Improving the procedural safety and efficacy of radiofrequency catheter ablation for atrial fibrillation

Studies with special focus on non-paroxysmal atrial fibrillation

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Contents

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2 Abstract

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, and it is responsible for increased mortality and a reduced quality of life. Its prevalence is rapidly increasing. Catheter ablation has emerged during the past decade as a promising treatment option for paroxysmal and non-paroxysmal AF patients. We investigated various aspects of catheter ablation for AF, particularly in non-paroxysmal AF, with the aim of improving the safety and efficacy of such procedures.

Aims and methods

The patients enrolled in these studies were burdened by symptomatic, drug-refractory AF. Non-paroxysmal AF was the clinical arrhythmia in the majority of the individuals. All patients underwent an electrophysiological study and subsequently an ablation procedure that included pulmonary vein isolation and in selected cases, complex fractionated electrogram (CFE) ablation. The first study aimed to assess long-term outcomes in a population of exclusively non-paroxysmal AF patients who were followed up regularly for an average of 40 months. In the second study we investigated the effects of flecainide on the distribution and extension of CFE areas. For this purpose, two separate CFE maps (before and after flecainide administration) were created and compared. In the third study we assessed the correlation between catheter-tissue contact force and impedance fall. Qualified ablation points were selected and the corresponding contact force and impedance fall data were retrieved and analyzed.

Results and conclusions

An approach consisting of pulmonary vein isolation and CFE ablation appears to provide favorable long-term outcomes in a high proportion of patients. Multiple procedures are often required to attain positive results. Although post-ablation atrial tachycardia frequently occurs, it may represent a step towards long-term success. Longer AF duration and female gender appear to predict a higher likelihood of procedural failure.

Intraprocedural administration of flecainide in non-paroxysmal AF patients reduces the extension of CFE areas but preserves their original localization. The employment of a CFE-mean cut-off of 80 ms may facilitate the identification of stable CFE areas. The CFE areas that thus disappear may be functional and therefore may be an inappropriate target for ablation.

Increasing degrees of catheter-to-tissue contact force lead to a larger impedance fall suggesting improved lesion formation. Under stable catheter conditions, a contact force greater than 5 g seems to create adequate lesions. However, a contact force beyond 20 g is associated with late impedance rise, and may be a warning of an increased risk of complications.

3 List of publications

1) De Bortoli A, Ohm OJ, Hoff PI, Sun LZ, Schuster P, Solheim E, Chen J. Long-term outcomes of adjunctive complex fractionated electrogram ablation to pulmonary vein isolation as treatment for non-paroxysmal atrial fibrillation. J Interv Card Electrophysiol. 2013;38:19-26.

2) De Bortoli A, Shi LB, Wang YC, Sun LZ, Solheim E, Hoff PI, Schuster P, Ohm OJ, Chen J. Intravenous flecainide reduces the extension of complex fractionated electrogram areas but preserves their spatial localization. Submitted. Journal of Interventional Cardiovascular Electrophysiology, September 2014.

3) De Bortoli A, Sun LZ, Solheim E, Hoff PI, Schuster P, Ohm OJ, Chen J. Ablation effect indicated by impedance fall is correlated with contact force level during ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2013;24:1210-5.

4 Abbreviations

AAD: antiarrhythmic drug

AF: atrial fibrillation

AFCL: atrial fibrillation cycle length

AT: atrial tachycardia

AV: atrioventricular

CF: contact force

CFE: complex fractionated electrogram

CS: coronary sinus

ECG: electrocardiogram

GP: ganglionated plexi

IF: impedance fall

LA: left atrium

LAA: left atrial appendage

LAD: left atrial diameter

LVEF: left ventricular ejection fraction

MR: magnetic resonance

MV: mitral valve

PV: pulmonary vein

PVI: pulmonary vein isolation

RA: right atrium

ROC: receiver operating characteristic

SR: sinus rhythm

5 Introduction

"*Fibrillation, like flutter, may also on occasion be terminated in the auricle by cold or pressure very locally applied*"
Sir Thomas Lewis, 1925

5.1 DEFINITION AND HISTORY

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by rapid and chaotic activation of the atria. As early as in the 17th century, Harvey observed ante-mortem chaotic motion in the atria (presumably representing AF) during open-chest examination of dogs[1-3]. A century later de Sénac correlated palpitations and irregular cardiac pulsation, two common AF symptoms, with the presence of abnormalities in the mitral valve (MV)[1, 2]. In the early 20th century, with the development of the electrocardiogram (ECG), AF began to be paid more attention[4]. An irregular ventricular response, the absence of P waves and presence of fibrillatory atrial activity are well established ECG criteria for the diagnosis of AF[5].

5.2 EPIDEMIOLOGY

AF is the sustained cardiac arrhythmia that is most commonly encountered in clinical practice[5, 6]. In the western world, its prevalence is estimated at between 1% and 2% of the adult population, but it is significantly higher among individuals over 70 years of age[5, 7].

The annual incidence of AF was estimated by the Framingham Study to be 3.1/1000 in males and 1.9/1000 in females aged 55 to 64 years[8]. When considering individuals of between 85 to 94 years of age, these figures increase to 38/1000 and 31/1000[8]. Males are affected by more symptomatic forms of AF which also tend to appear earlier in life than in females[5, 6, 8, 9]. Data from the Rotterdam study estimated the lifetime risk of developing AF at about 25% in individuals aged 40 or more[9]. Given the growing number of elderly people in the western society, the prevalence of AF is likely to increase in the near future[10]. Epidemiological projections estimate a rise in the number of AF patients of up to 12 million in the United States and 13 million in Europe by 2030[11, 12].

The presence of idiopathic AF (lone AF) in an otherwise healthy subject accounts for around 10% of all AF patients[13, 14]. In the majority of the cases, AF is secondary to cardiac or non-cardiac conditions. Important cardiac conditions for the development of AF are valvular heart disease, ischemic heart disease, cardiac surgery, hypertension, myocarditis, and dilative and hypertrophic cardiomyopathy[8]. Important non-cardiac conditions for the development of AF are chronic obstructive pulmonary disease, hyperthyroidism, sleep apnea syndrome, acute infections, pulmonary embolism, binge drinking, obesity and diabetes[15-18].

5.3 PATHOPHYSIOLOGY

Despite over a century of research, the precise mechanisms that start and perpetuate AF are incompletely understood. Like other cardiac arrhythmias, AF requires a trigger for its initiation and a substrate for its maintenance.

In pioneering work performed during the 1950s, Moe et al. suggested that AF was maintained by multiple independent wavelets propagating randomly in a tissue with highly dispersed refractoriness[19]. This “multiple wavelet theory” postulated that a critical myocardial mass would be required for AF to be sustained indefinitely.

Moe’s observations were confirmed almost 20 years later by the work of Allessie et al., which demonstrated simultaneous propagation of multiple independent wavelets in an acetylcholine dog model of AF[20]. The validity of this theory also found support in the positive outcomes of the Cox maze surgical procedure in which atrial lesions are created with the aim of compartmentalizing the left atrium (LA)[21]. The multiple wavelet theory is currently the most highly credited among clinical electrophysiologists.

At the beginning of the last century, Sir Thomas Lewis observed that the central excitation wave of AF showed a strong predilection for moving around a stable channel[22]. His statements, although criticized by his contemporaries, are nowadays being reconsidered. There is increasing evidence that, at least in some cases, AF propagates through stable circuits, also called rotors, as they rotate around an unexcited core[23-27].

5.3.1 Triggers

In the 1990s, the availability of more sophisticated recording systems contributed to the search for the triggers of AF. Haïssaguerre first reported a series of three patients in whom AF episodes were triggered by an ectopic atrial focus[28]. The subsequent milestone work demonstrated that episodes of AF are consistently initiated by focal activity, mostly (94%) originating from the pulmonary veins (PVs). Ablation targeting these foci resulted in the disappearance of AF in 62% of the patients during the follow-up[29]. Apart from the PVs, additional sources of focal activity may be found in the LA body (particularly in the ligament of Marshall and MV annulus), the right atrium (RA) body (particularly in the crista terminalis, fossa ovalis and Eustachian ridge), superior and inferior caval veins and the coronary sinus (CS)[29-35]. Histological studies showed that the nature of increased PVs automaticity depends on the anatomy of the LA[36, 37]. Myocardial muscular sleeves extend deeply into the wall of the PVs, particularly in the left PVs[36, 37].The intersection of myocardial and connective tissue from the PV wall determines anisotropic conduction, which creates the perfect substrate to enhance focal activity[36, 38]. These findings received remarkable resonance in the field of invasive electrophysiology and virtually launched the era of AF ablation.

5.3.2 Substrate

There is solid evidence that, with the perpetuation of AF, the atria undergo electrical and structural remodeling[39-45]. Electrical remodeling occurs within a few minutes of the onset of AF and leads to a shortening of the refractory period and a reduction in conduction velocity[39, 42-45]. The changes that account for structural remodeling take place over a longer period of time and include hypertrophy of the myocytes, an increase in interstitial fibrosis, changes in the expression of ionic channels and reversal to a fetal gene program[45]. The ultimate result of this process is almost invariably the dilation of the LA[45]. According to Moe's theory, AF termination is dependent on the statistical probability of all wavelets extinguishing simultaneously. This implies that in a larger LA more wavelets coexist, thus increasing the likelihood that AF will persist for longer periods.

The classic aphorism "AF begets AF" has been widely used to describe the clinical evolution of this arrhythmia[40].

5.3.3 Contributing factors

Tentative observations have suggested that autonomic nervous system activity may be implicated in the AF process[46-51]. It has been demonstrated that the onset and perpetuation of AF are preceded by variations in autonomic tone[46]. Specifically, it appears that a parasympathetic response increases vulnerability to AF and may elicit PV firing[50, 51]. These assertions are further supported by the promising results of catheter ablation aimed at the ganglionated plexi (GP)[47-49].

High circulating levels of inflammation markers, such as C-reactive protein and myeloperoxidase, are frequently found in AF patients, suggesting that there may be a correlation between AF and inflammation[16, 45, 52-55]. This association is also supported by the high incidence (up to 50%) of AF in patients undergoing cardiac surgery[52, 54, 56, 57]. However, currently available data do not clarify whether inflammation is the cause or the consequence of AF.

Finally, single and multiple gene mutations have been reported in families with a high burden of AF. Some of these genes codify for ion channel proteins (e.g. KCNx family) whilst others are implicated in intercellular connection (e.g. Connexin40)[58, 59]. Knowledge about AF genetics is growing rapidly. This new information will enhance our understanding of AF mechanisms and may enable a genotype-based medicine to be developed[60].

5.4 CLINICAL IMPLICATIONS

Common symptoms such as palpitations, fatigue, shortness of breath and dizziness are often correlated with the onset of AF. On the other hand, sustained AF episodes may lead to progressive deterioration of atrial and ventricular function that may culminate in overt congestive heart failure.

Episodes of AF occur in >50% of patients with concomitant dysfunction of the sinus node (sick sinus syndrome) which suggests a causal relationship[41, 61]. Sick sinus syndrome is currently the most common indication (>50%) for permanent pacemaker implantation[61, 62].

Because of reduced blood flow in the LA and left atrial appendage (LAA), AF poses a serious risk of systemic embolization, particularly to the brain[63]. Patients at high risk (assessed by their $CHADS_2$ or CHA_2DS_2VASC score) are therefore required to undergo systemic anticoagulation as a preventive measure against cerebrovascular accidents[64, 65]. Although stroke is the most feared complication of AF and results from major cerebral embolization events, some studies have suggested that micro-embolization over time could be related to various degrees of dementia[66, 67].

Finally, data from the Framingham Study have showed that the presence of AF alone is associated with a 1.5 to 1.9-fold increase in risk of mortality[68].

5.5 CLASSIFICATION

AF is classified according to the duration of the episodes: "*paroxysmal*" indicates recurrent AF episodes terminating spontaneously within seven days; "*persistent*" indicates AF lasting beyond seven days or requiring electrical or pharmacological cardioversion to be stopped; "*longstanding persistent*" indicates persistent AF lasting over one year[5, 69]. The term "non-paroxysmal", although not included in the current guidelines, is commonly used to identify persistent and longstanding persistent AF.

Finally, the expression "*permanent AF*" identifies those patients in whom AF is accepted and restoration of the sinus rhythm (SR) will no longer be attempted[5].

5.6 THERAPEUTIC OPTIONS

5.6.1 Direct current cardioversion

Direct current cardioversion is often employed in the management of AF patients. Although the acute success of this intervention is excellent, recurrences of AF are very common (71%-84% at one year)[5, 70, 71].

Direct current cardioversion alone is of limited importance in the long-term management of AF patients. However it may be an important tool when used in combination with medical therapy or with catheter ablation[5].

5.6.2 Antiarrhythmic medications

Antiarrhythmic drug (AAD) treatment has for several decades been the main treatment option for AF patients. All AADs currently available are flawed by their variable efficacy and by some degree of pro-arrhythmogenic effects[5].

AAD treatment can be employed in two different strategies: either aiming at controlling the ventricular rate (rate-control strategy), or at restoring and maintaining SR (rhythm-control strategy). In the AFFIRM study, over 4000 AF patients were randomized to either a rhythm-control or rate-control strategy and were followed for a median of 3.5 years. The rhythm-control group suffered higher mortality (although not statistically significant, $p=0.08$), more hospitalizations and more adverse events than the rate-control group[72]. However, a sub-analysis of the AFFIRM study suggested that in elderly patients the risk of drug adverse events may outweigh the benefit of a rhythm-control strategy. Moreover, they showed that the higher mortality in the rhythm-control group was mainly due to non-cardiovascular deaths[73]. The RACE study showed that rhythm-control therapy was associated with improvement of the left ventricular function and a reduction in the left atrial diameter (LAD)[74]. Similarly, the SAFE-T study concluded that sustained SR was associated with an improved quality of life and exercise performance[75].

