=0.482, Q(df=10) = 111.276, *P*<0.001, $I^2$ = 91.0%. (**D**). General health. Heterogeneity: $\tau^2$=0.577, Q(df=10) = 125.791, *P*<0.001, $I^2$ = 92.0%. (**E**). Role emotional. Heterogeneity: $\tau^2$=0.265, Q(df=10) = 65.670, *P*<0.001, $I^2$ = 84.7%. (**F**). Vitality. Heterogeneity: $\tau^2$ = 0.215, Q(df=10) = 52.832, *P*<0.001, $I^2$ = 81.1%. (**G**). Social functioning. Heterogeneity: $\tau^2$ = 0.327, Q(df=10) = 75.008, *P*<0.001, $I^2$ = 86.7%. (**H**). Mental health. Heterogeneity: $\tau^2$ = 0.253, Q(df=10) = 62.246, *P*<0.001, $I^2$ = 83.9%. SR=sinus rhythm; AF=atrial fibrillation.



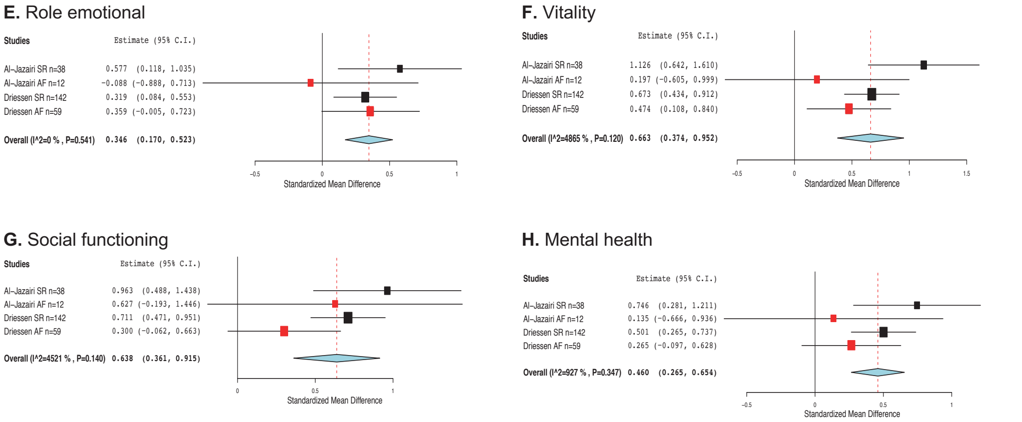



**Figure 2.** Forest plots showing the changes per Short-Form 36 quality of life variable after 12 months' follow-up, expressed by the standardized mean difference, comparing studies with 100% sinus rhythm (black box) with 100% atrial fibrillation (red box) after 12 months' follow-up. The weight given to each study is illustrated by the size of the square box, the point effect estimate by its mid-point and the degree of variance per study by the horizontal line through the box. A greater horizontal line indicates a greater 95% confidence interval for the effect estimates. Red boxes are studies where all patients had AF after 12 months. The overall effect estimate is represented by the diamante shape. (**A**). Physical functioning. Heterogeneity: $\tau^2$ = 0.069, Q(df=3) = 7.888, *P*=0.048, $I^2$ = 62.0%. (**B**). Role physical. Heterogeneity: $\tau^2$ = 0.069, Q(df=3) = 7.887, *P*=0.048, $I^2$ = 62.0%. (**C**). Bodily pain. $\tau^2$ = 0.000, Q(df=3) = 1.345, *P*=0.718, $I^2$ = 0%. (**D**). General health. Heterogeneity: $\tau^2$ = 0.095, $\chi$(df=3) = 9.990, *P*=0.019, $I^2$ = 70.0%. (**E**). Role emotional. Heterogeneity: $\tau^2$ = 0.000, Q(df=3) = 2.155, *P*=0.541, $I^2$ = 0%. (**F**). Vitality. $\tau^2$ = 0.040, Q(df=3) = 5.842, *P*=0.120, $I^2$ = 48.7%. (**G**). Social functioning. Heterogeneity: $\tau^2$ = 0.035, Q(df=3) = 5.476, *P*=0.140, $I^2$ = 45.2%. (**H**). Mental health. Heterogeneity: $\tau^2$ = 0.004, Q(df=3) = 3.306, *P*=0.347, $I^2$ = 9.3%. AF=atrial fibrillation; SR=sinus rhythm.



197

Primary outcome for concomitant procedures

Furthermore, 3 of the 9 included studies performed an extra analysis on comparing QOL outcomes of patients receiving cardiac surgery with and without add-on arrhythmia surgery for AF (add-on surgical AF ablation vs. control group).[18,23,24] While van Breugel et al. and von Oppell et al. randomized their patients between the two groups, the study by Joshibayev et al. did not.[18,23,24] As such, their patients undergoing add-on arrhythmia surgery had a higher rate of longstanding-persistent AF ($P$=0.02), greater LA size ($P$=0.004), lower LVEF ($P$=0.03) and a longer AF duration ($P$=0.05) compared to the control group. Yet this study showed the most improvement in QOL across all variables. Von Oppell et al. showed an improvement in five out of eight variables in the add-on arrhythmia group compared to their control group, but van Breugel et al. only reported a significant improvement in the variable bodily pain compared to the control group. We performed a meta-regression of the 3 abovementioned studies to evaluate the overall effect of add-on ablation concomitant with cardiac surgery on the QOL. This analysis showed that adding arrhythmia surgery to cardiac surgery as a concomitant procedure overall only leads to a significant improvement in the variable 'Role physical' at one year after the procedure (Table 4).

Follow-up

Of the 505 patients who completed the follow-up and reported on QOL using the SF-36 questionnaire, 73.8% (62.5 – 85.0) was in SR after 12 months. The type of rhythm monitoring differed across studies; most studies used a 24-hour Holter, followed by 72-hour Holter, while only one study used continuous monitoring and two used a 12-leads ECG for arrhythmia detection (Supplementary Materials, Table S5).

**Table 4.** Changes in SF-36 quality of life variables comparing cardiac surgery with and without (control group) add-on surgical AF ablation.

| Study | SF-36 variable | Add-on surgical AF ablation | | Control group | | *P*-value |
|---|---|---|---|---|---|---|
| | | Baseline | 1 year | Baseline | 1 year | |
| **Joshibayev *et al.*[6]** | | **n=54** | **n=54** | **n=93** | **n=93** | |
| | Physical functioning | 20.0 ± 7.0 | 84.0 ± 22.0 | 38.0 ± 12.0 | 49.0 ± 7.0 | <0.001 |
| | Role physical | 38.0 ± 13.0 | 81.0 ± 17.0 | 44.0 ± 9.0 | 47.0 ± 9.0 | <0.001 |
| | Bodily pain | 29.0 ± 23.0 | 79.0 ± 5.0 | 53.0 ± 11.0 | 51.0 ± 6.0 | <0.001 |
| | General health | 39.0 ± 7.0 | 89.0 ± 21.0 | 51.0 ± 5.0 | 54.0 ± 6.0 | <0.001 |
| | Vitality | 44.0 ± 12.0 | 88.0 ± 31.0 | 49.0 ± 5.0 | 60.0 ± 5.0 | <0.001 |
| | Social functioning | 39.0 ± 7.0 | 84.0 ± 21.0 | 33.0 ± 11.0 | 51.0 ± 17.0 | <0.001 |
| | Role emotional | 41.0 ± 23.0 | 89.0 ± 22.0 | 61.0 ± 11.0 | 50.0 ± 7.0 | <0.001 |
| | Mental health | 39.0 ± 7.0 | 89.0 ± 29.0 | 55.0 ± 13.0 | 59.0 ± 9.0 | <0.001 |
| **van Breugel *et al.*[9]** | | **n=65** | **n=65** | **n=67** | **n=67** | |
| | Physical functioning | 50.2 ± 24.1 | 68.4 ± 23.2 | 50.1 ± 24.2 | 61.2 ± 23.9 | 0.143 |
| | Role physical | 23.5 ± 35.3 | 53.2 ± 39.7 | 42.9 ± 42.1 | 47.9 ± 38.1 | 0.295 |
| | Bodily pain | 76.0 ± 25.0 | 77.7 ± 22.6 | 72.3 ± 24.6 | 72.8 ± 21.9 | 0.032 |
| | General health | 53.2 ± 19.7 | 56.0 ± 18.2 | 60.2 ± 17.4 | 54.9 ± 17.4 | 0.458 |
| | Vitality | 50.5 ± 22.4 | 61.4 ± 17.0 | 51.3 ± 21.8 | 60.0 ± 17.8 | 0.246 |
| | Social functioning | 66.9 ± 25.2 | 80.0 ± 19.3 | 67.0 ± 25.8 | 76.2 ± 24.7 | 0.410 |
| | Role emotional | 67.7 ± 42.9 | 72.1 ± 35.7 | 69.2 ± 42.0 | 69.5 ± 36.6 | 0.157 |
| | Mental health | 69.6 ± 20.0 | 77.7 ± 13.0 | 72.0 ± 22.0 | 74.0 ± 17.5 | 0.300 |
| **von Oppell *et al.*[10]** | | **n=24** | **n=24** | **n=25** | **n=25** | |
| | Physical functioning | 41.5 ± 25.6 | 61.8 ± 31.9 | 41.4 ± 29.3 | 80.3 ± 20.3 | <0.001 |
| | Role physical | 13.5 ± 25.5 | 54.5 ± 47.3 | 23.0 ± 38.1 | 58.8 ± 44.6 | <0.001 |
| | Bodily pain | 65.7 ± 34.2 | 70.1 ± 28.1 | 80.7 ± 27.3 | 92.2 ± 12.8 | NS |
| | General health | 58.2 ± 23.9 | 67.0 ± 25.0 | 55.1 ± 23.3 | 78.3 ± 16.8 | <0.001 |
| | Vitality | 31.9 ± 23.0 | 53.0 ± 26.2 | 30.2 ± 30.5 | 62.5 ± 19.9 | <0.001 |
| | Social functioning | 55.7 ± 36.9 | 68.8 ± 34.2 | 57.5 ± 29.8 | 88.8 ± 17.6 | <0.001 |
| | Role emotional | 51.4 ± 42.8 | 56.1 ± 47.6 | 58.7 ± 43.3 | 86.7 ± 33.2 | NS |
| | Mental health | 70.8 ± 19.8 | 74.0 ± 22.8 | 76.8 ± 17.4 | 84.4 ± 17.1 | NS |
| **Overall change** | | **Adjusted mean (95% CI)** | | **Adjusted mean (95% CI)** | | ***P*-value** |
| | Physical functioning | 1.8 (0.1 – 3.4) | | 1.0 (0.5 – 1.4) | | 0.403 |
| | Role physical | 1.5 (0.5 – 2.6) | | 0.3 (0.1 – 0.5) | | 0.037 |
| | Bodily pain | 1.1 (-0.5 – 2.6) | | 0.0 (-0.3 – 0.3) | | 0.230 |
| | General health | 1.2 (-0.3 – 2.8) | | 0.4 (-0.2 – 1.1) | | 0.371 |
| | Vitality | 1.1 (0.4 – 1.7) | | 1.3 (0.4 – 2.1) | | 0.704 |
| | Social functioning | 1.3 (-0.0 – 2.5) | | 0.9 (0.4 – 1.4) | | 0.654 |
| | Role emotional | 0.8 (-0.3 – 1.8) | | -0.2 (-1.1 – 0.7) | | 0.178 |
| | Mental health | 1.0 (-0.1 – 2.1) | | 0.3 (0.1 – 0.5) | | 0.203 |

Data are presented as mean ± standard deviation or adjusted mean between QOL scores after 12 months versus baseline scores, followed by the 95% CI. NS=non-significant. SF=Short-Form 36. AF=atrial fibrillation. CI=confidence interval. *P*-value of the meta-regression was computed using the metric ‘Standardized mean difference’ in a binary random-effects model using add-on surgery as covariate factor.

## Discussion

This systematic review and meta-analysis summarizes the effect of arrhythmia surgery for AF on quality of life (QOL). Overall, arrhythmia surgery leads to an improvement in QOL in patients with AF. This improvement seems to be related to the success of the procedure, because the improvement in QOL is higher in studies who reported a higher rate of SR after 12 months of follow-up. This is especially true for patients undergoing standalone AF surgery and less in patients undergoing concomitant AF surgery.