5.6.3 Surgery

As cardiac surgery improved, more and more interest was focused on developing a surgical treatment for cardiac arrhythmias. After extensive testing on dog models in the mid-1980s, Cox managed to establish a surgical approach (Cox maze procedure) that could be employed in humans and that gave excellent results in both paroxysmal and non-paroxysmal AF[21].

Despite refinements in the technique, the Cox maze procedure remains highly invasive. Nowadays only AF patients who have to undergo cardiac surgery for other reasons (bypass graft, valve replacement, etc.) are considered as candidates for this operation[69].

In the last decade, off-pump techniques such as surgical AF ablation and the totally endoscopic AF ablation have been developed. Pulmonary vein isolation (PVI) and LAA obliteration can be additionally performed in these procedures. However, the indications for and clinical importance of these new approaches are still unclear[69].

5.6.4 Catheter ablation

In an attempt to offer a less invasive alternative to the Cox maze procedure, catheter ablation for AF was developed and promptly emerged as an additional therapeutic option. Following several randomized trials, it is now recognized that catheter ablation is superior to AADs in improving AF symptoms and quality of life[76-78]. Furthermore, a number of retrospective studies were able to show that AF-free patients following successful ablation are at similar risk of stroke and mortality as patients without AF[79-81]. However, a definite answer to whether catheter ablation improves stroke and mortality risk is still awaited and will probably follow the completion of specifically designed multicenter, randomized trials such as the CABANA and EAST trials[82, 83].

5.6.5 Atrioventricular (AV) node ablation

Symptomatic AF patients who are refractory to AADs and who do not qualify for AF ablation (because of exclusion criteria, poor prognosis or patient's preference) can be referred to pacemaker implantation (preferably biventricular pacing devices) and subsequently to AV node ablation. In this brief procedure, the physiological AV conduction is permanently interrupted by means of catheter ablation[84, 85]. In this way, AF will continue in the atria, but the ventricular response will be regulated by the pacemaker. Previous studies demonstrated that this strategy can improve symptoms and increase left ventricular ejection fraction (LVEF) in selected patients[86, 87].

5.7 CATHETER ABLATION TECHNIQUES

Catheter ablation is a percutaneous procedure in which catheters are advanced to the heart from a mini-invasive vascular access. The procedure is performed under fluoroscopic guidance and, more recently, assisted by a three-dimensional navigation system. Catheter ablation for AF can be performed using various energy sources (such as cryoenergy, ultrasound and laser) but radiofrequency is by far the most frequently used worldwide. Application of radiofrequency energy induces irreversible thermal damage in the myocardium thus preventing impulse formation and/or conduction in the targeted area.

5.7.1 Trigger-based ablation

Successful ablation aimed at focal sources of AF was first reported in 1994 by Haïssaguerre[28]. Following the definition of the important role of electrical activity arising from the PVs, focal ablation at these foci was initially attempted[29]. Modest outcomes and high incidence of PV stenosis following focal ablation led to the development of PVI procedures[88, 89]. This strategy was first performed with a segmental approach, targeting the earliest site of activation (breakthrough) at the PV ostium[90, 91]. Later, Pappone introduced the circumferential approach, in which PVI was achieved by deploying circumferentially contiguous lesions at a distance ≥5 mm from the PV ostia (Figure 1)[92]. This purely anatomical approach provided satisfactory results with shorter procedures and an improved safety profile.

PVI has now become the cornerstone of AF ablation. There is unanimous agreement that PVI represents the minimum endpoint for ablation of both paroxysmal and non-paroxysmal AF[69]. Moreover, restored PV conduction can be demonstrated in the vast majority of patients admitted for a repeated ablation procedure[93-95]. Electrical reconnection of the PVs is believed to be the principal responsible mechanism for recurrences of AF. Finally, patients in whom extra-PV ectopies have been demonstrated can benefit by additional ablation targeting these foci[31, 33, 34].

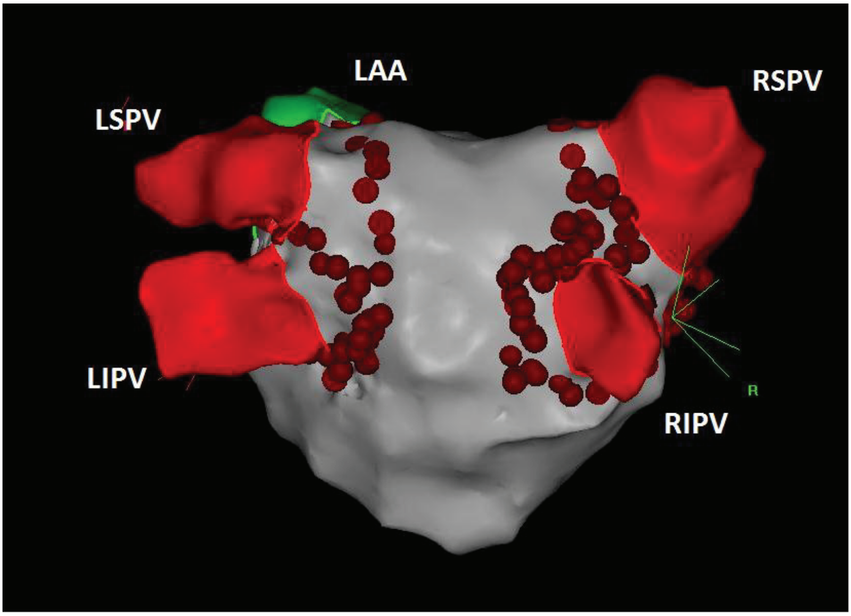

Figure 1 – Posteroanterior view of the left atrium (reconstructed by the Carto3™ system), showing displacement of ablation lesions (red dots) for circumferential pulmonary vein (PV) isolation. LAA: left atrial appendage, LSPV: left superior PV, LIPV: left inferior PV, RIPV: right inferior PV, RSPV: right superior PV.

5.7.2 Substrate-based ablation

Although stand-alone PVI has provided satisfactory clinical results in paroxysmal AF, its application appears to be insufficient in non-paroxysmal AF. With the exception of a minority of centers, there is agreement that in these patients there is a need to additionally target the substrate that is perpetuating the arrhythmia[34, 69].

Current strategies to modify AF substrate include linear ablation, complex fractionated electrogram (CFE) ablation, GP ablation and rotor ablation.

The first report of curative catheter ablation for non-paroxysmal AF was presented by Swartz et al. in 1994, and consisted of a set of linear lesions in the LA[96]. In the same year, a similar approach with linear ablation targeting the RA was described by Haïssaguerre[97].

Although successful, linear ablation was initially restrained by the limited technology available and by a high rate of complications. Nowadays, several centers perform a roof line (connecting the left superior PV with the right superior PV) and a mitral isthmus line (from the inferior aspect of the left inferior PV to the MV annulus) as an adjunctive strategy to PVI (Figure 2)[98].

In the late 1990s, the presence of fractionated electrograms (later denominated CFEs) was first associated with areas of slow conduction and pivot points and believed to represent crucial regions for AF maintenance[99]. In an immunohistological study, CFE areas were found to represent enhanced tissue fibrosis with a reduced expression of gap junction proteins[100].

Involvement of CFE areas in AF maintenance is further supported by the clinical results following ablation aiming at these regions. Nademanee et al. established a new ablation approach by solely targeting CFE areas in paroxysmal and non-paroxysmal patients. AF termination was achieved in 95% of the patients and SR maintenance in 91% at one year follow-up[101]. However, these results could not be reproduced by other centers.

In spite of the questionable worth of stand-alone CFE ablation, adjunctive CFE ablation to PVI is used by several centers in the treatment of non-paroxysmal AF (Figure 3)[98].

A combination of linear and CFE ablation is performed in the "stepwise approach"[102, 103]. In this technique, ablation is aimed at sequential targets: PVI, superior vena cava and CS isolation, ablation at sites of complex electrical activity and finally roof and mitral lines. Previous reports have shown remarkable acute and long-term success following these extensive procedures[102, 104, 105]. Moreover, their authors were able to show that the order of the targets was irrelevant to the clinical outcomes, suggesting similar importance of all these mechanisms to the maintenance of AF[103].

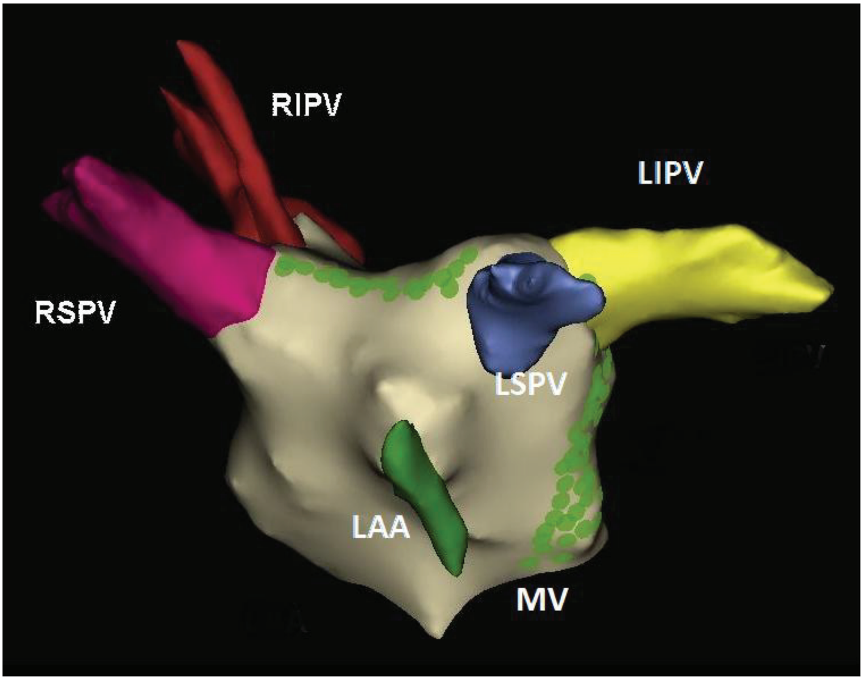

Figure 2 – Anteroposterior view of the left atrium (reconstructed by the EnSite NavX™ system), showing displacement of ablation lesions for roof line (green dots between RSPV and LSPV) and mitral isthmus line (green dots between LIPV and the MV annulus). MV: mitral valve, other abbreviations as in Figure 1.

The epicardial localization of GPs makes them amenable to ablation. It is widely accepted that autonomic innervation is involved in the pathophysiology of AF.

However, clinical outcomes from GP ablation, either alone or in combination with PVI, are not consistent and more research is needed to assess the importance of these targets in AF ablation[47-49].

Recent developments in mapping tools have led to the reconsideration of the localized source hypothesis whereby organized rotors may drive and maintain human AF. Narayan et al. employed custom software to map AF rotors and reported impressive outcomes following PVI and rotor ablation[26]. The results of ongoing multicenter trials may well produce more evidence in support of rotor mapping and ablation.

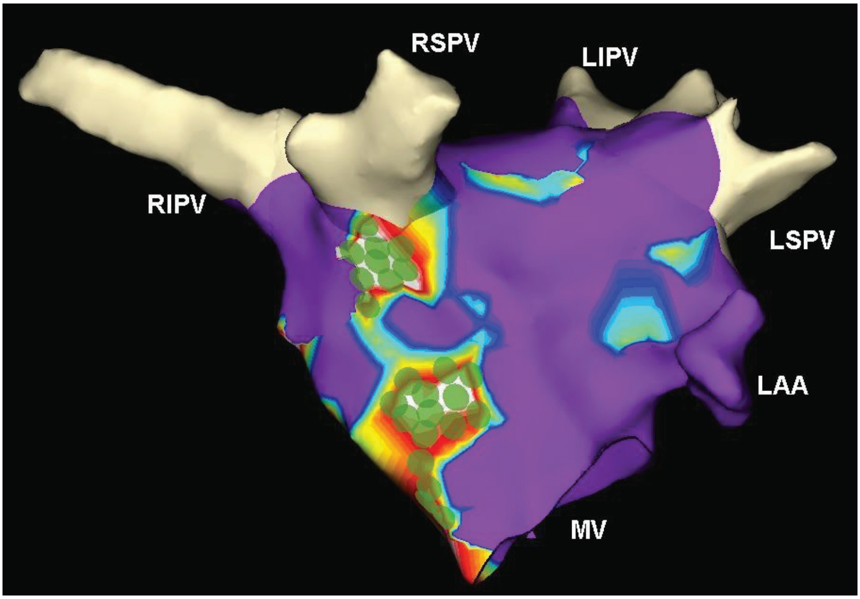

Figure 3 – Right anterior oblique view of the left atrium (reconstructed by the EnSite NavX™ system), showing a complex fractionated electrogram map and displacement of ablation lesions (green dots) corresponding with areas of high fractionation (white and red color). Abbreviations as in Figures 1 and 2.

5.7.3 Procedural endpoints

One of the factors contributing to the widespread use of PVI is its straightforward endpoint. Electrical conduction block from the LA to the PV is used by most centers to document PVI, and is considered a sufficient endpoint for paroxysmal AF ablation[106]. A small proportion of operators may employ additional pacing maneuvers to increase the specificity of PVI assessment[107, 108].

Conversely, catheter ablation in non-paroxysmal AF is currently restrained by undefined endpoints. AF termination, non-inducibility, conduction block over linear lesions, CFE abatement and the disappearance of vagal responses have all been utilized in clinical practice. While some of these endpoints are technically difficult to assess, others are flawed by a high degree of subjectivity and their clinical importance has yet to be confirmed[109].

5.7.4 Indications for atrial fibrillation ablation

Catheter ablation is a therapeutic option that is currently considered only for symptomatic AF patients who are refractory or intolerant to at least one Class I or Class III AAD[69]. The latest HRS/EHRA/ECAS expert consensus statement suggests the following indications:

Paroxysmal AF: catheter ablation is recommended, class I, level of evidence A

Persistent AF: catheter ablation is reasonable, class IIa, level of evidence B

Longstanding persistent AF: catheter ablation may be considered, class IIb, level of evidence B

It is recognized that in certain cases, catheter ablation may also be regarded as first-line therapy for AF. Finally, it is emphasized that such indications only apply if AF ablation is performed in experienced centers by appropriately trained electrophysiologists[69].

5.7.5 Clinical outcomes

The field of AF ablation has undergone a huge expansion in the past decade. In order to improve outcomes, new ablation techniques and technology have been developed.

For several reasons, outcomes of AF ablation as retrieved from the literature have been inconsistent. As suggested by a recent meta-analysis, heterogeneity in outcomes may have its origin in differences between patient populations, ablation techniques, definitions of procedural success and follow-up monitoring modalities[110].

It is acknowledged that the outcomes of paroxysmal and non-paroxysmal AF should be considered separately, as they reflect two different stages of the disease[69]. In five randomized clinical trials in which PVI was compared to AAD treatment for paroxysmal AF, success rates of ablation ranged between 66% and 89% whereas AAD outcomes lay between 16% and 42%[76-78, 111, 112].

Recently, two independent studies (RAAFT-2 and MANTRA-PAF) compared in a randomized fashion AADs to catheter ablation as first-line therapy in patients with paroxysmal AF[113, 114]. The RAAFT-2 study concluded that patients undergoing catheter ablation experienced a lower rate of recurrences of AF than those administered AADs[114]. The MANTRA-PAF study, on the other hand, found no significant difference in the cumulative AF burden after a two-year follow-up[113].

Outcomes of non-paroxysmal AF are more controversial as there is no consensus on what should be the endpoint after successful PVI. Moreover, several ablation strategies are employed and the results are usually inconsistent between different centers[115, 116]. Stand-alone PVI is believed to be insufficient in these patients and clinical success is poor (20%)[109, 116]. Adjunctive roof and mitral linear ablation produces improved outcomes in patients with non-paroxysmal AF. Arya et al. reported a 12-months success rate of 75% while Willems et al. had a 69% success rate after a mean follow-up of 16 months[109, 117]. Adjunctive CFE ablation after PVI has also been shown to be beneficial with outcomes ranging from 56% to 94% in several single and multi-center trials[118-120]. Ultimately, a step-wise approach seems to confer the best outcomes, with the proportion of AF-free patients lying between 79% and 95%[104, 121].

Data from a worldwide survey on the efficacy of AF ablation reported a medium-term success rate of around 75% in paroxysmal AF and 64% in non-paroxysmal AF patients off all AADs[122].

5.7.6 Shortcomings

Recurrences of arrhythmias

Recurrences of arrhythmias following AF ablation are frequent. The most common arrhythmia to relapse is AF. A large-scale study revealed AF recurrence rates of 31.5% in paroxysmal and 41.0% in non-paroxysmal AF patients[123]. Similar findings were demonstrated by other studies[110, 124, 125]. AF recurrences are most frequent in the mid-term (<1 year) but can also occur >3 years after the index procedure[124, 126]. Patients who experience multiple AF recurrences are often considered for a repeat ablation procedure.

Recurrences of atrial tachycardia (AT) on the other hand, mostly occur during the first months following ablation and particularly in non-paroxysmal AF patients[119, 127, 128]. Occurrences of AT are believed to be mediated by catheter ablation itself and can significantly complicate the management of these patients[129]. These arrhythmias respond poorly to AAD and they usually lead to higher ventricular rates and more severe symptoms. A repeat dedicated ablation session is the most effective treatment for post-ablation AT.

Complications

Catheter ablation for AF may lead to a wide range of complications, some of which may be life-threatening. A worldwide survey incorporating over 16,000 patients and 20,000 procedures reported an overall complication rate of 4.5%, with death occurring in 0.15% of the patients. The most common complications were cardiac perforation leading to cardiac tamponade (1.31%), neurological events (stroke or transient ischemic attack, 0.94%) and access-site vascular complications (1.47%)[122]. It must be noted that this survey had a potential bias. Complication rates in the "real world" might be higher. Other known complications of AF ablation include PV stenosis, phrenic nerve damage and atrio-esophageal fistula, the latter being very rare but almost invariably fatal[130].

Finally, concerns have been raised for the remaining atrial functionality in those non-paroxysmal AF patients who have undergone extensive ablation[131]. Preliminary results from an analysis of 40 patients after step-wise ablation suggest that in spite of significant scarring, left atrial functionality recovered in those who maintained SR[105].

Cost-effectiveness

Despite the increasing enthusiasm for AF ablation, it must be reminded that the techniques are still under development and that these procedures may also increase the economic burden on healthcare systems.

Compared to AAD treatment, AF ablation has a high initial cost. Canadian data estimated a total cost per AF ablation procedure of 9,590 C$. Another report suggested that AF ablation was cost-neutral compared to AAD, four years after the procedure[132, 133]. Similarly in the UK, AF ablation was found potentially cost-effective if the benefits in terms of quality of life were maintained for five years[134]. Although these studies seem to favor AF ablation, it must be noted that they rely on the assumption that outcomes at 12 months are maintained until five years from the initial procedure. Moreover, these studies do not take into account that a significant proportion of patients continue AAD treatment after having undergone AF ablation thus leading to additional cost and risk of AAD side-effects[135]. A recent review concluded that the scientific evidence currently available (particularly in regard to hard endpoints) is insufficient to permit conclusions about the cost-effectiveness of AF ablation to be drawn[135].

5.8 CURRENT CHALLENGES AND CONTROVERSIES OF AF ABLATION

Challenging and unresolved aspects of AF ablation include patient selection, incomplete understanding of the mechanisms involved in AF and quality assurance of ablation lesions.

Clinical outcomes of AF ablation can be very different from patient to patient. It is reasonable to suppose that improved patient selection would ameliorate ablation outcomes and avoid the risk of complications in individuals with a poor prognosis. The definition of pre-procedural parameters that can predict long-term outcomes is therefore an open issue in AF ablation.

So far parameters such as age, gender, AF type, body mass index, LAD, LVEF, AF cycle length (AFCL), AF history, presence of diabetes, hypertension or other cardiac disease have been examined with widely variant results[121, 123, 124, 136-139]. Even echocardiographic measurement of LAD, a parameter which may depict the degree of remodeling of the LA, has not shown consistency between studies[140-142]. Moreover, these parameters may be related and act as reciprocal confounders. For this reason it could be worthwhile to define statistical models that allow such complex interactions to be taken into account.

Although there is unanimous agreement on the importance of electrical activity arising from the PVs in triggering AF, the mechanisms that sustain the arrhythmia are poorly understood. This aspect is particularly relevant in non-paroxysmal AF patients in whom a trigger-based ablation (with stand-alone PVI) does not appear to be sufficient to guarantee satisfactory results[109, 116]. New insights into the pathophysiology of AF may allow the development of a mechanistic (rather than empirical) ablation strategy for non-paroxysmal AF patients. Such a strategy may enable us to obtain positive long-term outcomes with the minimum extent of collateral myocardial damage. A definition of precise procedural endpoints is also required to improve reproducibility between different centers.

Electrical reconnection of the PVs is often observed in AF patients who are accepted for a second ablation procedure[93-95]. A repeat PVI usually improves long-term results. Catheter ablation is mostly performed under fluoroscopic guidance. Although three-dimensional navigation systems are extremely useful to the electrophysiologist, catheter stability and contact with the atrial wall are highly dependent on the experience and the tactile skills of the operator.

Although this has never been formally demonstrated, it is believed that intermittent or poor contact during the first few seconds of ablation may result in the development of local myocardial edema that can hamper lesion transmurality[143]. Under such circumstances, the tissue is only partially damaged and the healing of the edema (a process that can take from hours to days) may restore electrical conduction (leading for instance to PV reconnection)[144, 145].

Proposed strategies to tackle this issue include pacing maneuvers, prolonged observation time, administration of steroids, isoproterenol or adenosine and improved catheter stability and contact[31, 34, 106-108, 146, 147]. The latter aspect is believed to be crucial. No matter what the ablation target is, good quality lesions are fundamental to obtaining the best results from catheter ablation[95]. Previous experimental work has shown that higher contact force (CF) leads to larger and deeper lesions[148].

In the past, parameters such as catheter tip temperature, electrogram voltage reduction and impedance fall (IF) have been used as surrogates for catheter-tissue contact to monitor lesion development[149]. Although useful, these parameters are flawed by various limitations which make their interpretation rather poor and unspecific.

Recently, CF sensing ablation catheters, which allow accurate, quantitative measurement of the CF applied to the cardiac tissue, have been developed. Data from initial experience suggest that this technology is of great value, although further investigations are still needed to define and validate a safe and effective range of CF for clinical application[94, 150-152].

6 Aims

The aims of these studies were to investigate clinical results and technical aspects of AF ablation.

1. To analyze long-term follow-up results and predictors of arrhythmia recurrence in a population of non-paroxysmal AF patients treated exclusively with a combined PVI + CFE ablation strategy.

2. To determine the effects of intravenous flecainide on the distribution and extension of CFE areas in patients undergoing catheter ablation for non-paroxysmal AF.

3. To evaluate the relationship between catheter-to-tissue CF and IF during catheter ablation for AF.

7 Methods

Patient Material

These three studies included a total of 124 symptomatic AF patients that had previously attempted at least one AAD without success. Paper I and II involved only non-paroxysmal AF patients, while paper III involved mostly paroxysmal AF patients (94.3%) undergoing a first ablation procedure.

The average age of the patients was 59±8 years. Females were in a minority (18/124, 14.5%). Hypertension was common (51/124, 41.1%), but there was a low incidence of structural cardiac disease (17/124, 13.7%). The echocardiographic data indicated a tendency to LA enlargement although the LVEF was preserved (>45%) in all the patients. Beta-blocker was by far the most common class of AAD attempted.

All patients underwent systemic anticoagulation with warfarin. An international normalized ratio value within the therapeutic range (>2.0) for at least four weeks was required before AF ablation. Detailed information about patient demographics is provided in each paper.

Patients were referred to our institution from all over Norway. The study population was enrolled from the operation schedule. The studies were approved by the Regional Ethics Committee of Western Norway and were performed in accordance with the Declaration of Helsinki.

Electrophysiological study and ablation set-up

All the procedures included in the studies were performed at Haukeland University Hospital between 2007 and 2013. Conscious sedation with diazepam and morphine was used in all the patients and the procedures. Patients were admitted at the hospital one day prior to procedure, and warfarin was stopped two days before the procedure. Low molecular weight heparin was administered if necessary.

Vascular access was obtained by puncturing the right and left femoral veins. Left atrial catheterization was performed via a transseptal puncture or via a patent foramen ovale, where available. A 20-pole mapping catheter (Livewire™, St Jude Medical) was positioned in the RA with the distal poles in the CS. A 10-pole circular catheter (Lasso™, Biosense Webster or Optima™, St. Jude Medical) was inserted through a long sheath in the LA and was used to confirm PV isolation. Finally, an open-irrigated ablation catheter (specific models are reported in each individual paper) was advanced in the LA through the same transseptal puncture as for the long-sheath and was used for mapping and ablation.

A three-dimensional electroanatomical system (Carto3™, Biosense Webster or EnSite NavX™, St. Jude Medical) was employed in all the procedures for catheter navigation and for mapping purposes. An advanced recording system (Lab System Pro™, Bard Electrophysiology) was used to visualize and record intracardiac electrograms.

Radiofrequency ablation was always delivered in a temperature-controlled mode at an irrigation flow-rate of 15-20 ml/min and a temperature cut-off of 50°C. Energy was generally delivered for 60 s at each location and the power was titrated to a maximum of 35W for PVI or 40W for cavotricuspid isthmus ablation. In paper III, power was limited to 30W.

Ablation targets

PVI was performed by ablating circumferentially, in a point-by-point pattern at the PV antra (1-2 cm proximally to the ostium). Entrance block (confirmed by the 10-pole circular catheter) was used as endpoint for PVI. Differential pacing from the LAA was used to confirm PVI in the left PVs. Patients in AF at the end of the procedure received a direct current cardioversion before sheath removal in order to document PVI in SR.

CFE ablation was performed in non-paroxysmal AF patients targeting areas of highly fragmented potentials (CFE-mean<80 ms). Prior to ablation, a CFE map was created by the electroanatomical mapping system by sampling continuous recording from the distal electrode of the ablation catheter. In paper II, a second CFE map was collected before ablation but after administration of intravenous flecainide.

CFE mapping and ablation were performed in the LA in all patients. Additional mapping and ablation were delivered in the CS and RA in selected patients at the operator's discretion. The endpoint of CFE ablation was the disappearance of fractionated electrograms.

Linear ablation was performed exclusively to treat ATs. Activation mapping and entrainment pacing were employed to locate the critical isthmus. Endpoints of linear ablation were AT termination and, if possible, demonstration of conduction block across the line.