In 1991, drs. Cox and Schuessler designed the Cox-Maze procedure after extensive epicardial mapping studies.[25] The surgical technique is based on an anatomical approach to prevent macro reentrant circuits in both atria. Although new surgical tools and alternative surgical approaches were developed, the basic concept of the procedure did not change and still forms the basis of present-day concomitant AF surgery. Even though the procedure has been shown to be very effective in restoring SR[26] and concomitant AF surgery had a class I indication in 2017,[27] it was recently downgraded to a class IIa indication.[8] A potential reason is that the add-on of AF surgery does not result in improved QOL nor reduced stroke and mortality at 1 year follow-up.[8]

Overall effect on QOL following arrhythmia surgery for AF

In this meta-analysis, there was an improvement in QOL after cardiac surgery with concomitant AF ablation compared to baseline. However, it is difficult to distinguish between the effect of the cardiac surgical procedure itself and the effect of the add-on arrhythmia surgery on the improvement in QOL. When the results are plotted in relation to the success rate of the arrhythmia surgery in terms of SR after 12 months, the forest plots (Figure 1 and 2) suggest that the improvement in QOL is higher in the studies that report a higher freedom of AF. Of course, these results should be interpreted with caution. First, the type of surgical lesions is not consistent between the different studies. While a large variability of lesion sets was performed, at least all studies performed PVI, which represents the cornerstone for AF ablation.[28] Furthermore, in 10 out of 12 studies the LAA was electrically isolated in at least half of their patients. In the BELIEF trial, isolation of the LAA lowered the incidence of AF without increasing the periprocedural complication rate.[29] Moreover, the overall reported stroke incidence in the present study was low

(0.8%). As the LAA is considered the main source of thromboembolism in AF, oral anticoagulation and other techniques such as isolating the LAA are key in stroke prevention in AF patients, which may contribute to the QOL.[30] Secondly, follow-up was conducted with different monitoring devices. While using continuous monitoring devices is the most reliable way to keep track of (asymptomatic) palpitations, this was only used by two studies. Thirdly, no data on AAD use was given, though most of the included patients in this analysis had longstanding-persistent AF (41.9%) and treatment with AAD's seems to be less efficient in this patient population for rhythm control and symptom management.[31] Moreover, for the study of Lonnerholm, the reported % SR in the forest plot represents the outcome directly after surgery, while in the other studies it represents the outcome after 12 months.[32] Nevertheless, it seems that the improvement in QOL is related to the outcome of the AF ablation.

Primary outcome: concomitant AF surgery and QOL

The analysis of the 3 studies that compared cardiac surgery with and without add-on arrhythmia surgery failed to show an overall improvement in QOL between the patients that did and did not undergo add-on arrhythmia surgery.[18,24,33] While QOL scores after one year were improved compared to baseline for both the add-on and stand-alone arrhythmia group, differences were insignificant. These differences between the studies regarding the improvement in QOL is very obvious, suggesting that even if there is an effect of add-on arrhythmia on QOL for concomitant procedures, it is not very strong. Joshibayev et al. reported a very strong improvement in QOL, but this study did not randomize between both arms and therefore it cannot be excluded that there was a selection bias in the patients that received arrhythmia surgery.[18] Furthermore, it is surprising that there was almost no improvement in QOL between baseline and 12 months follow-up in the control group, despite the fact that all patients in the control group underwent mitral valve (MV) surgery. The other 2 studies were randomized, but only the study of von Oppel found an increase in QOL in several parameters, while in the study of van Breugel, only the SF-36 parameter 'Bodily pain' improved.[24,33] In both studies, patients received CABG or aortic or mitral valve procedures concomitant to ablation. Interestingly, the study by Grady et al. further examined the improvement of health-related QOL using the SF-36 between patients undergoing different isolated cardiac procedures.[34] At baseline, patients with MV disease had a better physical component summary (PCS), but lower mental component summary (MCS) than patients undergoing aortic valve (AV) surgery, CABG or a Maze procedure. Three and six months after surgery, PCS scores improved reliably in all groups compared to baseline, except for patients who underwent MV surgery, probably due to their healthier preoperative scores and receiving early intervention. Furthermore, a strong trend was seen for better PCS scores of CABG patients than for AV patients. For changes in MCS scores, the improvement was faster for patients undergoing a Maze procedure compared with the other groups, and patients undergoing MV surgery did not show a clinically important improvement after three months.

Primary outcome: standalone AF surgery and QOL

In standalone AF surgery, the effect of arrhythmia surgery on QOL can be better evaluated, since there is no other surgical procedure that can act as a confounding factor. All studies evaluating QOL using the SF-36 questionnaire in standalone AF surgery showed an increase in QOL at 12 months compared to baseline.[16,17,20,22] It must be noted that patients who are referred for an isolated surgical ablation for AF are highly symptomatic and undergo a surgical intervention as a last resort treatment. Accordingly, they usually have a worse QOL at baseline compared to the general population. As such, it is not unexpected that a rapid and significant improvement in QOL follows after a successful surgical ablation, returning patients to normal SR.[34] Furthermore, 2 studies specifically compared the improvement in QOL between patients who were in SR and patients who were in AF 12 months after the procedure.[17,22] Both studies showed that the improvement in QOL was greater if surgical AF ablation resulted in SR. As such, it can be concluded that successful standalone arrhythmia surgery does result in increased QOL. Despite this improvement in QOL and the fact that standalone surgical AF ablation, epicardial or in a hybrid setting, is associated with higher success rates compared to catheter ablation,[35,36] it remains to have a class II recommendation due to the paucity of RCT's.[8,9]

Different techniques and lesion sets in concomitant and stand-alone AF ablation

The inconsistency in the type of lesions performed during concomitant arrhythmia surgery makes it difficult and challenging to compare the different studies. For example, the studies of Joshibayev et al. and von Oppell et al. included a variety of lesions and a mixture of unipolar and bipolar radio frequent energy. This stands in contrast with the studies evaluating standalone AF surgery, that adhere more to a fixed ablation protocol. As such, it can be concluded that arrhythmia surgery does result in an improvement in QOL, but it requires a dedicated lesion set. Finally, a potential reason for the greater improvement in QOL after stand-alone AF than concomitant arrhythmia surgery is that stand-alone AF surgery is performed by dedicated teams, while concomitant AF surgery is also performed by surgeons without an extensive experience in AF ablation.

**Limitations**

This study contains some limitations. Ideally, we aimed to compare the improvements in QOL outcomes obtained by RCT's in our meta-analysis. Unfortunately, solely 2 studies have evaluated this outcome in an RCT. Due to this gap in literature, we worked with pre- and post-surgical QOL values in our meta-analysis of studies using the SF-36 questionnaire and performed a sub-study based on rhythm outcome after one year. Furthermore, since there is no golden standard for measuring QOL following arrhythmia surgery for AF, the included studies have used a variety of questionnaires to estimate the effect of ablation surgery on QOL. While being an important endpoint for ablation studies, QOL remains a rather subjective endpoint and comes along with (at least some) expectation bias. As such, the placebo effect of undergoing surgery as rhythm therapy was most likely present in at least some degree for all patients. In this meta-analysis, risk of bias due to other factors such as selection, confounding factors and publication was present as well. Moreover, marked differences between lesion sets between the studies was present. As such, not only statistical but also clinical heterogeneity was present in this study and results about the effectiveness of arrhythmia surgery and the improvement in QOL should be interpreted with caution. Lastly, the analyses in this study were based on a specific subgroup of highly symptomatic patients, which is especially true for patients undergoing stand-alone surgical ablation for AF. As such, these papers reflect only a small subset of all AF patients and thus the findings of improved QOL in this group should not be used as an endorsement for surgery for less symptomatic AF patients.

## Conclusion

Overall, arrhythmia surgery does result in an improvement in QOL in patients with AF when a dedicated lesion set is used. This effect seems to be related to the outcome in terms of SR after 1 year, both in concomitant as in standalone AF ablation. However, studies evaluating QOL following arrhythmia surgery are scarce and analysis based on small, heterogenic, single-arm studies in a random-effects model hinders drawing definite conclusions. Therefore, future trials reporting on AF surgery, both concomitant and standalone, should include the evaluation of patient reported outcomes such as QOL.

## Acknowledgements

We acknowledge the authors of the included studies for their cooperation in providing the required additional data.

## Source of funding

None.

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## Supplementary Materials

### Glossary of Abbreviations

| | |
|---|---|
| AF | Atrial fibrillation |
| AFEQT | AF Effect on QualiTy-of-life Questionnaire |
| AFSS | AF Symptom and Severity score |
| C-cap | Cardiff cardiac ablation prom |
| CCS-SAF | Canadian Cardiovascular Society Severity of AF |
| EHRA | European Heart Rhythm Association |
| EQ-5D | Euroqol 5d |
| Hrqol | Health related quality of life |
| MFI | Multidimensional fatigue inventory |
| Prom | Patient recorded outcome |
| SF-12 | Short Form 12 |
| SSQ | Symptom and Severity Questionnaire |
| Vas-score | Visual analogue scale |

### Methods

*Literature search PubMed*

((((((((((((((((((((((patient recorded outcome measures) OR prom) OR patient recorded outcomes) OR QoL) OR quality of life) OR SF-36) OR short form 36) OR hrqol) OR health related quality of life) OR EQ5D) OR EQ-5D) OR euroqol 5d) OR c-cap questionnaire) OR cardiff cardiac ablation prom) OR vas-score) OR visual analogue scale) OR MFI-20 questionnaire) OR multidimensional fatigue inventory) OR afeqt) OR atrial fibrillation effect on quality of life) AND (((((((((((((((((((Arrhythmia surgery) OR arrhythmia ablation) OR Surgical ablation) OR Thoracoscopic ablation) OR Totally thoracoscopic maze) OR TT maze) OR Cox maze) OR Maze procedure) OR mini maze) OR Minimally invasive surgical ablation) OR VATS) OR VATS ablation) OR video assisted thoracoscopic surgery) OR Hybrid ablation) OR Hybrid procedure) OR Hybrid approach) OR Epicardial-endocardial procedure) OR Epicardial-endocardial ablation) OR Epicardial-endocardial approach)) AND ((((((atrial fibrillation) OR paroxysmal) OR persistent) OR longstanding-persistent). Date search: 06/07/2021.

*Literature search Cochrane*

((((((((((patient recorded outcome measures) OR prom) OR patient recorded outcomes) OR QoL) OR quality of life) OR SF-36) OR short form 36) OR hrqol) OR health related quality of life) AND (((((((((((((((((Arrhythmia surgery) OR arrhythmia ablation) OR Surgical ablation) OR Thoracoscopic ablation) OR Totally thoracoscopic maze) OR TT maze) OR Cox maze) OR Maze procedure) OR mini maze) OR Minimally invasive surgical ablation) OR VATS) OR VATS ablation) OR video assisted thoracoscopic surgery) OR Hybrid ablation) OR Hybrid procedure) OR Hybrid approach) OR Epicardial-endocardial procedure) OR Epicardial-endocardial ablation) OR Epicardial-endocardial approach)) AND ((((((atrial fibrillation) OR paroxysmal) OR persistent) OR longstanding-persistent). Date search: 07/07/2021.

## Results

In total, 12 studies identified by the PubMed search were included in this meta-analysis. The Cochrane database did not identify any additional studies for the analysis, since the only 4 eligible studies had already been found in the PubMed database.[1-4] Studies that were excluded based on reporting on other QOL questionnaires, overlapping patients, studies who presented quality of life data other than mean ± standard deviation, descriptive quality of life studies or studies who reported on quality of life using other questionnaires than the SF-36 are listed below.[5-28] No studies could be supplemented by manually screening the reference and cited lists of included studies.