A cavotricuspid isthmus line was performed in patients with a clinically documented history of typical atrial flutter. Bidirectional conduction block was the endpoint of cavotricuspid isthmus ablation.

Follow-up

Patients were monitored for 24 hours and usually discharged the day after the procedure under warfarin. Anticoagulation and AAD were continued for at least three months regardless of procedural outcome. All patients were followed up on an ambulatory basis at three, six and 12 months with clinical examination, ECG and echocardiography. Depending on arrhythmia recurrence and symptoms, medications were either discontinued or modified. After the first year, follow-up was performed in selected patients depending on the clinical situation.

We defined "success" when patients remained completely arrhythmia-free after a blanking period of three months; "clinical improvement" when previously persistent AF patients had only occasional short episodes of self-terminating arrhythmia but great improvement of symptoms; "failure" when patients experienced recurrences of persistent arrhythmia.

Paper I included repeated ablation procedures that were scheduled in 36 unsuccessful patients at least six months after the index procedure. In paper II clinical outcomes were evaluated only by considering the index procedure.

Data collection

Data in paper I were retrieved from the procedural reports and from the patients' medical journal.

Data in paper II were retrieved from the three-dimensional navigation system (EnSite NavX). Every CFE mapping point was annotated on a pre-formatted form with the corresponding CFE-mean value, average electrogram amplitude and anatomical location. CFE and scar areas were measured by the system and expressed in cm^2.

Data in paper III were retrieved from the three-dimensional navigation system (Carto3). Qualified lesion points were selected according to specific enrolling criteria. CF and impedance data were registered automatically by the system. Anatomical location of points and force-direction angle were annotated on a pre-formatted form by a remote operator.

Statistics

Continuous variables were presented as mean ± standard deviation or as median and interquartile range when data did not follow a normal distribution. The Kolmogorov-Smirnov test was used to confirm normal distribution of the data. Categorical variables were presented as percentages and compared by the chi-squared test. For comparison between continuous variables we used paired and unpaired t-tests, Wilcoxon signed-rank test and Mann-Whitney U test as appropriate. In paper III we used the Kruskal-Wallis test and the Friedman test as non-parametric alternatives for the analysis of variance. Associations between continuous variables were presented as rank correlations (Spearman's rho). Univariate and multivariate logistic regressions were used for predictor analysis. Optimal cut-offs for specific continuous predictors were determined by minimizing the distance from the optimal test in a receiver operating characteristic (ROC) curve. Statistical analysis was performed with SPSS Statistics for Windows, Version 19.0 (IBM Corp. 2010). All tests were two-tailed. A p-value <0.05 was considered to be statistically significant.

8 Results

Paper I

We studied 66 non-paroxysmal AF patients (mean age 58±9 years, 86% male) who underwent exclusively PVI + CFE ablation and were followed up for a mean of 40±14 months.

After the first ablation procedure, 21 (31.8%) patients were arrhythmia-free, 20 (30.3%) displayed clinical improvement and 25 (37.9%) suffered recurrences of persistent atrial arrhythmias. After multiple procedures (112 in total, mean 1.7±0.7 per patient), 38 (57.6%) patients were arrhythmia-free, 15 (22.7%) displayed clinical improvement and 13 (19.7%) suffered recurrences of persistent atrial arrhythmias.

A total of five major complications were recorded (4.5%). Twenty-five patients (37.9%) developed AT following PVI + CFE ablation. In 12 cases a repeat ablation session was required to treat the AT.

Thirty-six patients (54.5%) underwent multiple procedures. In all the repeat procedures, manifest electrical reconnection of one or more PVs was observed and additional PVI was therefore performed. All 12 of those who started the repeat procedure in SR and all 8 of those who started in AT displayed a procedural benefit, compared to 9 out of 16 of those who started the repeat procedure in persistent AF ($p<0.05$).

Multivariate analysis revealed that female gender and duration of uninterrupted AF were independent predictors of long-term procedural failure ($p=0.01$ and 0.004 respectively, OR 12.31 and 1.49 respectively). ROC analysis estimated an uninterrupted AF duration of 3.5 years as the optimal cut-off point for predicting procedural failure (sensitivity 85%, specificity 74%).

Paper II

We enrolled 23 non-paroxysmal AF patients (mean age 59±7 years, 91% male) to study the effect of intravenous flecainide on the distribution and extension of CFE areas.
Before flecainide administration, a CFE-mean value cut-off <120 ms resulted in CFE areas covering an average of 52.6±26.6% of the total LA surface. A lower CFE-mean cut-off resulted in a significantly smaller proportion of the CFE area.

Following flecainide administration, the duration of the QRS complex was slightly but significantly prolonged (104±15 vs. 111±18 ms, p<0.001). The CFE-mean value increased in all patients, from an average of 111.5±55.3 ms to 132.3±65.0 ms (p<0.001). An analogous increase was found by separately analyzing each segment. AFCL in the LAA was similarly affected (155.1±20.8 vs. 195.0±27.1 ms, p<0.001). Overall, average atrial electrogram amplitude decreased significantly after flecainide administration (0.30±0.31 vs. 0.25±0.20 mV, p<0.001) as well as the electrogram amplitude measured in the LAA (0.96±0.68 vs. 0.64±0.34 mV, p<0.01). The area detected as scar by the system increased (1.6±4.2 to 4.2±6.6 cm^2, p<0.01) in all patients following flecainide administration. Prolongation of CFE-mean values and abatement of electrogram amplitude led to a decrease in the extension of CFE areas. We observed a reduction of CFE area in all regions and in all the patients (average 32.9%) after flecainide administration. We observed a large degree of spatial preservation of CFE areas following flecainide administration, with an average of 80.9% of preserved CFE areas.

A lower CFE-mean value was found in the portions of CFE areas that were preserved than in those that disappeared (73.8±17.4 vs. 89.4±17.1 ms; p<0.001). ROC analysis estimated a CFE-mean value of 78 ms as the best cut-off point for predicting the disappearance of CFE areas following flecainide administration (71% sensitivity, 66% specificity). A higher electrogram amplitude was found in the preserved CFE portions compared to those that disappeared (0.37±0.28 vs. 0.28±0.20 mV; p<0.001). After a mean follow-up of 22.1±5.0 months, 65.2% of patients maintained stable SR.

Paper III

We studied 35 AF patients (mean age 61±9 years, 80% male) to explore the relationship between catheter-to-tissue CF and IF during ablation.

Average CF recorded was 9.0 g (IQR 9.0, total range 1-48 g). Higher CF and maximum IF were recorded in the right superior PV than in the left inferior ($p<0.001$) and left superior PV ($p<0.05$).

Data points were allocated to five groups according to CF value. Group I included points with CF ranging from 1 to 5 g (n=107), Group II from 6 to 10 g (n=131), Group III from 11 to 15 g (n=76), Group IV from 16 to 20 g (n=36) and Group V for lesions exceeding 20 g (n=44). All the groups showed an acute IF in the first 10 s of ablation, followed by a plateau phase in Group I and by a progressive fall in the other groups. Maximum IF appeared at 50 s of ablation in Groups II, III and IV, and at 40 s in Group V. Group V showed a statistically significant rise in impedance during the last 20 s of ablation, from a median IF of 20.0 Ω to 15.0 Ω ($p<0.01$).

Comparisons between the groups showed that levels of IF were statistically different ($p<0.001$) at each time point between all groups, except between Groups III and IV. Similar results were found for maximum IF. A linear correlation was demonstrated between maximum IF and CF (Spearman's rho=0.54; $p<0.01$).

Finally, we evaluated the impact of force-direction angle on CF and maximum IF. The median CF of the points with 0-30° (4.0 g) was significantly lower than those with 30-60° (11.0 g, $p<0.001$) and 60-135° (10.0 g, $p<0.001$). Similar results were also found for maximum IF (10.0 Ω, 15.0 Ω and 16.0 Ω) in lesions with force-direction angles of 0-30°, 30-60° and 60-135° respectively ($p<0.001$).

9 General discussion

The field of AF ablation has expanded significantly in recent years. Regarded as an experimental approach less than two decades ago, this treatment has now become a routine procedure[69]. Although it was initially developed for paroxysmal AF patients, catheter ablation is also increasingly used in the treatment of non-paroxysmal AF. In this subgroup of patients however, evidence is still scarce and controversial[115, 116, 153].

A multicenter randomized trial recently compared ablation and AAD in persistent AF[154]. At the end of the one-year follow-up, 70.4% of the patients in the ablation group were arrhythmia-free, compared to 43.7% in the AAD group. A similar single-center non-randomized investigation reported an arrhythmia-free proportion of 76% in patients who underwent ablation versus 46% in those who were managed with AAD[155]. Patients receiving AAD were additionally more likely to undergo electrical cardioversion and to develop side-effects from their medications[155].

In spite of these encouraging findings, which favor the potential advantage of catheter ablation, the definition of clinical outcomes in non-paroxysmal AF has been more challenging than in paroxysmal AF[116]. Heterogeneity in patient selection, procedural strategy, technological equipment and follow-up may represent plausible causes of this lack of consistency[115, 153].

9.1 Patient selection: a key to improving clinical outcomes of non-paroxysmal AF ablation

It is recognized that non-paroxysmal AF represents a highly heterogeneous group of patients in terms of symptoms and cardiac comorbidities. Patient selection in non-paroxysmal AF is therefore an important variable in the assessment of clinical outcomes of catheter ablation[35]. In the above-mentioned work by Mont et al., the inclusion of relatively young and healthy AF patients may have contributed substantially to the final outcomes[154].

Several parameters have been previously investigated as potential predictors of long-term outcomes but the results are inconsistent[117, 121, 123, 136, 138, 139, 156-158]. In paper I, we showed that the duration of uninterrupted AF was a strong predictor of AF recurrence. While clinical outcomes were satisfactory with an AF duration ≤4 years, poor results were obtained in patients with an AF duration >4 years. Although the duration of uninterrupted AF has previously been reported as a potential predictor, some authors have suggested an AF duration <2 years as a prudent indication for AF ablation[137, 139, 156, 158]. Larger studies are needed to clarify this discrepancy and to define an ideal AF duration cut-off as inclusion criteria for non-paroxysmal AF ablation.

Because of the propensity of AF to self-perpetuation, AF duration and left atrial size might be closely correlated. In paper I we did not find any association between LAD and long-term outcomes. Contrasting findings suggest that echocardiographic measurement of LAD does not represent an accurate estimate of real LA size[140, 142, 159]. Some authors have suggested that other measurements such as LA sphericity or LA volume obtained from magnetic resonance (MR) scans may be more reliable indicators of AF remodeling[140, 144, 159].

MR has also recently been employed to quantify fibrosis in the LA[35, 160]. Preliminary reports have shown that a lower amount of fibrosis yields to better long-term outcomes after catheter ablation[35, 160]. This new information suggests that atrial remodeling not only contributes to the perpetuation of AF but may also limit the efficacy of curative AF ablation. Most interestingly, it has been demonstrated that the remodeling process can be stopped and reversed by the presence of SR, and that measures that aim to restore SR before ablation may have positive effects on the long-term outcomes[142, 161-164].

In paper I we also observed that females had significantly poorer prognoses than males. This finding has been previously shown, although inconsistently, and the reasons are unclear[138, 165]. The prevalence of extra-PV foci seems to be higher in females. Extra-PV foci mapping and ablation can be challenging and are not routinely performed[32, 163, 164, 166]. A number of authors have additionally observed that female

AF patients are managed less aggressively than their male counterparts in terms of AADs and direct current cardioversions. When finally offered catheter ablation, female patients are subject to a delayed referral to this procedure possibly with more advanced stages of atrial remodeling[157, 166]. Finally, in paper II we reported that female patients manifested by far the lowest proportion of CFE area in the LA (<5%). This observation may support the hypothesis that the AF substrate could be different in females and males. If this is the case, future AF ablation techniques could be specifically tailored to female patients.

9.2 Procedural strategy: PVI+CFE ablation is a plausible approach for non-paroxysmal AF

An additional factor complicating the comparison of clinical trials for non-paroxysmal AF is the variety of ablation strategies employed. Most authors agree that stand-alone PVI is not sufficient in non-paroxysmal AF[69]. Linear and CFE ablation are currently widely employed as adjunctive strategies although it is not yet clear which provides the best results. The results from the multicenter, randomized, STAR-AF II trial may throw light on this issue[120].

In paper I we showed that a procedural strategy consisting exclusively of PVI plus adjunctive CFE ablation led to satisfactory long-term results in a mixed population with persistent and long-standing persistent AF. After multiple procedures and an average follow-up of over three years, 80.3% of the patients enjoyed clinical benefits from the treatment including 57.6% that remained arrhythmia-free.

Ablation of CFE areas is an accepted strategy, albeit controversial, for the treatment of non-paroxysmal AF. The conflicting results described in the literature could originate from a lack of consensus regarding the definition of CFE, mapping technique or ablation endpoint[167-169].

In localizing CFE areas for instance, dedicated CFE mapping tools are employed by some centers while others only use “visual inspection”. Moreover, there is no agreement regarding what should be the endpoint of CFE ablation; AF termination, CFE disappearance and CFE organization have all been adopted[101, 118, 119, 170, 171]. These incongruences affect not only clinical results but also the safety profile and duration of these procedures. As shown in paper II, CFE areas are widespread and, according to the criteria used, may cover >50% of the LA surface. In order to abolish all these areas, extensive ablation must be performed, with potentially increased procedural time and risk of complications[119, 128, 167, 172].

Arguments in support of CFE ablation include the high degree of stability of CFE areas, frequent occurrence of AFCL prolongation or AF termination during targeting of these areas and plausible mechanistic association with the AF substrate.

The temporal and spatial stability of CFE areas is crucial to prove any involvement of these regions with the substrate maintaining AF. A complete lack of stability on the other hand, would suggest that CFEs originate from passive atrial activation and that their role in AF is only functional[173, 174]. In paper II we demonstrated a high degree of spatial and temporal stability of CFE areas. Over 80% of CFE areas registered 40 minutes after flecainide administration were localized within the spatial limits of previously mapped CFE areas. Although conflicting data concerning CFE stability have been published, the semi-automated measurements performed in our study may strengthen our results as well as the consistency of our findings among patients.

Several authors reported that changes in AF (prolongation of AFCL or termination into AT or SR) occur frequently during CFE ablation[101, 118, 119, 175, 176]. Such acute changes may suggest that ablation targeting these areas does in fact affect the substrate maintaining AF. In paper I we reported an acute termination of AF into SR in 36.6% of the procedures during CFE ablation, either directly from AF or via AT. However, it should be remembered that the mechanism by which CFE ablation contributes to changes in AF is still unclear.

Finally, CFEs were originally linked to areas of fibrosis that may have represented pivot points of rotors perpetuating AF[99, 101, 118]. The wide distribution of CFEs in patients with persistent and long-standing persistent AF could be a consequence of an increased amount of fibrosis due to AF remodeling[100]. Some reports have also shown that CFE areas are characterized by lower electrogram amplitude than non-CFE areas[177]. However, discordant results concerning the relationship between CFE and fibrosis are reported in the literature[27, 178]. Recently, Jadidi et al. investigated the correlation between fibrosis and CFEs using delayed enhancement MR and found that 41% of continuous CFE areas were found in regions of "patchy fibrosis" and 11% in regions of dense fibrosis, while the majority (48%) were found in areas of healthy tissue[178]. These interesting results add to previously published data and prove that at least some CFEs are functional and represent unspecific targets for ablation[176, 179, 180]. It has been suggested that, if CFE ablation is pursued, it would be of importance to distinguish between culprit and functional CFEs[180].

In paper II we showed that intravenous flecainide can be administered in order to partially eliminate functional CFE, estimated to be more than 30% and to highlight culprit CFE. A CFE-mean cut-off of 80 ms may facilitate the identification of stable CFE areas. Long-term outcomes of ablation targeting exclusively CFE areas after flecainide and with a CFE-mean <80 ms were comparable to previous studies, thus supporting that disappeared areas are functional[169].

The implementation of these two measures in clinical practice could greatly reduce the amount of atrial myocardium targeted for CFE ablation with potentially great benefit for procedural safety. It has in fact been suggested that extensive ablation in the LA may bring a higher risk of complications and increase the incidence of post-ablation ATs[181, 182].

9.3 Technological advances: contact force monitoring

The main limitation of radiofrequency catheter ablation today is the unpredictable formation and endurance of its lesions. Although it has not been formally demonstrated, there is agreement that poor lesion quality leads to a transient effect and may eventually result in arrhythmia recurrences[143, 149].

Experimental studies have shown that sub-optimal CF is associated with inadequate lesion formation[148, 149]. Following the availability of CF-sensing catheters, a great deal of research has been focusing on this topic[94, 95, 150-152, 183-186].

Previous studies have shown how CF varies significantly in different locations in the LA. Lower degrees of CF are achieved in the left PVs and particularly in the left superior PV[94, 184]. These observations may explain the difficulty of isolating the left superior PV and the frequent occurrence of its electrical reconnection.

Several investigations have also sought to validate the utility of this technology in assessing lesion development; IF has often been selected as the parameter of comparison for this purpose[93, 184-187]. In paper III we demonstrated a significant association between catheter tip-to-tissue CF and IF. Although other authors have confirmed our results, the correlation coefficient (Spearman's rho=0.54) found in paper III between CF and IF was higher than had been observed in similar studies[184, 187]. The reasons for this difference may be found in the rigorous selection of qualified points in our study based on a strict assessment of catheter stability. In this light, the results of paper III acquire additional significance, and suggest that CF plays an even more important role when employed together with improved catheter stability. This supposition is confirmed by the positive effects of adopting a steerable sheath (a tool that potentially improves catheter stability) to support the ablation catheter during AF ablation[117, 188].

Recently, findings from preliminary studies on CF technology have been used to develop annotation algorithms that may improve real-time assessment of lesion quality. A recent study investigated the clinical benefits of an algorithm that validates only ablation points characterized by an IF >5% and by a catheter movement <2 mm. When applied to AF ablation, these parameters led to a significant reduction in acute PV reconnection and a higher (although not statistically significant) proportion of arrhythmia-free patients[93].

Impedance monitoring has also previously been used in the prevention of acute complications. Under stable catheter conditions, a sudden rise in impedance during ablation may be observed ahead of steam pops or thrombus formation, and indicates that energy delivery should cease[189]. The results of paper III show that a high CF (>20 g) may lead to a late impedance rise occurring after 40 s of ablation; this underlines the fact that procedural safety may benefit from the constant monitoring of CF and IF. Controlling CF or alternatively, reducing ablation duration when a high CF is obtained, may curtail the incidence of complications.

9.4 Follow-up considerations: definition of clinical endpoints and impact of arrhythmia recurrences after ablation

The latest expert consensus document draws attention to the importance of standardized follow-up routines for the evaluation of clinical trials involving AF patients. Total freedom from atrial arrhythmia in the absence of AAD is the most objective definition of success and should be the preferred endpoint for all AF ablation trials[69]. In a clinical setting, however, this may be difficult to achieve in non-paroxysmal AF patients.

Recently, Tondo et al. have shown that 46% of patients after ablation experienced AF recurrences that were completely asymptomatic[190]. Other reports have underlined how quality of life improves significantly with the reduction of AF burden, even when AF recurs[191, 192]. Finally, AADs can reduce significantly AF recurrences after catheter ablation[118, 193, 194]. How should these outcomes be considered in a clinical setting?

The current guidelines state that referral to catheter ablation is mainly dependent on the presence of symptomatic AF[69]. This thus acknowledges that the disappearance or improvement of AF symptoms should be regarded as satisfactory outcomes[69, 190, 191].

In paper I, besides the 57.6% of patients who remained arrhythmia-free after the procedure, a further 22.7% had significant improvement of their symptoms. Most of these patients remained in stable SR for a long time and later experienced episodes of self-terminating paroxysmal AF.

An additional issue concerns the intensity of the follow-up after ablation. Martinek et al. showed that the proportion of arrhythmia-free patients fell with the implementation of more sensitive tools for arrhythmia detection[195].

Patients included in paper I were followed up for an average of over three years with Holter recordings, ECG and clinical examination. A stricter follow-up was employed in the first year from the ablation, with visits at three, six and 12 months. The intensity of further follow-up depended on the clinical situation.

Previous studies have shown that recurrences of arrhythmia following AF ablation are most common in the first 12 months but may occur up to three years following ablation[123-125]. Recurrences of AF after ablation also seem to appear more often in non-paroxysmal AF patients[110, 124, 125]. The results of paper I confirm these findings: while recurrences occurred during the first 12 months in 42 patients (63.6%), only three (4.5%) suffered late recurrences (>12 months) up to 40 months from the initial procedure. Although rare, the development of very late recurrences raises a dilemma on the safety of discontinuing anticoagulation in those patients at high cerebrovascular risk.

With regard to late arrhythmia recurrences, it is also of interest to consider AT and AF separately. Previous work has suggested that when AF is the clinical arrhythmia that recurs in the follow-up, PV reconnection may be the main mechanism involved[93-95, 146]. In paper I, all the patients who underwent a repeat procedure had signs of reconnection of at least one PV. This is consistent with other observations[125, 196].

Recurrences of AT are relatively more frequent among non-paroxysmal AF patients[119, 127, 128]. It has been reported that the incidence of AT is linked to the extension of ablation performed in the LA[129, 181]. It is not clear which ablation strategy produces the highest risk of developing AT [119, 167]. When linear ablation is chosen as the procedural strategy, post-ablation ATs are often characterized by a macro-reentry caused by recovered conduction over the lines[129]. When CFE areas are targeted, post-ablation ATs can be characterized by either a macro- or a micro-reentry caused by areas of extremely slow conduction[197, 198].

Post-ablation ATs may complicate the management of non-paroxysmal AF patients, but at the same time, they could also be regarded as a favorable prognostic factor. Although this often requires an extra procedure, mapping and ablation of AT is feasible. Patients who have undergone a repeat ablation session because of AT have a better long-term prognosis than those with a repeat ablation because of recurrences of AF[127, 199]. Results from paper I show that all the patients (100%) who underwent a repeat ablation procedure because of AT had clinical improvement at follow-up compared with only 56% of those whose repeat ablation was due to persistent AF. It thus appears reasonable to suggest that AT should not be regarded as a complication but as an encouraging step towards stable SR. Future research should be addressed to the improvement of mapping techniques in order to facilitate ablation treatment of these arrhythmias.

Study limitations

Our results come from three single-center, non-randomized studies in which no control group was employed. The number of patients involved, especially females, was relatively small. However, this is consistent with previous literature and reflects the actual proportion of female patients referred for catheter ablation.

Paper I was a retrospective study and, because of the follow-up protocol, we realize that some asymptomatic recurrences of arrhythmia may have been underestimated.

In paper II, the study material was retrieved only from the LA. Conclusions therefore cannot be extrapolated to the PVs, RA and CS.

In paper III, there were significant differences between the number of points in the different CF groups. Obtaining stable catheter contact is more challenging when high CF is applied and these differences probably express this difficulty.

10 Conclusions

1. After long-term follow-up, a strategy of combined PVI + CFE ablation seems to provide a reasonable rate of arrhythmia-freedom and clinical improvement in non-paroxysmal AF patients. Patients with uninterrupted AF duration ≤ 4 years appear to benefit most from this ablation strategy. Female gender and longer duration of uninterrupted AF are predictors of long-term failure.

2. Flecainide reduces the extension of CFE areas in non-paroxysmal AF patients by slowing atrial conduction velocity and diminishing complexity and amplitude of atrial electrograms. CFE areas appear to be spatially and temporally stable after flecainide administration. These findings may influence approaches to CFE ablation and reduce ablation time and procedural duration.

3. IF correlates significantly with catheter tip-tissue CF level during 60 s of ablation. CF exceeding 5 g produces greater IF, which probably indicates adequate lesion formation. CF greater than 20 g may lead to late tissue overheating.

11 References

1. Lip GY, Beevers DG. ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. BMJ. 1995;311:1361-3.
2. McMichael J. History of atrial fibrillation 1628-1819 Harvey - de Senac - Laënnec. Br Heart J. 1982;48:193-7.
3. Harvey W. Exercitatio anatomica de motu cordis et sanguinis in animalibus. Trans Keynes G. Birmingham: Leslie B. Adams, Jr; 1978. p. 28-34.
4. Schweitzer P, Keller S. A history of atrial fibrillation. Vnitr Lek. 2002;48 Suppl 1:24-6.
5. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohnloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12:1360-420.
6. Prystowsky EN, Benson DW, Jr., Fuster V, Hart RG, Kay GN, Myerburg RJ, Naccarelli GV, Wyse DG. Management of patients with atrial fibrillation. A Statement for Healthcare Professionals. From the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. Circulation. 1996;93:1262-77.
7. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation: executive summary. Eur Heart J. 2007;28:2803-17.
8. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271:840-4.

9. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006;27:949-53.
10. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114:119-25.
11. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol. 2013;112:1142-7.
12. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013;34:2746-51.
13. Kozlowski D, Budrejko S, Lip GY, Rysz J, Mikhailidis DP, Raczak G, Banach M. Lone atrial fibrillation: what do we know? Heart. 2010;96:498-503.
14. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. JAMA. 1985;254:3449-53.
15. Chen YC, Chen SA, Chen YJ, Chang MS, Chan P, Lin CI. Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes. J Am Coll Cardiol. 2002;39:366-72.
16. Conway DS, Buggins P, Hughes E, Lip GY. Predictive value of indexes of inflammation and hypercoagulability on success of cardioversion of persistent atrial fibrillation. Am J Cardiol. 2004;94:508-10.
17. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study. Circulation. 2005;112:1736-42.

18. Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC. New risk factors for atrial fibrillation: causes of 'not-so-lone atrial fibrillation'. Europace. 2008;10:668-73.

19. Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn Ther. 1962;140:183-188.

20. Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J (eds.) Cardiac electrophysiology and arrhythmias. Orlando: Grune & Stratton; 1985. p. 265-75.

21. Cox JL, Schuessler RB, D'Agostino HJ, Jr., Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg. 1991;101:569-83.

22. Lewis T. The mechanism and graphic registration of the heart beat. 3rd ed. London: Shaw & Sons; 1925. p. 319-74.

23. Haissaguerre M, Hocini M, Shah AJ, Derval N, Sacher F, Jais P, Dubois R. Noninvasive panoramic mapping of human atrial fibrillation mechanisms: a feasibility report. J Cardiovasc Electrophysiol. 2013;24:711-7.

24. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. Cardiovasc Res. 2002;54:204-16.

25. Jalife J, Berenfeld O, Skanes A, Mandapati R. Mechanisms of atrial fibrillation: mother rotors or multiple daughter wavelets, or both? J Cardiovasc Electrophysiol. 1998;9:S2-12.

26. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol. 2012;60:628-36.