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## Figures

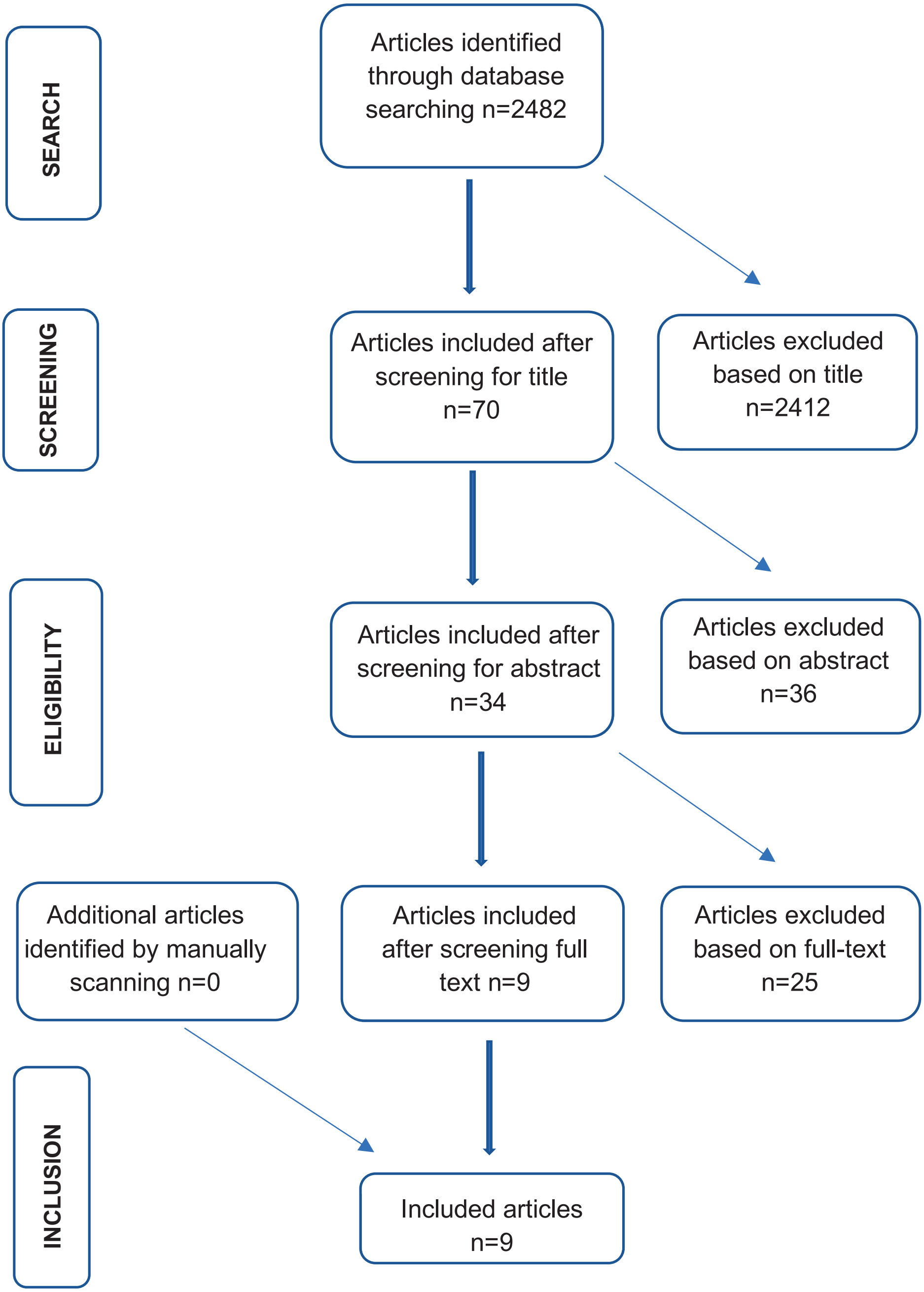


**Figure S1.** PubMed search.

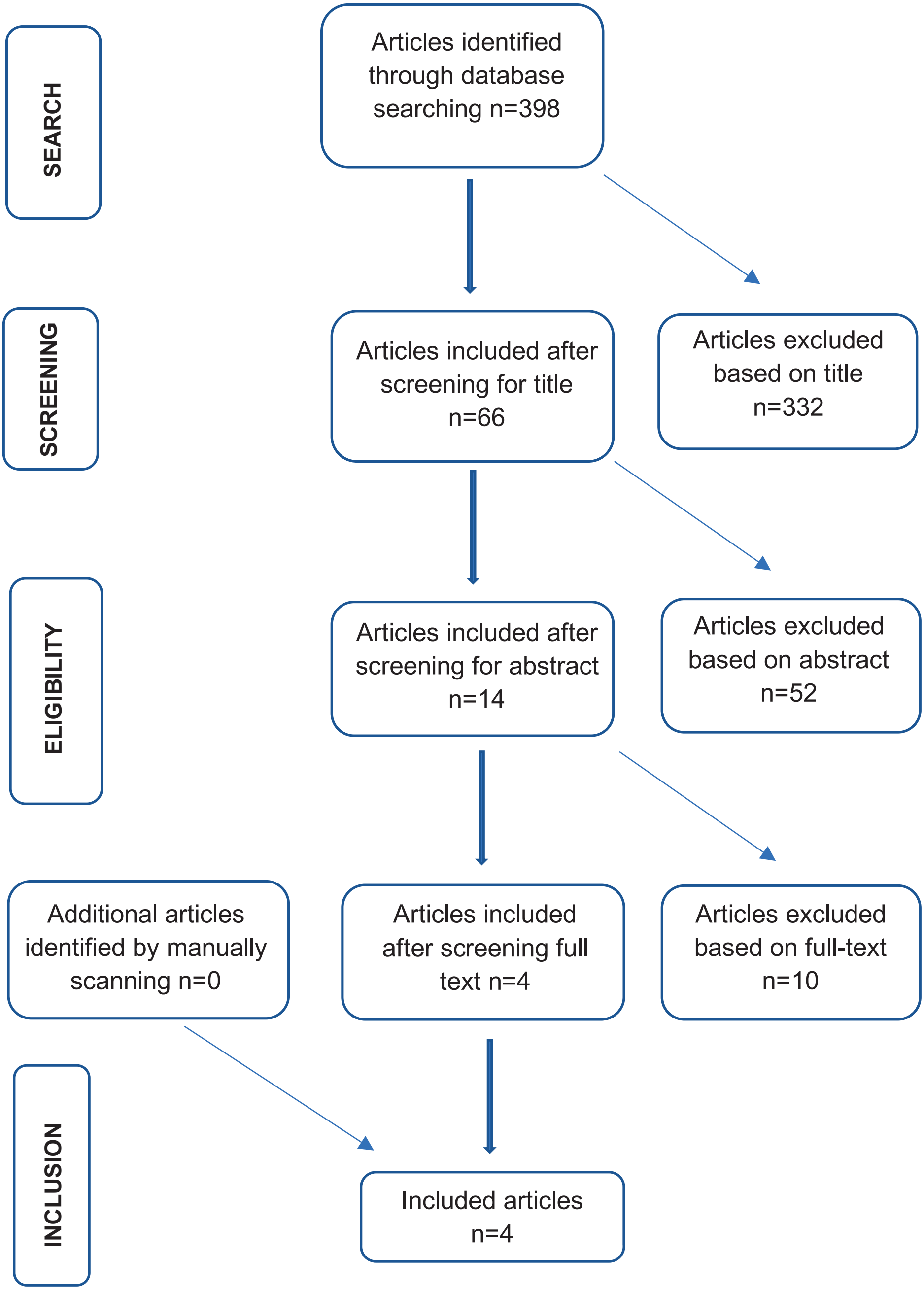


**Figure S2.** Cochrane search.

## Tables

**Table S1.** Overview of included studies in this systematic review.

| Study | Year | Title | Country |
|---|---|---|---|
| Al-Jazairi et al. | 2019 | Hybrid atrial fibrillation ablation in patients with persistent atrial fibrillation or failed catheter ablation | The Netherlands |
| Bagge et al. | 2009 | Epicardial off-pump pulmonary vein isolation and vagal denervation improve long-term outcome and quality of life in patients with atrial fibrillation | Sweden |
| Buist et al. | 2019 | Quality of life after catheter and minimally invasive surgical ablation of paroxysmal and early persistent atrial fibrillation: results from the SCALAF trial | The Netherlands |
| Driessen et al. | 2017 | Quality of life improves after thoracoscopic surgical ablation of advanced atrial fibrillation: Results of the Atrial Fibrillation Ablation and Autonomic Modulation via Thoracoscopic Surgery (AFACT) study | The Netherlands |
| Gehi et al. | 2013 | Hybrid epicardial-endocardial ablation using a pericardioscopic technique for the treatment of atrial fibrillation | United States of America |
| Gillinov et al. | 2015 | Surgical ablation of atrial fibrillation during mitral-valve surgery | United States of America |
| Joshibayev et al. | 2016 | Early and long-term outcomes and quality of life after concomitant mitral valve surgery. left atrial size reduction. and radiofrequency surgical ablation of atrial fibrillation | Kazakhstan |
| Lonnerholm et al. | 2000 | Effects of the maze operation on health-related quality of life in patients with atrial fibrillation | Sweden |
| Lundberg et al. | 2008 | Long-term health-related quality of life after maze surgery for atrial fibrillation | Sweden |
| Osmancik et al. | 2019 | Improvement in the quality of life of patients with persistent or long-standing persistent atrial fibrillation after hybrid ablation | Czech-Republic |
| van Breugel et al. | 2010 | A prospective randomized multicentre comparison on health-related quality of life: the value of add-on arrhythmia surgery in patients with paroxysmal, permanent or persistent atrial fibrillation undergoing valvular and/or coronary bypass surgery | The Netherlands |
| von Oppell et al. | 2009 | Mitral valve surgery plus concomitant atrial fibrillation ablation is superior to mitral valve surgery alone with an intensive rhythm control strategy | United Kingdom |

SF-36=Short Form 36; AFSS=Atrial Fibrillation Symptom and Severity score; EHRA=European Heart Rhythm Association; SSQ=Symptom and Severity Questionnaire; CCS-SAF=Canadian Cardiovascular Society (CCS) Severity of Atrial Fibrillation; SF-12=Short Form 12; AFEQT=Atrial Fibrillation Effect on QualiTy-of-Life; MFI=Multidimensional Fatigue Index.

**Table S2.** Lesion set per study.

| **Study** | **Lesion set** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PVI | Box | SCV to ICV | CS | TV | RA free wall | Mitral annulus | Posterior LA | CTI | CFAE | Bi-atrial maze | LA reduction | GP | LM | Roof line |
| **Al-Jazairi et al.** | X | X | X | | | | | | X | X | | | | | |
| **Bagge et al.** | X | | | | | | | | | | | | X | X | |
| **Buist et al.** | X | | | | | | | | | | | | | | |
| **Driessen et al.** | X | X | | | | | | | | | | | | | |
| **Joshibayev and Bolatbekov et al.** | X | X | X | X | X | X | X | | | | | X | | | |
| **Lonnerholm et al.** | X | | | | | X | X | X | | | | | | | |
| **Lundberg et al.** | X | | | | | X | X | X | | | | | | | |
| **van Breugel et al.** | X | | | | | | | | | | | | | | X |
| **von Oppell et al.** | X | X | X | X | X | X | X | | | | | | | | |

CTI=cavotricuspid isthmus; CFAE=complex fractionated atrial electrograms; GP=ganglionated plexi; LA=left atrial; LM=Ligament of Marshall; PVI=pulmonary vein isolation; SCV=superior caval vein; TV=tricuspid valve.

**Table S3**. Quality of life scores per Short-Form 36 variable per study at baseline and one year after cardiac arrhythmia surgery.

| Study | Physical functioning | | Role physical | | Bodily pain | | General health | | Role emotional | | Vitality | | Social functioning | | Mental health | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T0 | T1 | T0 | T1 | T0 | T1 | T0 | T1 | T0 | T1 | T0 | T1 | T0 | T1 | T0 | T1 |
| **Al-Jazairi *et al.* SR** | 60±27 | 84±19 | 43±46 | 81±36 | 89±20 | 91±18 | 56±20 | 69±22 | 76±35 | 93±19 | 49±22 | 72±18 | 73±25 | 92±13 | 74±16 | 85±14 |
| **Al-Jazairi *et al.* AF** | 59±23 | 75±18 | 20±37 | 45±42 | 87±19 | 86±15 | 60±20 | 61±23 | 83±30 | 80±42 | 60±22 | 64±17 | 66±26 | 81±19 | 80±13 | 82±16 |
| **Bagge *et al.*** | 64±27 | 82±21 | 32±38 | 58±44 | 70±31 | 74±26 | 52±21 | 64±24 | 49±44 | 74±38 | 41±23 | 59±29 | 64±27 | 82±21 | 68±22 | 79±20 |
| **Buist *et al.*** | 64±24 | 79±17 | 46±48 | 78±32 | 68±28 | 85±22 | 51±19 | 67±13 | 71±44 | 87±32 | 44±22 | 65±11 | 64±32 | 88±19 | 75±19 | 86±11 |
| **Driessen *et al.* SR** | 68±25 | 85±18 | 37±42 | 75±37 | 81±22 | 81±23 | 63±19 | 71±20 | 75±41 | 86±30 | 51±20 | 64±19 | 69±24 | 85±20 | 73±17 | 81±16 |
| **Driessen *et al.* AF** | 62±26 | 69±25 | 39±44 | 54±42 | 83±21 | 79±23 | 57±20 | 54±20 | 66±44 | 80±35 | 45±24 | 56±21 | 63±26 | 71±23 | 70±19 | 75±17 |
| **Joshibayev and Bolatbekov *et al.*** | 20±7 | 84±22 | 38±13 | 81±17 | 29±23 | 79±5 | 39±7 | 89±21 | 41±23 | 89±22 | 44±12 | 88±31 | 39±7 | 84±21 | 39±7 | 89±29 |
| **Lonnerholm *et al.*** | 57±26 | 91±11 | 17±34 | 85±23 | 70±30 | 83±26 | 56±16 | 84±19 | 37±43 | 87±32 | 41±19 | 81±17 | 59±24 | 92±18 | 65±18 | 86±17 |
| **Lundberg *et al.*** | 61±18 | 83±17 | 30±38 | 69±41 | 74±27 | 86±22 | 56±20 | 77±17 | 42±42 | 73±41 | 39±20 | 65±24 | 64±25 | 85±20 | 66±21 | 80±17 |
| **van Breugel *et al.*** | 50±24 | 68±23 | 24±35 | 53±40 | 76±25 | 78±23 | 53±20 | 56±18 | 68±43 | 72±36 | 51±22 | 61±17 | 67±25 | 80±19 | 70±20 | 78±13 |
| **von Oppel *et al.*** | 42±26 | 62±32 | 14±26 | 55±47 | 66±34 | 70±28 | 58±24 | 67±25 | 51±43 | 56±8 | 32±23 | 53±27 | 56±37 | 69±34 | 71±20 | 74±23 |

Data are presented as mean ± standard deviation. AF=atrial fibrillation; SR=sinus rhythm. T0=baseline; T1=1 year.