27. Narayan SM, Shivkumar K, Krummen DE, Miller JM, Rappel WJ. Panoramic electrophysiological mapping but not electrogram morphology identifies stable sources for human atrial fibrillation: stable atrial fibrillation rotors and focal

sources relate poorly to fractionated electrograms. Circ Arrhythm Electrophysiol. 2013;6:58-67.

28. Haissaguerre M, Marcus FI, Fischer B, Clementy J. Radiofrequency catheter ablation in unusual mechanisms of atrial fibrillation: report of three cases. J Cardiovasc Electrophysiol. 1994;5:743-51.

29. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659-66.

30. Chen SA, Tai CT. Catheter ablation of atrial fibrillation originating from the non-pulmonary vein foci. J Cardiovasc Electrophysiol. 2005;16:229-32.

31. Elayi CS, Di Biase L, Bai R, Burkhardt JD, Mohanty P, Santangeli P, Sanchez J, Hongo R, Gallinghouse GJ, Horton R, Bailey S, Beheiry S, Natale A. Administration of isoproterenol and adenosine to guide supplemental ablation after pulmonary vein antrum isolation. J Cardiovasc Electrophysiol. 2013;24:1199-206.

32. Lee SH, Tai CT, Hsieh MH, Tsao HM, Lin YJ, Chang SL, Huang JL, Lee KT, Chen YJ, Cheng JJ, Chen SA. Predictors of non-pulmonary vein ectopic beats initiating paroxysmal atrial fibrillation: implication for catheter ablation. J Am Coll Cardiol. 2005;46:1054-9.

33. Yamaguchi T, Tsuchiya T, Miyamoto K, Nagamoto Y, Takahashi N. Characterization of non-pulmonary vein foci with an EnSite array in patients with paroxysmal atrial fibrillation. Europace. 2010;12:1698-706.

34. Dixit S, Lin D, Frankel DS, Marchlinski FE. Catheter ablation for persistent atrial fibrillation: antral pulmonary vein isolation and elimination of nonpulmonary vein triggers are sufficient. Circ Arrhythm Electrophysiol. 2012;5:1216-23.

35. Akoum N, Daccarett M, McGann C, Segerson N, Vergara G, Kuppahally S, Badger T, Burgon N, Haslam T, Kholmovski E, Macleod R, Marrouche N. Atrial fibrosis helps select the appropriate patient and strategy in catheter

ablation of atrial fibrillation: a DE-MRI guided approach. J Cardiovasc Electrophysiol. 2011;22:16-22.

36. Saito T, Waki K, Becker AE. Left atrial myocardial extension onto pulmonary veins in humans: anatomic observations relevant for atrial arrhythmias. J Cardiovasc Electrophysiol. 2000;11:888-94.

37. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 1999;10:1525-33.

38. de Bakker JM, Ho SY, Hocini M. Basic and clinical electrophysiology of pulmonary vein ectopy. Cardiovasc Res. 2002;54:287-94.

39. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995;91:1588-95.

40. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92:1954-68.

41. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Electrophysiological remodeling. Circulation. 1996;94:2953-60.

42. Goette A, Honeycutt C, Langberg JJ. Electrical remodeling in atrial fibrillation. Time course and mechanisms. Circulation. 1996;94:2968-74.

43. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res. 2002;54:230-46.

44. Platonov PG. Interatrial conduction in the mechanisms of atrial fibrillation: from anatomy to cardiac signals and new treatment modalities. Europace. 2007;9 Suppl 6:vi10-6.

45. Casaclang-Verzosa G, Gersh BJ, Tsang TS. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. J Am Coll Cardiol. 2008;51:1-11.

46. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation. 2002;105:2753-9.
47. Pokushalov E, Romanov A, Artyomenko S, Turov A, Shugayev P, Shirokova N, Katritsis DG. Ganglionated plexi ablation for longstanding persistent atrial fibrillation. Europace. 2010;12:342-6.
48. Calo L, Rebecchi M, Sciarra L, De Luca L, Fagagnini A, Zuccaro LM, Pitrone P, Dottori S, Porfirio M, de Ruvo E, Lioy E. Catheter ablation of right atrial ganglionated plexi in patients with vagal paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol. 2012;5:22-31.
49. Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, Camm AJ, Ioannidis JP. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol. 2013;62:2318-25.
50. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm. 2005;2:624-31.
51. Schauerte P, Scherlag BJ, Patterson E, Scherlag MA, Matsudaria K, Nakagawa H, Lazzara R, Jackman WM. Focal atrial fibrillation: experimental evidence for a pathophysiologic role of the autonomic nervous system. J Cardiovasc Electrophysiol. 2001;12:592-9.
52. Ishii Y, Schuessler RB, Gaynor SL, Yamada K, Fu AS, Boineau JP, Damiano RJ, Jr. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation. 2005;111:2881-8.
53. Marott SC, Nordestgaard BG, Zacho J, Friberg J, Jensen GB, Tybjaerg-Hansen A, Benn M. Does elevated C-reactive protein increase atrial fibrillation risk? A Mendelian randomization of 47,000 individuals from the general population. J Am Coll Cardiol. 2010;56:789-95.
54. Kaireviciute D, Lip GY, Balakrishnan B, Uzdavinys G, Norkunas G, Kalinauskas G, Sirvydis V, Aidietis A, Zanetto U, Sihota H, Maheshwari M,

Blann AD. Intracardiac expression of markers of endothelial damage/dysfunction, inflammation, thrombosis, and tissue remodeling, and the development of postoperative atrial fibrillation. J Thromb Haemost. 2011;9:2345-52.

55. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol. 2012;60:2263-70.

56. Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. Europace. 2012;14:159-74.

57. Narducci ML, Pelargonio G, Rio T, Leo M, Di Monaco A, Musaico F, Pazzano V, Trotta F, Liuzzo G, Severino A, Biasucci LM, Scapigliati A, Glieca F, Cavaliere F, Rebuzzi AG, Massetti M, Crea F. Predictors of postoperative atrial fibrillation in patients with coronary artery disease undergoing cardiopulmonary bypass: a possible role for myocardial ischemia and atrial inflammation. J Cardiothorac Vasc Anesth. 2013. doi: 10.1053/j.jvca.2013.06.002. (accessed 29 april 2014).

58. Ki CS, Jung CL, Kim HJ, Baek KH, Park SJ, On YK, Kim KS, Noh SJ, Youm JB, Kim JS, Cho H. A KCNQ1 mutation causes age-dependant bradycardia and persistent atrial fibrillation. Pflugers Arch. 2014;466:529-40.

59. Yang YQ, Liu X, Zhang XL, Wang XH, Tan HW, Shi HF, Jiang WF, Fang WY. Novel connexin40 missense mutations in patients with familial atrial fibrillation. Europace. 2010;12:1421-7.

60. Mahida S, Ellinor PT. New advances in the genetic basis of atrial fibrillation. J Cardiovasc Electrophysiol. 2012;23:1400-6.

61. Lamas GA, Lee K, Sweeney M, Leon A, Yee R, Ellenbogen K, Greer S, Wilber D, Silverman R, Marinchak R, Bernstein R, Mittleman RS, Lieberman EH, Sullivan C, Zorn L, Flaker G, Schron E, Orav EJ, Goldman L. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. Am Heart J. 2000;140:541-51.

62. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice G, American Association for Thoracic S, Society of Thoracic S. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51:e1-62.

63. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978;28:973-7.

64. Larsen TB, Lip GY, Skjoth F, Due KM, Overvad K, Hvilsted Rasmussen L. Added predictive ability of the CHA2DS2VASc risk score for stroke and death in patients with atrial fibrillation: the prospective Danish Diet, Cancer, and Health cohort study. Circ Cardiovasc Qual Outcomes. 2012;5:335-42.

65. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J. 2008;156:57-64.

66. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med. 2013;158:338-46.

67. Thacker EL, McKnight B, Psaty BM, Longstreth WT, Jr., Sitlani CM, Dublin S, Arnold AM, Fitzpatrick AL, Gottesman RF, Heckbert SR. Atrial fibrillation and cognitive decline: a longitudinal cohort study. Neurology. 2013;81:119-25.

68. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98:946-52.

69. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr., Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012;14:528-606.

70. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD005049. doi: 10.1002/14651858.CD005049.pub3.

71. Schilling RJ. Cardioversion of atrial fibrillation: the use of antiarrhythmic drugs. Heart. 2010;96:333-8.

72. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of

rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825-33.

73. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, Campbell WB, Havranek E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler M, Nasco EM, Greene HL. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Circulation. 2004;109:1973-80.

74. Hagens VE, Van Veldhuisen DJ, Kamp O, Rienstra M, Bosker HA, Veeger NJ, Tijssen JG, Crijns HJ, Van Gelder IC. Effect of rate and rhythm control on left ventricular function and cardiac dimensions in patients with persistent atrial fibrillation: results from the RAte Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study. Heart Rhythm. 2005;2:19-24.

75. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005;352:1861-72.

76. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation. 2008;118:2498-505.

77. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA. 2005;293:2634-40.

78. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA. Comparison of antiarrhythmic drug therapy

and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA. 2010;303:333-40.

79. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22:839-45.

80. Lin YJ, Chao TF, Tsao HM, Chang SL, Lo LW, Chiang CE, Hu YF, Hsu PF, Chuang SY, Li CH, Chung FP, Chen YY, Wu TJ, Hsieh MH, Chen SA. Successful catheter ablation reduces the risk of cardiovascular events in atrial fibrillation patients with CHA2DS2-VASc risk score of 1 and higher. Europace. 2013;15:676-84.

81. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, Di Biase L, Schweikert RA, Saliba WI, Horton R, Mohanty P, Patel D, Burkhardt DJ, Wazni OM, Bonso A, Callans DJ, Haissaguerre M, Raviele A, Natale A. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol. 2010;55:735-43.

82. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. Am Heart J. 2013;166:442-8.

83. Cleland JG, Coletta AP, Buga L, Ahmed D, Clark AL. Clinical trials update from the American College of Cardiology meeting 2010: DOSE, ASPIRE, CONNECT, STICH, STOP-AF, CABANA, RACE II, EVEREST II, ACCORD, and NAVIGATOR. Eur J Heart Fail. 2010;12:623-9.

84. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. Europace. 2012;14:1490-7.

85. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients

with coexistent atrial fibrillation and heart failure: a systematic review. J Am Coll Cardiol. 2012;59:719-26.

86. Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. Circ Arrhythm Electrophysiol. 2012;5:68-76.

87. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation : a meta-analysis. Circulation. 2000;101:1138-44.

88. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation. 1999;100:1879-86.

89. Scanavacca MI, Kajita LJ, Vieira M, Sosa EA. Pulmonary vein stenosis complicating catheter ablation of focal atrial fibrillation. J Cardiovasc Electrophysiol. 2000;11:677-81.

90. Haissaguerre M, Shah DC, Jais P, Hocini M, Yamane T, Deisenhofer I, Chauvin M, Garrigue S, Clementy J. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. Circulation. 2000;102:2463-5.

91. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F, Jr., Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation. 2002;105:1077-81.

92. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. Circulation. 2000;102:2619-28.

93. Anter E, Tschabrunn CM, Contreras-Valdes FM, Buxton AE, Josephson ME. Radiofrequency ablation annotation algorithm reduces the incidence of linear gaps and reconnection following pulmonary vein isolation: ablation annotation

algorithm to improve electrical contiguity during PVI. Heart Rhythm. 2014;11:783-90.

94. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D, Lambert H, Yulzari A, Wissner E, Kuck KH. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. Circ Arrhythm Electrophysiol. 2013;6:327-33.

95. Park CI, Lehrmann H, Keyl C, Weber R, Schiebeling J, Allgeier J, Schurr P, Shah A, Neumann FJ, Arentz T, Jadidi AS. Mechanisms of pulmonary vein reconnection after radiofrequency ablation of atrial fibrillation: the deterministic role of contact force and interlesion distance. J Cardiovasc Electrophysiol. 2014. doi: 10.1111/jce.12396. (accessed 29 April 2014).

96. Swartz JF, Pellersels G, Silvers J, Patten L, Cervantez D. A catheter-based curative approach to atrial fibrillation in humans. Circulation. 1994;90(supplement I):I-335 (Abstract).

97. Haissaguerre M, Gencel L, Fischer B, Le Metayer P, Poquet F, Marcus FI, Clementy J. Successful catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 1994;5:1045-52.

98. Arbelo E, Brugada J, Hindricks G, Maggioni A, Tavazzi L, Vardas P, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse G, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G, Trines S. ESC-EURObservational research programme: the atrial fibrillation ablation pilot study, conducted by the European Heart Rhythm Association. Europace. 2012;14:1094-103.

99. Konings KT, Smeets JL, Penn OC, Wellens HJ, Allessie MA. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. Circulation. 1997;95:1231-41.

100. Liu X, Shi HF, Tan HW, Wang XH, Zhou L, Gu JN. Decreased connexin 43 and increased fibrosis in atrial regions susceptible to complex fractionated atrial electrograms. Cardiology. 2009;114:22-9.

101. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004;43:2044-53.

102. Jais P, Hocini M, Sanders P, Hsu LF, Takahashi Y, Rotter M, Rostock T, Sacher F, Clementy J, Haissaguerre M. Long-term evaluation of atrial fibrillation ablation guided by noninducibility. Heart Rhythm. 2006;3:140-5.

103. O'Neill MD, Jais P, Takahashi Y, Jonsson A, Sacher F, Hocini M, Sanders P, Rostock T, Rotter M, Pernat A, Clementy J, Haissaguerre M. The stepwise ablation approach for chronic atrial fibrillation - evidence for a cumulative effect. J Interv Card Electrophysiol. 2006;16:153-67.

104. Haissaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clementy J, Jais P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. J Cardiovasc Electrophysiol. 2005;16:1138-47.

105. Takahashi Y, O'Neill MD, Hocini M, Reant P, Jonsson A, Jais P, Sanders P, Rostock T, Rotter M, Sacher F, Laffite S, Roudaut R, Clementy J, Haissaguerre M. Effects of stepwise ablation of chronic atrial fibrillation on atrial electrical and mechanical properties. J Am Coll Cardiol. 2007;49:1306-14.

106. Duytschaever M, De Meyer G, Acena M, El-Haddad M, De Greef Y, Van Heuverswyn F, Vandekerckhove Y, Tavernier R, Lee G, Kistler P. Lessons from dissociated pulmonary vein potentials: entry block implies exit block. Europace. 2013;15:805-12.

107. Ip JE, Markowitz SM, Cheung JW, Liu CF, Thomas G, Lessner SJ, Lee JM, Lerman BB. Method for differentiating left superior pulmonary vein exit conduction from pseudo-exit conduction. Pacing Clin Electrophysiol. 2013;36:299-308.

108. Steven D, Reddy VY, Inada K, Roberts-Thomson KC, Seiler J, Stevenson WG, Michaud GF. Loss of pace capture on the ablation line: a new marker for complete radiofrequency lesions to achieve pulmonary vein isolation. Heart Rhythm. 2010;7:323-30.

109. Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, Risius T, Lutomsky B, Meinertz T. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. Eur Heart J. 2006;27:2871-8.

110. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2:e004549. doi: 10.1161/JAHA.112.004549. (accessed 29 April 2014).

111. Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, De Sanctis V, Pappalardo A, Laurenzi F, Avella A, Casella M, Dello Russo A, Romeo F, Pelargonio G, Tondo C. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. J Cardiovasc Electrophysiol. 2009;20:22-8.

112. Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, Kangkagate C. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. J Med Assoc Thai. 2003;86 Suppl 1:S8-16.

113. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012;367:1587-95.

114. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A. Radiofrequency ablation vs antiarrhythmic

drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA. 2014;311:692-700.

115. Parkash R, Tang AS, Sapp JL, Wells G. Approach to the catheter ablation technique of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomized controlled trials. J Cardiovasc Electrophysiol. 2011;22:729-38.

116. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm. 2010;7:835-46.

117. Arya A, Hindricks G, Sommer P, Huo Y, Bollmann A, Gaspar T, Bode K, Husser D, Kottkamp H, Piorkowski C. Long-term results and the predictors of outcome of catheter ablation of atrial fibrillation using steerable sheath catheter navigation after single procedure in 674 patients. Europace. 2010;12:173-80.

118. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. Heart Rhythm. 2008;5:1658-64.

119. Estner HL, Hessling G, Biegler R, Schreieck J, Fichtner S, Wu J, Jilek C, Zrenner B, Ndrepepa G, Schmitt C, Deisenhofer I. Complex fractionated atrial electrogram or linear ablation in patients with persistent atrial fibrillation - a prospective randomized study. Pacing Clin Electrophysiol. 2011;34:939-48.

120. Verma A, Sanders P, Macle L, Deisenhofer I, Morillo CA, Chen J, Jiang CY, Ernst S, Mantovan R. Substrate and trigger ablation for reduction of atrial fibrillation trial-part II (STAR AF II): design and rationale. Am Heart J. 2012;164:1-6.e6.

121. Rostock T, Salukhe TV, Steven D, Drewitz I, Hoffmann BA, Bock K, Servatius H, Mullerleile K, Sultan A, Gosau N, Meinertz T, Wegscheider K, Willems S. Long-term single- and multiple-procedure outcome and predictors

of success after catheter ablation for persistent atrial fibrillation. Heart Rhythm. 2011;8:1391-7.

122. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:32-8.

123. Wokhlu A, Hodge DO, Monahan KH, Asirvatham SJ, Friedman PA, Munger TM, Cha YM, Shen WK, Brady PA, Bluhm CM, Haroldson JM, Hammill SC, Packer DL. Long-term outcome of atrial fibrillation ablation: impact and predictors of very late recurrence. J Cardiovasc Electrophysiol. 2010;21:1071-8.

124. Sorgente A, Tung P, Wylie J, Josephson ME. Six year follow-up after catheter ablation of atrial fibrillation: a palliation more than a true cure. Am J Cardiol. 2012;109:1179-86.

125. Sotomi Y, Inoue K, Ito N, Kimura R, Toyoshima Y, Masuda M, Iwakura K, Fujii K. Incidence and risk factors for very late recurrence of atrial fibrillation after radiofrequency catheter ablation. Europace. 2013;15:1581-6.

126. Cheema A, Vasamreddy CR, Dalal D, Marine JE, Dong J, Henrikson CA, Spragg D, Cheng A, Nazarian S, Sinha S, Halperin H, Berger R, Calkins H. Long-term single procedure efficacy of catheter ablation of atrial fibrillation. J Interv Card Electrophysiol. 2006;15:145-55.

127. Ammar S, Hessling G, Reents T, Fichtner S, Wu J, Zhu P, Kathan S, Estner HL, Jilek C, Kolb C, Haller B, Deisenhofer I. Arrhythmia type after persistent atrial fibrillation ablation predicts success of the repeat procedure. Circ Arrhythm Electrophysiol. 2011;4:609-14.

128. Shah AJ, Jadidi A, Liu X, Miyazaki S, Forclaz A, Nault I, Rivard L, Linton N, Xhaet O, Derval N, Sacher F, Bordachar P, Ritter P, Hocini M, Jais P, Haissaguerre M. Atrial tachycardias arising from ablation of atrial fibrillation: a proarrhythmic bump or an antiarrhythmic turn? Cardiol Res Pract. 2010:950763. doi:10.4061/2010/950763. (accessed 29 April 2014).

129. Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:243-8.

130. Nair KK, Shurrab M, Skanes A, Danon A, Birnie D, Morillo C, Chauhan V, Mangat I, Ayala-Paredes F, Champagne J, Nault I, Tang A, Verma A, Lashevsky I, Singh SM, Crystal E. The prevalence and risk factors for atrioesophageal fistula after percutaneous radiofrequency catheter ablation for atrial fibrillation: the Canadian experience. J Interv Card Electrophysiol. 2014;39:139-44.

131. Gibson DN, Di Biase L, Mohanty P, Patel JD, Bai R, Sanchez J, Burkhardt JD, Heywood JT, Johnson AD, Rubenson DS, Horton R, Gallinghouse GJ, Beheiry S, Curtis GP, Cohen DN, Lee MY, Smith MR, Gopinath D, Lewis WR, Natale A. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. Heart Rhythm. 2011;8:1364-71.

132. Khaykin Y, Morillo CA, Skanes AC, McCracken A, Humphries K, Kerr CR. Cost comparison of catheter ablation and medical therapy in atrial fibrillation. J Cardiovasc Electrophysiol. 2007;18:907-13.

133. Blackhouse G, Assasi N, Xie F, Gaebel K, Campbell K, Healey JS, O'Reilly D, Goeree R. Cost-effectiveness of catheter ablation for rhythm control of atrial fibrillation. Int J Vasc Med. 2013:262809. doi:10.1155/2013/262809. (accessed 29 April 2014).

134. McKenna C, Palmer S, Rodgers M, Chambers D, Hawkins N, Golder S, Van Hout S, Pepper C, Todd D, Woolacott N. Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom. Heart. 2009;95:542-9.

135. Neyt M, Van Brabandt H, Devos C. The cost-utility of catheter ablation of atrial fibrillation: a systematic review and critical appraisal of economic evaluations. BMC Cardiovasc Disord. 2013;13:78.

136. Balk EM, Garlitski AC, Alsheikh-Ali AA, Terasawa T, Chung M, Ip S. Predictors of atrial fibrillation recurrence after radiofrequency catheter ablation: a systematic review. J Cardiovasc Electrophysiol. 2010;21:1208-16.

137. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J Am Coll Cardiol. 2012;60:1921-9.

138. Heist EK, Chalhoub F, Barrett C, Danik S, Ruskin JN, Mansour M. Predictors of atrial fibrillation termination and clinical success of catheter ablation of persistent atrial fibrillation. Am J Cardiol. 2012;110:545-51.

139. McCready JW, Smedley T, Lambiase PD, Ahsan SY, Segal OR, Rowland E, Lowe MD, Chow AW. Predictors of recurrence following radiofrequency ablation for persistent atrial fibrillation. Europace. 2011;13:355-61.

140. Bisbal F, Guiu E, Calvo N, Marin D, Berruezo A, Arbelo E, Ortiz-Perez J, de Caralt TM, Tolosana JM, Borras R, Sitges M, Brugada J, Mont L. Left atrial sphericity: a new method to assess atrial remodeling. Impact on the outcome of atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2013;24:752-9.

141. Kornej J, Hindricks G, Kosiuk J, Arya A, Sommer P, Husser D, Rolf S, Richter S, Huo Y, Piorkowski C, Bollmann A. Comparison of CHADS2, R2CHADS2 and CHA2DS2-VASc scores for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation: the Leipzig Heart Center AF ablation registry. Circ Arrhythm Electrophysiol. 2014;7:281-7.

142. Solheim E, Off MK, Hoff PI, De Bortoli A, Schuster P, Ohm OJ, Chen J. N-terminal pro-B-type natriuretic peptide level at long-term follow-up after atrial fibrillation ablation: a marker of reverse atrial remodelling and successful ablation. J Interv Card Electrophysiol. 2012;34:129-36.

143. Buch E, Boyle NG, Shivkumar K. Catheter Ablation: Technical Aspects. In: Zipes DP, Jalife J (eds.) Cardiac Electrophysiology: From Cell to Bedside. 6th ed. Philadelphia: Elsevier; 2013. p. 1199-1208.

144. D'Silva A, Wright M. Advances in imaging for atrial fibrillation ablation. Radiol Res Pract. 2011:714864. doi: 10.1155/2011/714864. (accessed 29 April 2014).

145. Okada T, Yamada T, Murakami Y, Yoshida N, Ninomiya Y, Shimizu T, Toyama J, Yoshida Y, Ito T, Tsuboi N, Kondo T, Inden Y, Hirai M, Murohara T. Prevalence and severity of left atrial edema detected by electron beam tomography early after pulmonary vein ablation. J Am Coll Cardiol. 2007;49:1436-42.

146. Andrade JG, Khairy P, Nattel S, Vanella A, Rivard L, Guerra PG, Dubuc M, Dyrda K, Thibault B, Talajic M, Mondesert B, Roy D, Macle L. Corticosteroid use during pulmonary vein isolation is associated with a higher prevalence of dormant pulmonary vein conduction. Heart Rhythm. 2013;10:1569-75.

147. Arentz T, Macle L, Kalusche D, Hocini M, Jais P, Shah D, Haissaguerre M. "Dormant" pulmonary vein conduction revealed by adenosine after ostial radiofrequency catheter ablation. J Cardiovasc Electrophysiol. 2004;15:1041-7.

148. Thiagalingam A, D'Avila A, Foley L, Guerrero JL, Lambert H, Leo G, Ruskin JN, Reddy VY. Importance of catheter contact force during irrigated radiofrequency ablation: evaluation in a porcine ex vivo model using a force-sensing catheter. J Cardiovasc Electrophysiol. 2010;21:806-11.

149. Wittkampf FH, Nakagawa H. RF catheter ablation: Lessons on lesions. Pacing Clin Electrophysiol. 2006;29:1285-97.

150. Piorkowski C, Sih H, Sommer P, Miller SP, Gaspar T, Teplitsky L, Hindricks G. First in human validation of impedance-based catheter tip-to-tissue contact assessment in the left atrium. J Cardiovasc Electrophysiol. 2009;20:1366-73.

151. Reddy VY, Shah D, Kautzner J, Schmidt B, Saoudi N, Herrera C, Jais P, Hindricks G, Peichl P, Yulzari A, Lambert H, Neuzil P, Natale A, Kuck KH. The relationship between contact force and clinical outcome during radiofrequency catheter ablation of atrial fibrillation in the TOCCATA study. Heart Rhythm. 2012;9:1789-95.

152. Marijon E, Fazaa S, Narayanan K, Guy-Moyat B, Bouzeman A, Providencia R, Treguer F, Combes N, Bortone A, Boveda S, Combes S, Albenque JP. Real-Time Contact Force Sensing for Pulmonary Vein Isolation in the Setting of Paroxysmal Atrial Fibrillation: Procedural and 1-Year Results. J Cardiovasc Electrophysiol. 2013; doi: 10.1111/jce.12303

153. Chen HS, Wen JM, Wu SN, Liu JP. Catheter ablation for paroxysmal and persistent atrial fibrillation. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD007101. doi: 10.1002/14651858.CD007101.pub2.

154. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, Arribas F, Fernandez-Lozano I, Bodegas A, Cobos A, Matia R, Perez-Villacastin J, Guerra JM, Avila P, Lopez-Gil M, Castro V, Arana JI, Brugada J. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). Eur Heart J. 2013;35:501-7

155. Blandino A, Toso E, Scaglione M, Anselmino M, Ferraris F, Sardi D, Battaglia A, Gaita F. Long-term efficacy and safety of two different rhythm control strategies in elderly patients with symptomatic persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2013;24:731-8.

156. Matsuo S, Lellouche N, Wright M, Bevilacqua M, Knecht S, Nault I, Lim KT, Arantes L, O'Neill MD, Platonov PG, Carlson J, Sacher F, Hocini M, Jais P, Haissaguerre M. Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. J Am Coll Cardiol. 2009;54:788-95.