**Table S4.** Peri-operative major and minor complications of all patients reporting on quality of life using the SF-36 questionnaire.

| Complications | Number of patients per complication of total group (n=545) | Adjusted mean % (95% CI) |
|---|---|---|
| Bleeding: reoperation | n=16 | 2.0% (0.9 – 3.2) |
| Bleeding: transfusion | n=15 | 1.8% (0.5 – 3.0) |
| Conversion to sternotomy | n=7 | 1.5% (0.2 – 3.5) |
| Hemodynamic instability/cardiac failure | n=0 | 0.5% (-0.1 – 1.1) |
| Mortality <30 days | n=8 | 1.7% (0.6 – 2.8) |
| Myocardial infarction | n=7 | 0.8% (-0.1 – 1.6) |
| Pacemaker implantation | n=14 | 2.0% (0.8 – 3.1) |
| Pericarditis | n=6 | 1.3% (0.4 – 2.2) |
| Phrenic nerve palsy | n=5 | 1.1% (0.2 – 2.0) |
| Pleural effusion | n=11 | 1.8% (0.7 – 2.9) |
| Pneumonia | n=7 | 1.6% (0.5 – 2.6) |
| Pneumothorax | n=8 | 1.4% (0.4 – 2.4) |
| Renal failure | n=0 | 0.5% (-0.1 – 1.1) |
| Respiratory failure (requiring intubation) | n=0 | 0.5% (-0.1 – 1.1) |
| Stroke/TIA | n=3 | 0.8% (0.0 – 1.6) |
| Tamponade | n=1 | 0.7% (0.0 – 1.5) |

Data are presented as the total number of patients of all cardiac arrhythmia surgery studies per complication, followed by the adjusted mean of proportion and the 95% CI in a binary random-effects model. Statistical test peri-operative complications: one-arm meta-regression 'Freeman-Tukey Double Arcsine Proportion'. CI=confidence interval; SR=sinus rhythm; TIA=transient ischemic attack.

**Table S5**. Follow-up of patients reporting on quality of life using the Short Form-36 questionnaire.

| | Adjusted mean (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Total % SR after 12 months of follow-up (n=505)** | 73.8% (62.5 – 85.0) | | | | | | |
| **Study** | **Follow-up duration (months)** | **Patients at 1 year follow-up (n)** | **% SR post-operative** | **% SR 3 months** | **% SR 6 months** | **% SR 12 months** | **Rhythm monitoring** |
| **Al-Jazairi *et al.*** | 12 | 50 | - | - | - | 76 | 72-h Holter |
| **Bagge *et al.*** | 12 | 33 | - | - | - | 76 | 24-h Holter |
| **Buist *et al.*** | 12 | 23 | - | - | - | 33 | ILR |
| **Driessen *et al.*** | 12 | 201 | - | - | - | 71 | 24-h Holter |
| **Joshibayev and Bolatbekov *et al.*** | 12 | 54 | 63 | 38 | 72 | 78 | 12-lead ECG |
| **Lonnerholm *et al.*** | 12 | 25 | 97 | - | - | - | 12-lead ECG |
| **Lundberg *et al.*** | 12 | 34 | - | - | - | 94 | 24-h Holter |
| **van Breugel *et al.*** | 12 | 65 | - | - | - | 57 | 24-h Holter |
| **von Oppel *et al.*** | 12 | 24 | | 50 | - | 75 | 24-h Holter |

The follow-up duration is followed by the number of patients at one-year follow-up, the percentage of patients that was in SR direct after surgery, after three, six and twelve months and how heart rhythm was monitored. CI=confidence interval; ILR=implanted rhythm monitoring; SR=sinus rhythm.

# CHAPTER 9

## General Discussion

## General Discussion

Atrial fibrillation (AF) is characterized by the self-aggravating processes of electrical, functional and structural remodeling.[1] As AF becomes more and more complex with its duration, adequate rhythm control management can become extremely difficult. As such, one could even state that not only AF begets AF, but catheter ablation begets catheter ablation. Be that as it may, it remains important to strive for rhythm control to lower patient burden, as AF is often symptomatic, may result in tachycardiomyopathy and is associated with an increased risk of stroke, overall morbidity and mortality and an impaired quality of life.[2]

### 1. Post-operative atrial fibrillation; a different sort of AF?

Postoperative AF (POAF) is an interesting type of AF, as it occurs after surgery in patients that never had AF before. Early POAF (occurring between postoperative day 0 and 5) is characterized by a typical time course, peaking between the second and the fourth postoperative day.[3] In clinical practice, early POAF is often considered transient and relatively benign. Nonetheless, the contrary is true, as an episode of early POAF after cardiac surgery is an important predictor for the development of late AF (occurring between postoperative day 6 and 30) and cardiovascular mortality.[4] The development and clinical consequences of late POAF is beyond the scope of this discussion.
To prevent the clinical manifestation of POAF and its adverse consequences, it is important to gain a better understanding of the underlying mechanisms responsible for early POAF. As we know, the occurrence of POAF is multifactorial, where both acute factors related to the surgery itself (inflammation, oxidative stress and sympathetic activation) and chronic factors (reflecting structural remodeling) are involved.[3] This suggests that the clinical manifestation of early POAF is due to acute, surgical triggers on top of an established, but latent, underlying AF substrate.[3] Still, underlying mechanisms predisposing for POAF in the individual patient are still incompletely understood.
The fact that epicardial adipose tissue (EAT) plays a role in the early development of clinical AF due to the early fat infiltration in the myocardial wall,[5] triggers the hypothesis that EAT is also involved in the development of early POAF. Therefore, we explored the potential contribution of EAT to the development of POAF after cardiac surgery AF. Surprisingly, our hypothesis that EAT is associated with POAF was rejected based on our

CT-scan analyses.[6] Even though in our study nearly half of the population developed POAF, no correlation between EAT and POAF could be demonstrated. One explanation could be that our sample size was not large enough to detect a statistically relevant association. Also, the arrhythmogenic effect of EAT leading to POAF may be obscured by the acute, surgical related triggers.[3] On the other hand, the absence of statistical significancy between EAT volume and POAF does not rule out an important clinical association. Perhaps, CT-scan analysis is not adequate enough to detect differences in the rather thin layer of EAT surrounding the atria of patients who develop POAF and who do not. Although currently still preliminary, future studies could implement the use of innovative techniques such as high resolution 3-dimensional magnetic resonance imaging to not only quantify EAT volume more reliably, but also evaluate its evolution over time.[7]

Our results might also just indicate that there is no role for EAT in the occurrence of POAF and that its underlying mechanism in clinical AF is unrelated to AF after (cardiac) surgery. In our study, evaluation of EAT was limited to volume quantification, but it could be that fatty infiltration and EAT quantity are less important in the development of POAF, while the paracrine effects of EAT play a more relevant role. These paracrine effects might even be partially responsible for the development of the acute, surgical triggers that cause POAF, such as inflammation. Therefore, it would be interesting to investigate the local biodynamics and metabolic activity of pro- and anti-inflammatory cytokines. Interestingly, a recent randomized controlled trial (RCT) found that a simple posterior left pericardiotomy reduces the incidence of POAF after cardiac surgery.[8] The hypothesis behind this finding is that the evacuation of activated blood in the pericardial sac towards the left pleural cavity prevents atrial epicarditis, thereby reducing arrhythmogenic triggers causing AF.

## 2. The hybrid approach: a very effective strategy for patients with complex AF

To restore sinus rhythm (SR) in patients with paroxysms of AF, catheter ablation has shown excellent rhythm outcomes.[9] Unfortunately, the procedure is far less effective for patients with more persistent forms of AF.[10] Thoracoscopic ablation on the other hand is an effective treatment strategy for complex AF, but the technique is more demanding, requires a learning curve and naturally carries a greater risk for complications than a truly

minimally invasive percutaneous procedure.[11,12] The idea of combining both techniques into one procedure led to the development of the thoracoscopic hybrid AF procedure.[11] Previous studies from our group have suggested that the hybrid procedure is very successful in patients with long-lasting AF.[11,12]
In this thesis, we further explored the essential aspects of the hybrid treatment approach in patients with complex AF, whether hybrid ablation indeed leads to good patient outcomes, and how to further optimize its technical aspects.

2.1 Should a hybrid procedure become a first line treatment for complex AF?

To test the hypothesis that hybrid ablation is superior to catheter ablation in patients with complex and persAF in terms of rhythm and safety outcome, we first performed a systematic review and meta-analysis. As expected, hybrid ablation was more efficacious, as the procedure resulted in more SR until 1 year off anti-arrhythmic drugs (AAD) (71% versus 50%, $P$=0.001), but the procedure was also associated with a slightly higher complication rate.[13] These results are clinically relevant, as they showed for the very first time that hybrid ablation is more efficacious than catheter ablation for persistent and complex AF patients. The higher complication rate was mainly explained by the learning curve of the surgical procedure as well as the fact that although minimally invasive, the hybrid procedure is still a surgical intervention. Still, the definition of some complications, such as a pneumothorax, is debatable, differs between surgeons and cardiologists and its severity remains semantic. Although these results seem promising, they must also be interpreted with caution. Statistically, meta-analyses are study designs with the highest hierarchical ranking because they allow for an objective appraisal of evidence by pooling results from previously published studies into one overall effect estimate. Generally, the larger sample size of meta-analyses compared to individual studies also allows for testing with more statistical power. However, due to the lack of randomized studies directly comparing hybrid with catheter AF ablation, this meta-analysis was based on single-arm and mostly observational studies with significant clinical and statistical heterogeneity, which limits the translation of these results to daily clinical practice.
As such, it is important to not only base future recommendations on meta-analyses, but also on randomized studies. This important consideration was the driver to perform the first RCT directly comparing thoracoscopic hybrid ablation with transvenous catheter ablation: the HARTCAP-AF study.[14] In this study, 41 ablation-naive persAF patients

received the exact same lesion set by hybrid or catheter ablation, consisting of bilateral pulmonary vein isolation (PVI) in combination with posterior wall isolation (PWI). At one year, the hybrid procedure was more successful than stand-alone catheter ablation in terms of rhythm outcome (89% and 41% off AAD, $P$=0.001), without increasing the risk of complications. The unique aspect of the trial is that only ablation-naive patients with persistent AF were included, since multiple repeat ablations can eventually establish SR.[15,16] Although the included number of patients seemed small, a power calculation based on our own efficacy results of catheter and hybrid ablation revealed that 20 patients per group had to be included to reach statistical power of 90%.[17] Importantly, the difference in efficacy outcome between both groups was so obvious that the inclusion of more patients should even be considered unethical. Moreover, our results have recently been confirmed in the CEASE-AF trial.[18] Although efficacy results in terms of rhythm outcome, defined by the latest ESC AF Guidelines 2020 as freedom from atrial tachyarrhythmia (ATA) recurrences until 12 months off AAD,[2] seem lower than for the HARTCAP-AF trial (72% for hybrid ablation versus 39% for catheter ablation), the absolute difference between both groups was comparable. Perhaps even more important about both trials is that both safety analyses showed comparable procedural risk rates for the two treatment strategies, which can be explained by the increased surgical experience during the last two decades.

Interesting to discuss are the results of the CASA-AF trial, where stand-alone thoracoscopic surgical ablation was not superior to stand-alone catheter ablation for persAF patients.[19] Although limited experience was required from the surgeons in the surgical arm (only a minimum of 20 procedures performed as the primary operator, contributing to the long procedure times (265min; IQR: 220–310)) and patients in the catheter arm received additional ablation of a mitral isthmus or cavotricuspid isthmus line for atrial flutters, the most important limitation of this study is that the surgical arm lacked the endocardial validation and touch-up ablation to complete epicardial conduction caps during the procedure as it was not a hybrid approach.

Nevertheless, it is important to compare these outcomes with real-world data to frame our results and strengthen our conclusions. For that reason, an overview of long-term hybrid AF ablation outcomes, representing a pooled efficacy and safety analysis, was given of all studies reporting on consecutive patients undergoing thoracoscopic hybrid AF ablation.[12,20-26] Using a Kaplan-Meier survival analysis, the overall freedom from atrial tachyarrhythmia (ATA) recurrences after a thoracoscopic hybrid procedure until 1-, 2- and 3-years follow-up was 84±2%, 73±3% and 72±3% respectively (allowing the use of AAD) and 68±2%, 61±2% and 59±3% respectively (off AAD) (Figure 1).

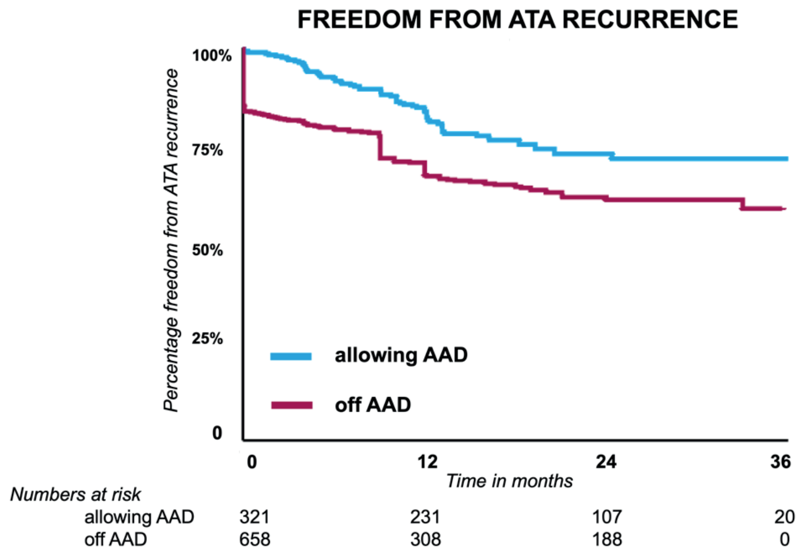


**Figure 1.** Reconstructed time-to-event data on freedom from ATA recurrence, from seven studies reporting on consecutive patients undergoing hybrid AF ablation. AAD=antiarrhythmic drugs; ATA=atrial tachyarrhythmia.

The pooled short-term safety outcomes comprised of major complications including conversion to sternotomy, rethoracotomy, stroke, bleeding and pacemaker implantation. Overall, complications were low (Table 1).

**Table 1.** Safety outcomes of all studies reporting on consecutive patients undergoing thoracoscopic hybrid AF ablation.

| Study | Number of patients | Conversion to sternotomy | Rethoracotomy | Stroke | Bleeding | PM |
|---|---|---|---|---|---|---|
| de Asmundis et al.[27] | 51 | 0 | NR | 0 | 0 | 0 |
| Dunnington et al.[28] | 455 | 2 | 4 | 2 | NR | 7 |
| Lapenna et al.[29] | 50 | 0 | 2 | 1 | NR | 0 |
| Maesen et al.[12] | 64 | 0 | NR | 0 | 0 | 0 |
| Mahapatra et al.[23] | 15 | NR | NR | 0 | 0 | NR |
| Pong et al.[30] | 84 | 4 | NR | 1 | NR | 0 |
| van der Heijden et al.[31] | 119 | 0 | 1 | 0 | 4 | 1 |
| Pooled data (%) [95% CI] | **838** | **0.7% [0.3-1.6]** | **1.1% [0.5-2.3]** | **0.5% [0.2-1.2]** | **1.6% [0.6-4.1]** | **1.0% [0.5-1.9]** |

Data were pooled with a random-effects model and presented as percentages and 95% confidence intervals. NR=not reported; PM=pacemaker implantation.

## 2.2 The strengths of the hybrid approach

Overall, the efficacy of thoracoscopic hybrid AF ablation and its superiority over catheter ablation can be explained by several factors.

First, thoracoscopic ablation allows for durable, epicardial lesions of the PVs and the posterior wall. The use of a biparietal bipolar radiofrequency (RF) energy clamp results in large, durable and continuous epicardial lesions. Furthermore, inherently to the surgical technique, epicardial posterior wall isolation also results in isolation of the Ligament of Marshall, harboring Marshall's vein, which is a source for triggers in persAF.[32] In addition, in patients with repeated ablations and who have trigger initiated AF, triggers originating from the superior caval vein (SCV) isolation can easily and effectively be created from the epicardium. Moreover, it is suggested that isolation of the posterior wall is important in complex and persAF for substrate modification. Surprisingly, adding linear lesions to PVI alone does not improve rhythm outcomes in persAF patients for catheter ablation, as demonstrated in the STAR-AF II trial.[10] Considering the fact that failure to achieve transmural lesions can even be pro-arrhythmogenic, these poor efficacy outcomes were recently confirmed in the CAPLA trial, where reconnection of the posterior wall was high (68%).[33] As it is generally accepted, creation of transmural lesions in the posterior wall via catheter ablation is technically more difficult and is limited by the risk of damaging the esophagus. Based on these results, it can even be questioned if empirical endocardial RF PWI should still be performed at all in persAF patients. Perhaps new energy sources such as pulsed-field ablation (PFA) can yield more-durable PWI, as the technique induces more homogeneous lesions than radiofrequency (RF) or cryo-ablation. It is suggested that the application of ultrarapid electrical fields to the tissue, collateral damage related to thermal ablation, including microvascular damage and hemorrhage causing fibrosis and poor LA contractility, esophageal and phrenic nerve injury and pulmonary vein stenosis are also reduced.[34] Although the results for paroxysmal AF patients are promising,[35] the creation of durable PWI remains to be determined in patients with more persistent forms of AF. In the future, it would be interesting to (1) compare results of a catheter procedure using PFA with thoracoscopic hybrid ablation and (2) integrate endocardial and epicardial PFA into a hybrid procedure and evaluate its short- and long-term durability and safety outcomes.

Secondly, as part of a hybrid procedure, epicardial left atrial appendage (LAA) exclusion can easily and safely be achieved with a clipping device. As surgical exclusion does not only occlude but also electrically isolate the appendage, the risk of stroke is reduced and rhythm outcome is improved.[36,37] As the LAAOS-III trial was performed in patients undergoing concomitant surgical AF ablation in patients with AF and other comorbidities, an interesting study is the LeAAPS trial (NCT05478304) that currently investigates stroke risk after surgical LAA exclusion concomitant to cardiac surgery in patients without AF, but with risk factors for AF and stroke. In any case, epicardial LAA exclusion stands in contrast to a solely endocardial approach, where electrical isolation needs to be combined with an endocardial occlusion device.

Thirdly, the endocardial procedure permits high resolution three-dimensional (3D) electrophysiological mapping and detailed testing of entrance and exit block, and if necessary, touch-up of gaps in epicardial ablation lesions and additional endocardial ablation of lines, including a mitral or cavotricuspid isthmus line. The close collaboration between the surgeon and the electrophysiologist allows for a better understanding of the anatomy and local transmurality of the tissue. In any case, careful treatment selection should be based on a patient-individual level where efficacy and risks should be balanced against each other.

2.3 The strive for minimally invasiveness

It is important to support the drive to reduce invasiveness in surgical procedures without compromising patient safety and outcomes.

First, we explored if we could optimize our hybrid strategy by performing the thoracoscopic approach from the left side only. Instead of a bilateral thoracoscopic approach, a unilateral left-sided techniques also allows for the ablation of all four PVs and exclusion of the LAA. Retrospective analysis of all patients undergoing this unilateral left-sided thoracoscopic AF ablation in our center demonstrated that the procedure is efficacious (80% and 67% free from ATA recurrences after 12 and 24 months respectively off AAD) and safe (5% major peri-operative complications).[38] While these outcomes are different from earlier data from our center (80% success in all consecutive patients with pAF and persAF undergoing thoracoscopic AF ablation after 3 years of follow-up),[12] they correspond well with the pooled efficacy outcomes based on the overview comprising of long-term hybrid AF ablation outcomes (Figure 1). This can be explained by the fact that, with increasing experience, we started to operate on more complex patients with more severe comorbidities. For example, patients had mainly (longstanding)-persistent AF (71%), severely dilated atria (mean LAVI 50±16ml/$m^2$), a long history duration of AF (61 [25-125] months) and chronic underlying diseases.

Secondly, we explored the feasibility of combining two minimally invasive cardiac procedures. Minimally invasive direct coronary bypass grafting (MIDCAB) and unilateral left-sided thoracoscopic AF ablation have both proven to be safe and efficacious stand-alone procedures. Our analysis showed that the combination of MIDCAB and left-sided thoracoscopic AF ablation in one procedure was feasible, efficacious and safe.[39]

The increasing drive to innovate in performing keyhole cardiac surgery is based on the intention to reduce complications and postoperative pain, faster recovery, reduce hospital length and cost effectiveness. For the patient, this may contribute to a faster return to normal physical activities and a subsequent improved quality of life.[40] Although promising, minimally invasive thoracoscopic AF surgery remains a challenge to operate on complex patients with for example (morbid) obesity, poor lung function or previous cardiac surgery due to the development of adhesions. Also, minimally invasive surgery via thoracoscopy, whether or not robot-assisted, requires advanced skills that comes along with a learning curve. Therefore, future centralization of these techniques to high-volume centers may lead to improved efficacy, safety and patient reported outcomes. Of course, these outcomes should be validated in RCTs comparing minimally invasive cardiac surgical techniques (standalone or concomitant) with percutaneous and pump-assisted approaches. We believe concomitant AF ablation should be a standard procedure of all patients undergoing cardiac surgery.[41] Therefore, it would be interesting to investigate if concomitant thoracoscopic AF ablation and/or clipping of the LAA is also desirable in other patient populations with AF that undergo minimally access aortic valve replacement such as transapical, thoracoscopic, mini-sternotomy, right atrial thoracotomy, along other novel minimally invasive procedures.

2.4 Technical aspects within the hybrid procedure

Besides innovation in minimally invasive surgical techniques, differences between epicardial ablation tools are present. In general, two thoracoscopic techniques can be distinguished: bilateral PVI with linear lesions in one continuous lesion or PVI with separate roof and floor lines. The proposed advantage of the bilateral clamping technique is that RF energy is applied with alternating and overlapping lesions from both jaws of the clamp that no longer requires a second (uniparietal) ablation device to ablate the roof and inferior lines for complete PWI.[42] On the other hand, failure of transmurality within this single lesion automatically results in a reconnection of the whole lesion set and as the technique requires a bilateral approach, it is unsuitable for patients with a poor lung function or hostile right thorax.

Secondly, epicardial ablation tools either use dry RF or irrigated RF. Compared to dry, non-irrigated RF devices, irrigated (wet) RF generates larger and more effective ablation lesions with evenly applied energy delivery that, in our experience, result in reliable transmural lesions and a more controlled way of heating the tissue.[43,44] Subsequently, it is suggested that the possible side effects of overheating including the formation of microbubbles, tissue coagulation and charring are prevented. Therefore, the most optimal technique would be to use an irrigated biparietal bipolar RF clamping device that can be used solely from the left side of the thorax, since this also allows for an adequate view of the LAA. Importantly, patient reported quality of life (QOL) should also be incorporated to obtain a more complete view of the pros and cons of the various techniques. Hopefully, these data can contribute to provide future recommendations in the ESC AF Guidelines.