157. Roten L, Rimoldi SF, Schwick N, Sakata T, Heimgartner C, Fuhrer J, Delacretaz E, Tanner H. Gender differences in patients referred for atrial fibrillation management to a tertiary center. Pacing Clin Electrophysiol. 2009;32:622-6.

158. Takahashi Y, Takahashi A, Kuwahara T, Fujino T, Okubo K, Kusa S, Fujii A, Yagishita A, Miyazaki S, Nozato T, Hikita H, Hirao K, Isobe M. Clinical

characteristics of patients with persistent atrial fibrillation successfully treated by left atrial ablation. Circ Arrhythm Electrophysiol. 2010;3:465-71.

159. Raviele A, Natale A, Calkins H, Camm JA, Cappato R, Ann Chen S, Connolly SJ, Damiano R, Jr., De Ponti R, Edgerton JR, Haissaguerre M, Hindricks G, Ho SY, Jalife J, Kirchhof P, Kottkamp H, Kuck KH, Marchlinski FE, Packer DL, Pappone C, Prystowsky E, Reddy VK, Themistoclakis S, Verma A, Wilber DJ, Willems S. Venice Chart international consensus document on atrial fibrillation ablation: 2011 update. J Cardiovasc Electrophysiol. 2012;23:890-923.

160. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon N, Hu N, Mont L, Deneke T, Duytschaever M, Neumann T, Mansour M, Mahnkopf C, Herweg B, Daoud E, Wissner E, Bansmann P, Brachmann J. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311:498-506.

161. Miyazaki S, Kuwahara T, Kobori A, Takahashi Y, Takei A, Sato A, Isobe M, Takahashi A. Pharmacological cardioversion preceding left atrial ablation: bepridil predicts the clinical outcome following ablation in patients with persistent atrial fibrillation. Europace. 2009;11:1620-3.

162. Rivard L, Hocini M, Rostock T, Cauchemez B, Forclaz A, Jadidi AS, Linton N, Nault I, Miyazaki S, Liu X, Xhaet O, Shah A, Sacher F, Derval N, Jais P, Khairy P, Macle L, Nattel S, Willems S, Haissaguerre M. Improved outcome following restoration of sinus rhythm prior to catheter ablation of persistent atrial fibrillation: a comparative multicenter study. Heart Rhythm. 2012;9:1025-30.

163. Patel D, Mohanty P, Di Biase L, Sanchez JE, Shaheen MH, Burkhardt JD, Bassouni M, Cummings J, Wang Y, Lewis WR, Diaz A, Horton RP, Beheiry S, Hongo R, Gallinghouse GJ, Zagrodzky JD, Bailey SM, Al-Ahmad A, Wang P, Schweikert RA, Natale A. Outcomes and complications of catheter ablation for atrial fibrillation in females. Heart Rhythm. 2010;7:167-72.

164. Takigawa M, Kuwahara T, Takahashi A, Watari Y, Okubo K, Takahashi Y, Takagi K, Kuroda S, Osaka Y, Kawaguchi N, Yamao K, Nakashima E, Sugiyama T, Akiyama D, Kamiishi T, Kimura S, Hikita H, Hirao K, Isobe M. Differences in catheter ablation of paroxysmal atrial fibrillation between males and females. Int J Cardiol. 2013;168:1984-91.

165. Zhang XD, Gu J, Jiang WF, Zhao L, Wang YL, Liu YG, Zhou L, Gu JN, Wu SH, Xu K, Liu X. The impact of age on the efficacy and safety of catheter ablation for long-standing persistent atrial fibrillation. Int J Cardiol. 2013;168:2693-8.

166. Patel D, Armaganijan LV, Morillo CA. Atrial fibrillation catheter ablation in females: same hardware, different findings. Expert Rev Cardiovasc Ther. 2011;9:1391-5.

167. Wu SH, Jiang WF, Gu J, Zhao L, Wang YL, Liu YG, Zhou L, Gu JN, Xu K, Liu X. Benefits and risks of additional ablation of complex fractionated atrial electrograms for patients with atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol. 2013;169:35-43.

168. Li WJ, Bai YY, Zhang HY, Tang RB, Miao CL, Sang CH, Yin XD, Dong JZ, Ma CS. Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation: a meta-analysis. Circ Arrhythm Electrophysiol. 2011;4:143-8.

169. Hayward RM, Upadhyay GA, Mela T, Ellinor PT, Barrett CD, Heist EK, Verma A, Choudhry NK, Singh JP. Pulmonary vein isolation with complex fractionated atrial electrogram ablation for paroxysmal and nonparoxysmal atrial fibrillation: A meta-analysis. Heart Rhythm. 2011;8:994-1000.

170. Jones DG, Haldar SK, Jarman JW, Johar S, Hussain W, Markides V, Wong T. Impact of stepwise ablation on the biatrial substrate in patients with persistent atrial fibrillation and heart failure. Circ Arrhythm Electrophysiol. 2013;6:761-8.

171. Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and

Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. Eur Heart J. 2010;31:1344-56.

172. de Vries LJ, Akca F, Khan M, Dabiri-Abkenari L, Janse P, Theuns DA, Peters E, de Ruiter G, Szili-Torok T. Clinical outcome of ablation for long-standing persistent atrial fibrillation with or without defragmentation. Neth Heart J. 2014;22:30-6.

173. Habel N, Znojkiewicz P, Thompson N, Muller JG, Mason B, Calame J, Calame S, Sharma S, Mirchandani G, Janks D, Bates J, Noori A, Karnbach A, Lustgarten DL, Sobel BE, Spector P. The temporal variability of dominant frequency and complex fractionated atrial electrograms constrains the validity of sequential mapping in human atrial fibrillation. Heart Rhythm. 2010;7:586-93.

174. Verma A, Wulffhart Z, Beardsall M, Whaley B, Hill C, Khaykin Y. Spatial and temporal stability of complex fractionated electrograms in patients with persistent atrial fibrillation over longer time periods: relationship to local electrogram cycle length. Heart Rhythm. 2008;5:1127-33.

175. Ammar S, Hessling G, Reents T, Paulik M, Fichtner S, Schon P, Dillier R, Kathan S, Jilek C, Kolb C, Haller B, Deisenhofer I. Importance of sinus rhythm as endpoint of persistent atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2013;24:388-95.

176. Hunter RJ, Diab I, Tayebjee M, Richmond L, Sporton S, Earley MJ, Schilling RJ. Characterization of fractionated atrial electrograms critical for maintenance of atrial fibrillation: a randomized, controlled trial of ablation strategies (the CFAE AF trial). Circ Arrhythm Electrophysiol. 2011;4:622-9.

177. Park JH, Pak HN, Kim SK, Jang JK, Choi JI, Lim HE, Hwang C, Kim YH. Electrophysiologic characteristics of complex fractionated atrial electrograms in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2009;20:266-72.

178. Jadidi AS, Cochet H, Shah AJ, Kim SJ, Duncan E, Miyazaki S, Sermesant M, Lehrmann H, Lederlin M, Linton N, Forclaz A, Nault I, Rivard L, Wright M, Liu X, Scherr D, Wilton SB, Roten L, Pascale P, Derval N, Sacher F, Knecht

S, Keyl C, Hocini M, Montaudon M, Laurent F, Haissaguerre M, Jais P. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high density mapping. J Am Coll Cardiol. 2013;62:802-12.

179. Rostock T, Rotter M, Sanders P, Takahashi Y, Jais P, Hocini M, Hsu LF, Sacher F, Clementy J, Haissaguerre M. High-density activation mapping of fractionated electrograms in the atria of patients with paroxysmal atrial fibrillation. Heart Rhythm. 2006;3:27-34.

180. Singh SM, D'Avila A, Kim SJ, Houghtaling C, Dukkipati SR, Reddy VY. Intraprocedural use of ibutilide to organize and guide ablation of complex fractionated atrial electrograms: preliminary assessment of a modified step-wise approach to ablation of persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2010;21:608-16.

181. Lin YJ, Chang SL, Lo LW, Hu YF, Chong E, Chao TF, Chung FP, Liao J, Li CH, Tsao HM, Kao T, Chen YY, Huang JL, Chen SA. A prospective and randomized comparison of limited versus extensive atrial substrate modification after circumferential pulmonary vein isolation in nonparoxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2014. doi: 10.1111/jce.12407. (accessed 29 April 2014).

182. Tilz RR, Chun KR, Schmidt B, Fuernkranz A, Wissner E, Koester I, Baensch D, Boczor S, Koektuerk B, Metzner A, Zerm T, Ernst S, Antz M, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: a lesson from circumferential pulmonary vein isolation. J Cardiovasc Electrophysiol. 2010;21:1085-93.

183. Sohns C, Karim R, Harrison J, Arujuna A, Linton N, Sennett R, Lambert H, Leo G, Williams S, Razavi R, Wright M, Schaeffter T, O'Neill M, Rhode K. Quantitative magnetic resonance imaging analysis of the relationship between contact force and left atrial scar formation after catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2013; doi: 10.1111/jce.12298. (accessed 29 April 2014).

184. Makimoto H, Lin T, Rillig A, Metzner A, Wohlmuth P, Arya A, Antz M, Mathew S, Deiss S, Wissner E, Rausch P, Bardyszewski A, Kamioka M, Li X, Kuck KH, Ouyang F, Tilz RR. In vivo contact force analysis and correlation with tissue impedance during left atrial mapping and catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014;7:46-54.

185. Reichlin T, Knecht S, Lane C, Kuhne M, Nof E, Chopra N, Tadros TM, Reddy VY, Schaer B, John RM, Osswald S, Stevenson WG, Sticherling C, Michaud GF. Initial impedance decrease as an indicator of good catheter contact: insights from radiofrequency ablation with force sensing catheters. Heart Rhythm. 2014;11:194-201.

186. Ullah W, Hunter RJ, Baker V, Dhinoja MB, Sporton S, Earley MJ, Schilling RJ. Target indices for clinical ablation in atrial fibrillation: insights from contact force, electrogram, and biophysical parameter analysis. Circ Arrhythm Electrophysiol. 2014;7:63-8.

187. Kumar S, Haqqani HM, Chan M, Lee J, Yudi M, Wong MC, Morton JB, Ling LH, Robinson T, Heck PM, Kelland NF, Halloran K, Spence SJ, Kistler PM, Kalman JM. Predictive value of impedance changes for real-time contact force measurements during catheter ablation of atrial arrhythmias in humans. Heart Rhythm. 2013;10:962-9.

188. Piorkowski C, Eitel C, Rolf S, Bode K, Sommer P, Gaspar T, Kircher S, Wetzel U, Parwani AS, Boldt LH, Mende M, Bollmann A, Husser D, Dagres N, Esato M, Arya A, Haverkamp W, Hindricks G. Steerable versus nonsteerable sheath technology in atrial fibrillation ablation: a prospective, randomized study. Circ Arrhythm Electrophysiol. 2011;4:157-65.

189. Kottkamp H, Hindricks G, Haverkamp W, Krater L, Borggrefe M, Bocker D, Gulker H, Breithardt G. [Biophysical aspects of high frequency catheter ablation. Studies of the significance of sudden changes in impedance]. Z Kardiol. 1992;81:145-51.

190. Tondo C, Tritto M, Landolina M, De Girolamo PG, Bencardino G, Moltrasio M, Russo AD, Bella PD, Bertaglia E, Proclemer A, De Sanctis V, Mantica M.

Rhythm-symptom correlation in patients on continuous monitoring after catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2013. doi: 10.1111/jce.12292. (accessed 29 April 2014).

191. Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Khaykin Y, Guerra PG, Nair G, Torrecilla EG, Verma A. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. Can J Cardiol. 2013;29:1211-7.

192. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, Morillo CA, Khaykin Y, Birnie D. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. JAMA Intern Med. 2013;173:149-56.

193. Medi C, Sparks PB, Morton JB, Kistler PM, Halloran K, Rosso R, Vohra JK, Kumar S, Kalman JM. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. J Cardiovasc Electrophysiol. 2011;22:137-41.

194. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009;2:349-61.

195. Martinek M, Aichinger J, Nesser HJ, Ziegler PD, Purerfellner H. New insights into long-term follow-up of atrial fibrillation ablation: full disclosure by an implantable pacemaker device. J Cardiovasc Electrophysiol. 2007;18:818-23.

196. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, Neven K, Kokturk B, Konstantinidou M, Metzner A, Fuernkranz A, Kuck KH. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation. 2010;122:2368-77.

197. Jais P, Matsuo S, Knecht S, Weerasooriya R, Hocini M, Sacher F, Wright M, Nault I, Lellouche N, Klein G, Clementy J, Haissaguerre M. A deductive

mapping strategy for atrial tachycardia following atrial fibrillation ablation: importance of localized reentry. J Cardiovasc Electrophysiol. 2009;20:480-91.

198. Deisenhofer I, Estner H, Zrenner B, Schreieck J, Weyerbrock S, Hessling G, Scharf K, Karch MR, Schmitt C. Left atrial tachycardia after circumferential pulmonary vein ablation for atrial fibrillation: incidence, electrophysiological characteristics, and results of radiofrequency ablation. Europace. 2006;8:573-82.

199. Zhao L, Wu S, Jiang W, Zhou L, Gu J, Wang Y, Liu Y, Zhang X, Liu X. Differential clinical characteristics and prognosis of patients with longstanding persistent atrial fibrillation presenting with recurrent atrial tachycardia versus recurrent atrial fibrillation after first ablation. J Cardiovasc Electrophysiol. 2013;25:259-65.