### 3. Left atrial function

The mechanisms responsible for left atrial (LA) remodeling during AF do not only create an electrophysiological substrate that complicates adequate rhythm control, they also negatively impact its normal function. Besides being a neurohormonal tissue, the left atrium serves as a reservoir, conduit and active contractile pump.[45] In chronic AF, the stiff and dilated LA becomes dysfunctional, which is clinically and prognostically relevant as it is associated with an increased risk of stroke, left ventricular dysfunction and overall morbidity and mortality.[46]

Although SR restoration is an important efficacy outcome, restoration of LA function may never fully recover, though it is also an important variable to determine patient symptomatology. We wondered how LA function relates to rhythm outcome and if an improvement in LA function and contractility can be detected after concomitant thoracoscopic AF ablation and thoracoscopic hybrid ablation.

First, we found that the LA emptying fraction improves after thoracoscopic AF ablation concomitant to MIDCAB surgery. Given the fact that the LA emptying fraction was significantly higher post-operatively compared to baseline (26% vs. 38%, $P$=0.01), the study clearly showed that electrical freedom from AF also leads to the restoration or improvement of LA contractility and thus function.[39] Then, we evaluated LA function and contractility in all patients undergoing a thoracoscopic hybrid procedure in our center. Overall, the LA function as well as LV ejection fraction improved after the procedure, while the LA volume reduced. Although the improvement in LA contractility and LAEF after thoracoscopic hybrid AF ablation seem to be mainly related to rhythm restoration in patients with (longstanding)-persAF, the procedure itself also results in enhanced LA reservoir strain and reversed LA remodeling by reducing LA volume. These findings suggest that the restoration of SR also leads to an improvement in LA transport function. Importantly, thoracoscopic AF ablation, either concomitant to MIDCAB or as part of a hybrid procedure, allows for epicardial PVI and posterior wall isolation combined with epicardial LAA exclusion. Overall, the dedicated lesion set and the use of biparietal bipolar RF clamps contribute to the creation of durable lesions that translate into good rhythm outcomes. On one hand, adequate electrical isolation of often multi-regional triggers and complex substrate in persAF is necessary to obtain SR. One might argue that the more extensive the ablation is, the more successful the procedure would be in terms of rhythm outcome. On the other hand, extensive scarring of the atrial myocardium results in the development of fibrosis and a large atrial mass that is unable to contract. In order to maintain or even improve LA function and contractility following any type of AF ablation, substantial healthy contractile myocardial tissue must be preserved in order to provide for a proper LA function. Moreover, the exact role of LAA exclusion after thoracoscopic (hybrid) ablation on LA function and cardiac hemodynamics remains incompletely understood. Although nearly all patients in both our studies underwent LAA exclusion, the LA function (including reservoir function) improved post-procedure. It would be interesting to evaluate in future studies what the long-term effects of LAA exclusion, either performed in the setting of a hybrid procedure or concomitantly to other cardiac procedures without LA ablation, are on the LA- and overall cardiac function.

Although not directly investigated in this study, the undeniable question is whether the improvement in reversed LA function and contractility also results in an improvement in QOL. Currently, the lack of studies reporting on rhythm outcome, LA function and QOL after ablation strategies prevent us from demonstrating causality between them. Still, we illustrated in our systematic review and meta-analysis that surgical AF ablation does improve QOL and that this improvement is positively correlated to a successful rhythm outcome.[47] Therefore, it seems only logical to assume that the improvement in LA function by SR restoration does improve QOL.

## 4. Quality of life

In the end, the main reason why we believe that restoring sinus rhythm and improving LA function is so important, is because the goal of any rhythm control strategy remains to improve patient-burden and symptomatology. We found in our meta-analysis comprising of world-wide data, that surgical ablation, either performed as a stand-alone or concomitant procedure, improves QOL.[47] This was confirmed in the HARTCAP-AF trial, which showed that patient reported QOL increases after hybrid and catheter ablation to an equal level.[14] Despite these crucial results, the indication for concomitant AF ablation during cardiac surgery was downgraded from a Class IA recommendation to a Class IIA recommendation in the latest ESC 2020 AF Guidelines.[2] Although exceedingly important, a potential explanation is the lack of randomized data describing the value of (add-on) arrhythmia surgery on the improvement of QOL. Perhaps this disinterest to report on QOL is due to the fact that patient reported outcomes, including QOL, are no solid markers for therapeutic success according to our current Guidelines.[2] Instead, the Guidelines have defined therapeutic success as freedom from any supraventricular recurrence lasting longer than 30 seconds, taking into account it can relatively easily be objectified by rhythm monitoring devices. Still, this rationale does not fully comprise the reduction in AF burden (percentage of time a person has AF) nor the burden of AF (clinical or economic impact) on patient symptomatology, which is still the primary indication for rhythm control strategies. Interestingly, persistent AF can become paroxysmal AF after ablation, potentially resulting in an improved cardiac function and lower AF burden. Moreover, according to the current definition of success, a patient with an isolated recurrence post-procedure and a patient with frequent recurrences are equally labeled as therapeutic failures. However, the latter patient is more likely to have a worse QOL due to the greater AF burden, which is potentially also accompanied with the demand for repeat ablation and rehospitalization compared to the patient with only a single recurrence. For this reason, disease burden and QOL should be incorporated to distinguish clinical freedom from AF from meaningful freedom from AF.

Other important aspects of QOL besides its relation to rhythm outcome that require further investigation as well are the constant drive for improving minimally invasive techniques and whether this genuinely reflects the best treatment option for the patient. Furthermore, although we believe that concomitant AF surgery and/or LAA management should at least be considered in all patients with AF, we still have little knowledge about the added value of LAA closure or a staged hybrid procedure concomitant to other cardiac surgeries and their effects on QOL, even in the long-term. Therefore, QOL requires further investigation in order to obtain a more holistic view of success of currently and in the future available AF rhythm control strategies to optimize our AF Guidelines and outcomes.

## 5. Conclusion

In this thesis, the mechanisms underlying post-operative atrial fibrillation are discussed, as well as a variety of important outcomes after hybrid and concomitant surgical ablation.

The main findings are:

**1.** There is no clear role for epicardial adipose tissue in postoperative AF. **2.** Hybrid AF ablation is more effective in restoring sinus rhythm than catheter ablation for complex and persistent AF patients. **3.** Thoracoscopic hybrid ablation is as safe as a truly minimally invasive catheter procedure and both improve patient reported quality of life to an equal level. **4.** Even in difficult to treat patients, a unilateral left-sided thoracoscopic approach offers an even less invasive alternative to a bilateral approach, with good 1- and 2-years rhythm and safety outcomes. **5.** An all-in-one minimally invasive approach combining left-sided thoracoscopic ablation with MIDCAB surgery is feasible, safe and efficacious and may represent a valid alternative to a sternotomy. **6.** A staged hybrid procedure can complete partial lesions inherent to a unilateral left-sided thoracoscopic technique. **7.** Left atrial size, function and contractility improve after thoracoscopic hybrid ablation, which reflects the favorable process of rhythm restoration and reversed left atrial remodeling. **8.** Although surgical AF ablation improves quality of life, especially when sinus rhythm is maintained, the different varieties within surgical ablation as well as its relation to functional outcomes requires further investigation.

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# CHAPTER 10

## Summary

## Background information

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in adults and is characterized by a chaotic contraction of the atria. This often leads to symptoms including palpitations or dyspnea. Since during AF the atria often contract rapidly and irregularly, they are in fact dysfunctional. As a result, the normal blood flow from the atria to the ventricles is impaired. Consequently, the cardiac function may be impaired and blood clots can develop, thereby increasing the risk for heart failure and stroke respectively. As such, AF is associated with a reduced quality of life and an increased risk of morbidity and mortality.

Atrial fibrillation may terminate spontaneously, but if AF persists, several AF-induced mechanisms aggravate the complexity of the arrhythmia even further. Consequently, the atria become progressively enlarged, stretched and stiff, leading to a substrate that is more refractory for intervention.

## Anti-arrhythmic therapies for atrial fibrillation

For many patients, anti-arrhythmic treatment using drugs and/or a catheter ablation procedure offer a good solution to treat the arrhythmia. During a catheter ablation procedure, the cardiologist inserts the ablation instruments into a vein in the groin towards the inside of the heart, where the ablation takes place (scarring of the tissue). For many patients, a catheter ablation offers successful results. Unfortunately, for patients with more persistent forms of AF and severely diseased atria, a catheter ablation procedure often has unsatisfactory results. As such, adequate treatment of AF in this patient category remains a real challenge. For such patients, a minimally invasive surgical ablation via the ribs may offer a solution. Back in the days, a surgical ablation procedure required a sternotomy and the use of cardiopulmonary bypass. Meanwhile, surgical AF ablation can be performed without opening the chest and on the beating heart. An important difference with catheter ablation is that during surgical ablation, the ablation lines are created on the outside of the atrium and different ablation instruments are used.

### Catheter versus minimally invasive surgical ablation

An important advantage of a catheter ablation, besides the natural less invasive character of the procedure, is that it allows the cardiologist to create a detailed electro-anatomical map of the atria by testing for signals. On such a map it is possible to validate the completeness of the ablated lesions. In case of incompleteness, immediate touch-up ablation to fulfil the lesion set can be performed. On the other hand, a surgical ablation offers the opportunity to exclude the left atrial appendage and considerably lower the risk of stroke. In addition, the use of certain instruments during a surgical ablation via the outside of the heart has shown to be more effective in creating lesions over the full length of the atrial myocardium than the instruments that are used during a catheter ablation procedure. Therefore, the surgical approach may be more successful in terminating the arrhythmia than a catheter ablation procedure. However, the cardiac surgeon does not dispose of such detailed information about the underlying tissue and arrhythmia compared to the cardiologist during a catheter ablation procedure.

Hybrid ablation procedure

In Maastricht, the cardiologist and cardiac surgeon have bundled their skills to further improve the current anti-arrhythmic treatment options for patients with advanced and complex AF. As such, the first thoracoscopic hybrid procedure was performed in 2010 in the MUMC+. During this procedure, the surgical ablation is combined with the endovascular procedure executed by the cardiologist. During the latter step, the cardiologist is able to validate the previously surgically created scars by testing for signals. If necessary, an extra ablation lesion can directly be created to complete the lesion set and improve rhythm outcomes.

**This thesis**

The aim of this thesis is to evaluate the beneficial aspects of a surgical (including hybrid) ablation procedure. In the **first chapter**, the general introduction describes underlying pathophysiological mechanisms of AF, current anti-arrhythmic therapies and other important outcome measures. Then, in the following **chapter 2**, the CT-scan analysis of a certain type of fatty tissue surrounding the left atrium and its relation to the occurrence of AF after cardiac surgery is described. Although this type of fatty tissue seems important in the early development of AF, there does not seem to be an association between this type of fat and the occurrence of AF in the postoperative setting. Hence, for this type of AF, other factors such as inflammation seem to play a more important role.

Thereafter, the following chapters focus on the outcomes after a surgical (including hybrid) ablation procedure. Although hybrid ablation yields promising outcomes, the procedure has never been compared to a catheter procedure alone. Therefore, **chapter 3** compares the efficacy and safety of a hybrid procedure with a catheter ablation procedure. Although this systematic review and meta-analysis shows that hybrid ablation is more effective than catheter ablation for people with persistent AF, the risk of complications was also higher.

To further validate our results in **chapter 4,** both techniques were directly compared with each other in a randomized study: the HARTCAP-AF trial. Again, the hybrid procedure was more effective than the catheter procedure. Interestingly, the hybrid procedure was as safe as a catheter procedure, since the risk of complications was comparable between both interventions. A possible explanation is that in this trial, all procedures were performed by an experienced team that had already overcome the effect of the learning curve.

Moreover, over the past few years surgical techniques have evaluated into a variety of less invasive keyhole alternatives. Currently, the thoracoscopic part of a hybrid procedure can also be performed from only one side instead of two. As such, **chapter 5** shows that a thoracoscopic hybrid procedure performed via only the left-side of the thorax is feasible, efficacious and safe. Importantly, sparing of the contralateral side of the thorax has the potential to reduce procedure related complications, thereby improving recovery time and subsequently quality of life.

In the category of minimally invasive procedures, we then describe the combination of two minimally invasive surgical procedures in one in **chapter 6**. For patients undergoing a robot-assisted bypass operation for treating their coronary artery disease, and who at the same time apply for a surgical treatment of AF, this combined all-in-one minimally invasive procedure performed in the MUMC+ should be considered. It turned out that the combined procedure was not only technically feasible, but also safe with satisfactory rhythm outcomes until 1 year. An additional analysis using cardiac echocardiography even showed a significant improvement in the left atrial function following the procedure. The latter finding triggered our curiosity and led to the idea of analyzing the left atrial function and contractility after the hybrid approach as well and if an association was present with successful rhythm outcome. In **chapter 7** we found that in general, the left atrial function improves and the left atrial size decreases after a hybrid procedure. The effect was mostly present in people with persistent AF due to rhythm restoration, but the procedure itself also resulted in reduced left atrial size. These are important findings, as they implicate that the progressive disease remodeling processes during AF are at least partially reversible when performing a hybrid procedure.

Besides rhythm or echocardiographic outcomes, patient reported outcomes such as quality of life are becoming increasingly important. After all, the goal of an ablation is symptom reduction and quality of life improvement. For this reason, we investigated in **chapter 8** the patient reported quality of life after a surgical AF ablation procedure, whether or not combined with another cardiac surgery procedure. The study was based on worldwide data and described in a systematic review and statistical meta-analysis. Quality of life improved for all patients undergoing surgical AF ablation and the improvement was even greater in patients where the arrhythmia could be treated successfully without the occurrence of recurrences.

# CHAPTER 11

## Samenvatting

## Achtergrondinformatie

Boezemfibrilleren is de meest voorkomende hartritmestoornis bij volwassenen en wordt gekarakteriseerd door het chaotisch samenknijpen van de boezems, hetgeen vaak leidt tot symptomen zoals hartkloppingen of kortademigheid. Doordat het hart ten tijde van boezemfibrilleren vaak zeer snel en onregelmatig klopt, zijn ze dysfunctioneel. Dit kan leiden tot een verminderde hartfunctie (hartfalen) of het ontstaan van bloedpropjes (beroerte). Dat maakt onder andere dat boezemfibrilleren geassocieerd is met een verminderde kwaliteit van leven en een verhoogd risico op overlijden.
Boezemfibrilleren kan vanzelf stoppen, maar indien het persisteert worden er verscheidene mechanismen in gang gezet om het hart initieel te beschermen. Helaas is het zo dat naarmate de ritmestoornis blijft bestaan, deze haar eigen complexiteit versterkt en het steeds moeilijker wordt om het boezemfibrilleren adequaat te kunnen behandelen.

## Ritme behandelingen

Katheter ablatie

Wanneer medicijnen onvoldoende helpen, kan een katheter ablatie uitkomst bieden. Tijdens een katheter ablatie brengt de cardioloog kleine instrumenten via een ader in de lies in die uitkomen in het hart, alwaar er littekens gebrand kunnen worden vanuit de binnenkant van het hart. Bij mensen met aanvallen van boezemfibrilleren is gebleken dat een katheter ablatie gunstige resultaten laat zien. Helaas is een katheter ablatie bij mensen met langer bestaand en complex boezemfibrilleren minder effectief. Dit komt mogelijk door het feit dat de littekens die via een katheter ablatie gemaakt worden in het hart niet overal door de volledige spierwand van de boezem kunnen worden gecreëerd. Hierdoor wordt de kans op het her optreden van boezemfibrilleren en zelfs het ontstaan van nieuwe hartritmestoornissen vergroot. Een belangrijk voordeel van de katheter ablatie is wel dat het een zeer minimaal invasieve ingreep is. Ook kan de cardioloog middels extra katheters de signalen over de boezem gericht meten en een gedetailleerde elektro-anatomische kaart te maken en beschikt daardoor over specifiekere kennis over de kenmerken van het onderliggende weefsel. Op deze kaart is namelijk te zien of de littekens compleet zijn en in het geval van incompleetheid, kunnen deze direct bij gebrand worden om de brandlijn te vervolledigen.

Minimaal invasieve chirurgische ablatie

Met name voor patiënten met complex en langer bestaan boezemfibrilleren kan een chirurgische ablatie via een kijkoperatie tussen de ribben uitkomst bieden. Waar men vroeger een openhartoperatie moest uitvoeren middels het gebruik van de hart long machine, is het nu mogelijk om de borstkas gesloten te laten en “op kloppend hart” de ablatie uit te voeren. Een belangrijk verschil met een katheter ablatie is dat via deze manier de littekens via de buitenkant van het hart gemaakt kunnen worden en dat een chirurgische ablatie de mogelijk biedt om een ablatieklem te gebruiken die erg goed blijkt in het creëren van littekens door de gehele spierwand van de boezem. Ook is het mogelijk om het linker hartoortje chirurgisch te verwijderen, waardoor niet alleen het risico op een beroerte afneemt, maar ook de succeskans van de ablatie wordt vergroot. Dit leidt ertoe dat een chirurgische ablatie effectiever is in het termineren van de hartritmestoornis dan katheter ablatie voor lastig te behandelen patiënten. Een nadeel van een chirurgische ablatie is echter wel dat de chirurg over minder kennis beschikt over het onderliggende mechanisme van het boezemfibrilleren dan de cardioloog.

De hybride ablatie

In Maastricht hebben de cardioloog en de chirurg hun krachten gebundeld in de behandeling van mensen met progressief en complex boezemfibrilleren. Zo is in 2010 de eerste hybride ablatie uitgevoerd, en deze vond plaats in ons centrum. Tijdens de hybride procedure maakt de chirurg als eerst de littekens via de kijkoperatie vanuit de buitenkant van het hart. Ook kan de chirurg een clip zetten op het linker hartoortje om het risico op een beroerte aanzienlijk te verlagen. Vaak nog tijdens dezelfde procedure voert de cardioloog de katheter ablatie uit, maar dit kan eventueel ook later in een tweede procedure. Hierin controleert de cardioloog eerst de littekens die door de chirurg gemaakt zijn middels het meten van signalen. Nadien kan er, indien nodig, een extra ablatie vanuit de binnenkant van het hart worden uitgevoerd. Zodoende combineert een hybride ablatie een chirurgische ablatie met een inwendige validatie en ablatie indien nodig.

**Dit proefschrift**

De doelstelling van dit proefschrift is om de gunstige effecten van de chirurgische (waaronder hybride) ablatie nader te onderzoeken. In het **eerste hoofdstuk** wordt een algemene introductie gegeven omtrent boezemfibrilleren, de rol van vet rondom de

boezems in het ontstaan van boezemfibrilleren, de huidige therapieën en de verschillende uitkomstmaten na een ritmebehandeling.
In **hoofdstuk 2** wordt de analyse op CT-scans van vet rondom de boezem en de relatie tot het optreden van boezemfibrilleren na verschillende vormen van hartchirurgie beschreven. Hoewel dit type vet wel belangrijk is in het ontstaan van “gewoon” boezemfibrilleren, lijkt er geen verband te bestaan met dit vet en het optreden van boezemfibrilleren in de postoperatieve setting. Voor dit type boezemfibrilleren lijken juist andere factoren, zoals ontsteking, een grotere rol te spelen dan dit type vet. De andere hoofdstukken gaan vervolgens dieper in op de uitkomsten na een chirurgische (inclusief hybride) operatie.
Daaropvolgend vergelijkt **hoofdstuk 3** de effectiviteit en veiligheid van de hybride ablatie met een katheter ablatie. Hoewel in deze review en meta-analyse de hybride ablatie effectiever bleek voor mensen met langer bestaand boezemfibrilleren en het risico op complicaties voor beide technieken laag, was het risico op complicaties na de hybride ablatie groter.
In het volgend **hoofdstuk 4** werden beide technieken direct met elkaar vergeleken in een gerandomiseerde studie: de HARTCAP-AF. Niet alleen bleek de hybride ablatie effectiever te zijn dan de katheter ablatie, maar ook even veilig met een vergelijkbaar risico op complicaties voor beide technieken. Mogelijks is dit te verklaren door de expertise van het opererend team dat haar leercurve reeds doorstaan heeft.
Omdat met de jaren chirurgische technieken steeds minder invasief moeten worden uitgevoerd via steeds kleinere (kijk)openingen, hebben wij onderzocht of het chirurgische deel van de hybride ablatie vanuit slechts één kant van de ribbenkast kan worden uitgevoerd. Uit **hoofdstuk 5** blijkt dat een procedure die enkel vanuit de linker kant van de ribbenkast wordt uitgevoerd doeltreffend en veilig is en de potentie heeft om complicaties te verminderen door de andere zijde van de borstkast te sparen. Dit zou zich kunnen vertalen in een vlotter herstel en een verbeterde kwaliteit van leven van de patiënt.
Om in de categorie van minimaal invasief te blijven, beschrijven we daaropvolgend in **hoofdstuk 6** de combinatie van twee minimaal invasieve operaties samengevoegd in één. Voor mensen die een bypassoperatie ondergaan voor kransslagaderlijden middels de robot, en tegelijkertijd in aanmerking komen voor een chirurgische behandeling van het boezemfibrilleren, kan deze gecombineerde techniek overwogen worden binnen het

MUMC+. Niet alleen bleek dat de operatie technisch goed uitvoerbaar en haalbaar was, maar ook veilig en effectief met goede 1-jaars resultaten. Een extra analyse middels een hartecho toonde tevens aan dat de functie van de linkerboezem substantieel verbeterde na deze procedure.

Deze bevinding zette ons aan het denken en leidde ertoe dat wij behoudens ritme uitkomst, ook de boezemfunctie na een hybride ablatie hebben onderzocht. Zodoende zagen wij in **hoofdstuk 7** dat in het algemeen de boezemfunctie verbetert na een hybride procedure en dat de boezemgrootte ook afneemt. Dit impliceert dat het ziekteproces van de boezem ten tijde van boezemfibrilleren deels reversibel is dankzij een hybride procedure. Het effect was met name zichtbaar in mensen met langer bestaand boezemfibrilleren vóór de operatie en bij mensen waarbij het boezemfibrilleren na de procedure ook wegbleef.

Naast ritme of echografische uitkomstmaten worden patiënt gerapporteerde uitkomstmaten steeds belangrijker. Uiteindelijk is het doel van een ablatie immers het verbeteren van kwaliteit van leven. Om die reden onderzochten wij in **hoofdstuk 8** de kwaliteit van leven na een chirurgische ablatie, al dan niet tegelijkertijd gecombineerd met een andere hartchirurgische ingreep, gebaseerd op wereldwijde data in een review en statistische meta-analyse. Het bleek dat de kwaliteit van leven dat door patiënten gerapporteerd was verbeterde voor beide groepen, met name als het boezemfibrilleren succesvol behandeld kon worden en er geen recidieven optraden.

# CHAPTER 12

## Impact and Valorization

## Impact and Valorization

Atrial fibrillation (AF) is a growing health problem worldwide, with a global prevalence in adults estimated between 2-4% in 2019.[1] Importantly, a 2-3-fold rise in this prevalence is expected in the next two to three decades,[2] which can be attributed to the ageing population, the better detection of AF and the growing incidence of comorbidities predisposing to AF.[3] Furthermore, AF significantly and adversely affects quality of life (QOL). This is related to the AF burden (the percentage of time an individual has AF), the incidence of AF-related complications (such as stroke or heart failure), hospitalizations and the need for medication such as oral anticoagulation or anti-arrhythmic drugs (AAD).[3] Importantly, AF is becoming one of the largest cardiovascular epidemics and transforming into a major public health concern worldwide. Consequently, AF places a substantial social and economic burden on society due to the increased utilization of health care resources.[4] This impact emphasizes the urgent need for preventive AF strategies by lowering risk factors predisposing for AF. As such, it is of paramount importance that health care professionals as well as patients are adequately informed about preventive- and optional rhythm control strategies to improve AF related symptoms, QOL and prevent recurrences.

Over the past years, invasive surgical AF ablation procedures via sternotomy requiring the use of cardiopulmonary bypass have developed into minimally invasive efficacious, feasible and safe beating heart alternatives. Meanwhile, the current European AF guidelines recommend minimally invasive thoracoscopic ablation, including hybrid AF ablation, for symptomatic, drug-resistant AF patients.[3] Therefore, the main aim of this thesis was to explore the beneficial aspects of hybrid ablation for AF.

In Maastricht, the ongoing adaptation and implementation of data evaluating the efficacy and safety has contributed to improved mid-term rhythm outcomes following thoracoscopic surgical and hybrid AF ablation. For example, we recently improved our thoracoscopic technique from a bilateral thoracoscopic approach to a unilateral left-sided approach.[5] Compared to a bilateral technique, a unilateral procedure has the potential advantage of preventing complications on the contralateral side, a faster recovery by lowering postoperative pain and minimal scarring of the skin, thereby potentially improving patient reported QOL and lowering health care costs. The unilateral thoracoscopic approach can safely and efficaciously be executed as a part of a hybrid strategy or concomitant to a MIDCAB procedure. In the latter case, patients only need one hospitalization to treat both their coronary artery disease and AF in an all-in-one minimally invasive approach and do not always need to undergo a sternotomy anymore. Moreover, technical improvements in thoracoscopy and the close cooperation between the cardiac surgeon and the electrophysiologist have contributed to improved rhythm outcomes after thoracoscopic hybrid AF ablation, endeavoring a patient tailored treatment approach. For example, we found in our systematic review and meta-analysis that for persistent AF patients, hybrid ablation is superior to catheter ablation with regards to rhythm outcome.[6] This was also confirmed in our HARTCAP-AF randomized controlled trial, where the freedom of atrial tachyarrhythmias off AADs 1 year after a thoracoscopic hybrid ablation procedure was high and superior to catheter ablation (89% vs. 41%, $P$=0.002).[7] Importantly, this implicates that the hybrid procedure could offer opportunities for patients with complex and persistent forms of AF, where medication or catheter ablation alone fail to restore sinus rhythm or improve QOL. In another systematic review and meta-analysis based on multicenter data, we found that surgical AF ablation, both stand-alone or concomitant, significantly improves patient reported outcomes such as QOL.[8] Moreover, thoracoscopic hybrid AF ablation improves left atrial contractility post-procedure and reduces left atrial volume. Especially when sinus rhythm is restored and the arrhythmia is terminated, left atrial contractility improves. These results are important, since the improved rhythm and functional outcomes may in turn lower rehospitalizations, AF socio-economic burden, AF-related symptoms and improve QOL.

**Future Perspectives**

What still remains to be investigated is the long-term efficacy, safety and cost-effectiveness after thoracoscopic hybrid AF ablation and this should be compared to other (minimally invasive) rhythm control strategies. Although initially a hybrid procedure is probably more costly than a percutaneous or thoracoscopic approach only, it is expected that the investment in a hybrid procedure will be more cost-effective than both strategies in the long-term. It is suggested that even in the long-term, hybrid ablation is as safe as catheter ablation, but still more efficacious and requires fewer repeat ablations, fewer emergency visits and rehospitalizations. Therefore, we await the long-term results of the HARTCAP-AF trial where besides rhythm and safety outcomes, also quality of life and cost-effectiveness until 3 years of follow-up are evaluated.[7]

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# CHAPTER 13

## Acknowledgements

Dearest readers of this thesis,

First of all, I would like to thank every person who helped me reach my goal to obtain a doctor's degree in clinical science. During my PhD-trajectory, I realized that doing a PhD is not only about the acquisition of an expertise, but also about knowledge sharing and collaborative working. As such, I felt that as a PhD-candidate I relied on a decent number of surrounding individuals. Consequently, the quality of the dissertation also depends on the quality and the input of all individuals involved. Naturally, I feel honored to present this dissertation and by doing so I would like to thank my colleagues, friends, family and *all* those who supported me in this process. As such, there are countless people to thank and be grateful for. Still, I prefer to express my gratitude in person and keep this (written) section of the thesis concise. Those who know me may acknowledge that my communication style is rather to the point and sincere. Therefore, not unsurprisingly, this section of the thesis resembles that style.

Dear family and friends,

Thank you for believing in me, supporting me, challenging me to believe in myself and make the best of every situation.

Dear professor Maessen,

Dear Jos,

Thank you for giving me the opportunity to obtain my very first experience as a young and inexperienced doctor within the field of cardio-thoracic surgery. Being part of your team in the operating room and in the clinic has made me grow as a doctor and for sure on a personal level as well. Also, I would like to thank you for helping me reach the next important step in my life, which was defending this dissertation. Many thanks for supporting me throughout these important steps in the start of my career.

Dear Bart,
If there is any person that deserves a big "*thank you*", it is you. When I reached out to you as a medical student because I wanted to develop myself in the field of cardiological and surgical research, you searched for possibilities and soon we had a plan.

Obviously, the main goal of a PhD is to be fully engaged in a certain topic and to become an expert in the field. As such, with your help as my daily mentor, I have learned a lot about atrial fibrillation, surgical ablation, electrophysiology and cardio-thoracic surgery. What I would like to point out is that from the start of my PhD-trajectory, you have given me opportunities to grow and chances to develop myself. In my opinion, what I appreciated most is that you have let me be in control over my own PhD, since you gave me autonomy and freedom. Everything was possible, as long as the job was done.

Besides, everywhere we went, you proudly introduced me as your talented PhD-candidate. You have supported me wherever we went, you challenged me as I for sure need some resistance from time to time and I could rely on you as I knew you would have my back. In the end, you always spoke highly of me. Honestly, the past few years have been fun, unforgettable and a part of me grieves that it has now come to an end. Although I am ready for the next step in my career, I will for sure miss our meetings in the way they have been. I hope to extent our collaboration to the future and to set a nice example of team-work between a surgeon and an electrophysiologist (if I am ever lucky enough to become one).

A very big thanks to you Bart, I feel honored and lucky to have had you as my (co)promotor.

# CHAPTER 14

## About the Author

Claudia van der Heijden was born in Maastricht on the 27th of July in 1995 and studied Biomedical Science (Molecular Life Science) at the Maastricht University. During her final year, she went to the University of Chichester in the United Kingdom to experience an Erasmus study abroad in Sports and Exercise Science. Thereafter, she combined a master degree in medicine and clinical research at the Maastricht University. During this period, she started her collaboration on several projects concerning atrial fibrillation. After graduation from university, she combined her passion for research with the start of a clinical career at the department of cardio-thoracic surgery at the MUMC+, under the supervision of professor Jos Maessen. Exactly one year later, she was excited to officially start her PhD-trajectory in surgical and hybrid ablation of atrial fibrillation, as she could combine her interests for cardio-thoracic surgery and cardiology. In the summer of 2022, she participated in a summer school in electrophysiology Bordeaux Lyric Institute, where she attended classes from pioneers worldwide. Furthermore, she has published and presented several abstracts at (inter)national congresses, which until now she still enjoys very much. During the joined international Dutch and Belgium NVT-BACTS meeting in 2022, she received the award for best abstract. On stage she is often recognized by her red suit.

Claudia likes to find challenges in her spare time as well. Her passion for sports has evolved into a running adventure where she wants to have run a marathon on each continent of the world. In addition, she also wants to finish the marathons that are part of the worldwide Big 6. Another hobby of hers is cycling, especially if it can be combined with a nice holiday abroad. Besides the sportive and adventurous events, she cares a lot about her family and friends. She likes traveling; she is curious and an enthusiastic person. Close friends and family members describe her as: sportive, fanatic, energetic, intelligent, fierce, determined, laughs a lot, caring, and yes, sometimes a bit too direct.

# CHAPTER 15

## List of Publications

1. **van der Heijden CAJ**, Vroomen M, Luermans JG, Vos R, Crijns H, Gelsomino S, La Meir M, Pison L, Maesen B. Hybrid versus catheter ablation in patients with persistent and longstanding persistent atrial fibrillation: a systematic review and meta-analysis. Eur J Cardiothorac Surg Jan 28 2019.
2. Maesen B, **van der Heijden CA**, Bidar E, Vos R, Athanasiou T, Maessen JG. Patient-reported quality of life after stand-alone and concomitant arrhythmia surgery: a systematic review and meta-analysis. Interactive cardiovascular and thoracic surgery 2022;34:339-348.
3. **van der Heijden CA**, Verheule S, Olsthoorn JR, Mihl C, Poulina L, van Kuijk SM, Heuts S, Maessen JG, Bidar E, Maesen B. Postoperative atrial fibrillation and atrial epicardial fat: Is there a link? IJC Heart & Vasculature 2022100976.
4. Verhaert DVM, Linz D, Chaldoupi SM, Westra SW, den Uijl DW, Philippens S, Kerperien M, Habibi Z, Vorstermans B, ter Bekke RMA, Beukema RJ, Evertz R, Hemels MEW, Luermans JGLM, Manusama R, Lankveld TAR, **van der Heijden CAJ,** Bidar E, Hermans BJM, Zeemering S, Bijvoet GP, Habets J, Holtackers RJ, Mihl C, Nijveldt R, van Empel VPM, Knackstedt C, Simons SO,Buhre WFFA, Tijssen JGP, Isaacs A, Crijns HJGM, Maesen B, Vernooy Kand Schotten U (2022) Rationale and Design of the ISOLATION Study: A Multicenter Prospective CohortStudy Identifying Predictors for Successful Atrial Fibrillation Ablation in an Integrated Clinical Care and Research Pathway.Front. Cardiovasc. Med.
5. **van der Heijden CA**, Bidar E, Maesen B. Concomitant arrhythmia surgery should be a standard procedure in AF patients undergoing cardiac surgery. Journal of Cardiac Surgery 2022;37:3014-3015.
6. **van der Heijden CA**, Segers P, Masud A, Weberndörfer V, Chaldoupi S-M, Luermans JG, Bijvoet GP, Kietselaer BL, van Kuijk SM, Barenbrug PJ. Unilateral left-sided thoracoscopic ablation of atrial fibrillation concomitant to minimally invasive bypass grafting of the left anterior descending artery. European Journal of Cardio-Thoracic Surgery 2022;62:ezac409.
7. **van der Heijden CA**, Weberndörfer V, Luermans JG, van Kuijk SM, Vroomen M, Bidar E, Maessen JG, Pison L, La Meir M, Maesen B. Hybrid ablation of atrial fibrillation: A unilateral left-sided thoracoscopic approach. Journal of Cardiac Surgery.

8. **van der Heijden CA,** Weberndörfer V, Vroomen M, Luermans JG, Chaldoupi S-M, Bidar E, Vernooy K, Maessen JG, Pison L, van Kuijk SM. Hybrid Ablation Versus Repeated Catheter Ablation in Persistent Atrial Fibrillation: A Randomized Controlled Trial. JACC: Clinical Electrophysiology. 2023.

**Glossary of Abbreviations**

| | |
|---|---|
| AAD | Antiarrhythmic drug |
| AF | Atrial fibrillation |
| AFL | Atrial flutter |
| AT | Atrial tachycardia |
| ATA | Atrial tachyarrhythmia |
| AV | Aortic valve |
| BMI | Body mass index |
| BSA | Body surface area |
| CA | Catheter ablation |
| CABG | Coronary artery bypass graft |
| CAD | Coronary artery disease |
| CCTA | Coronary Computed Tomographic angiography |
| CFAE | Complex fractionated atrial electrograms |
| CM | Contrast management |
| CT | Computed tomography |
| CTI | Cavotricuspid isthmus |
| CVA | Cerebrovascular accident |
| EAT | Epicardial adipose tissue |
| EAT-V | EAT-volume |
| EP | Electrophysiologic or electrophysiology |
| GP | Ganglionated plexi |
| HA | Hybrid ablation |
| HU | Hounsfield units |
| INR | International normalized ratio |
| kV | Kilovoltage |
| LA | Left atrium or left atrial |
| LAA | LA appendage |
| LAD | Left anterior descending |
| LAEF | LA ejection fraction |
| LAVI | LA volume index |
| LIMA | Left internal mammary artery |

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|---|---|
| LIPV | Left inferior pulmonary vein |
| LMWH | Low molecular weight heparin |
| LSPV | Left superior pulmonary vein |
| LVEF | Left ventricular ejection fraction |
| MI | Mitral valve insufficiency |
| MIDCAB | Minimally invasive direct coronary artery bypass graft |
| MV | Mitral valve stenosis |
| MYO | Myocardial |
| MYO-V | MYO-volume |
| OAC | Oral anticoagulation |
| PAF | Paroxysmal AF |
| PCI | Percutaneous coronary intervention |
| PersAF | Persistent AF |
| POAF | Post operative AF |
| PV | Pulmonary vein |
| PVI | PV isolation |
| QOL | Quality of life |
| RCT | Randomized controlled trial |
| RDP | Right descending posterior |
| RF | Radiofrequency |
| ROI | Region of interest |
| RIPV | Right inferior pulmonary vein |
| RSPV | Right superior pulmonary vein |
| SAE | Serious adverse event |
| SCV | Superior caval vein |
| SE | Standard error |
| SMD | Standardized mean difference |
| SF-36 | Short Form 36 |
| SR | Sinus rhythm |
| SVT | Supraventricular tachyarrhythmia |
| TI | Tricuspid valve insufficiency |
| TTE | Trans thoracic echocardiography |
| TV | Tricuspid valve |