Antti Hakalahti

Efficacy and Safety of Radiofrequency Catheter Ablation in the Treatment of Atrial Fibrillation

Universities of Oulu, Eastern Finland, and Central Finland Central Hospital
EFFICACY AND SAFETY OF RADIOFREQUENCY CATHETER ABLATION IN THE TREATMENT OF ATRIAL FIBRILLATION

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium A101 (Aapistie 7 A), on 30 October 2015, at 12 noon

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University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu; Oulu University Hospital; University of Eastern Finland; Central Finland Central Hospital
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract
Atrial fibrillation (AF) is a common arrhythmia in the clinical setting with a population prevalence of 1–2%. AF significantly increases the risk of stroke and death, worsens coexistent heart diseases and may leave the patient with disabling symptoms. The treatment of AF consists of the control of the underlying conditions, prevention of complications and symptom relief by controlling heart rate (rate control) or by targeting normal rhythm (rhythm control), with the latter achieved either by antiarrhythmic drug (AAD) therapy or catheter ablation (CA). Ablation therapy has generally been applied and studied after failure of AAD therapy.

The aim of this study was to evaluate the safety and efficacy of first-line CA in AF. The other objectives were to assess the safety of continuous warfarin therapy during CA and to identify prognostic markers for treatment outcome.

A meta-analysis of all randomised studies and a secondary analysis of one randomised study comparing CA and AAD as first-line therapy were performed. In the first study, ablation therapy reduced AF recurrences more than AAD therapy (HR 0.63) when provided as first-line therapy; the rate of complications was similar with both therapies. Some of the complications of ablation therapy were more serious than those encountered with AADs. The second study revealed that the antiarrhythmic efficacy of ablation therapy was more durable. In the third study, the efficacies of continuous and interrupted warfarin therapy were compared in 228 procedures; both strategies were found to be equally safe during a three month follow-up. Furthermore, an analysis of 2317 AF episodes revealed a new electrocardiographic feature at AF initiation, which was associated with AF relapse after the initiation of therapy. Finally, a thorough echocardiographic examination was performed in 49 patients prior to ablation therapy. Mild diastolic dysfunction was associated with AF recurrence.

In conclusion, CA was more effective as a first-line therapy than AADs but may cause more severe complications. Continuous warfarin therapy was found to be safe during CA. New electrocardiographic and echocardiographic markers for treatment outcome were recognised.

Keywords: antiarrhythmic drugs, atrial fibrillation, catheter ablation, therapy outcome
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Tiivistelmä


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To my beloved family
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Oulu, October 2015

Antti Hakalahti
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAD</td>
<td>antiarrhythmic drug</td>
</tr>
<tr>
<td>ACT</td>
<td>activated clotting time</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>AFL</td>
<td>atrial flutter</td>
</tr>
<tr>
<td>APB</td>
<td>atrial premature beat</td>
</tr>
<tr>
<td>AV</td>
<td>atroventricular</td>
</tr>
<tr>
<td>CA</td>
<td>catheter ablation</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CFAE</td>
<td>complex fractionated atrial electrogram</td>
</tr>
<tr>
<td>CV</td>
<td>cardioversion</td>
</tr>
<tr>
<td>E/e’</td>
<td>ratio of early diastolic mitral inflow and diastolic mitral annular velocity</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiography</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>ICE</td>
<td>intracardiac echocardiography</td>
</tr>
<tr>
<td>INR</td>
<td>international normalised ratio</td>
</tr>
<tr>
<td>LA</td>
<td>left atrium; left atrial</td>
</tr>
<tr>
<td>LAA</td>
<td>left atrial appendage</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>NOAC</td>
<td>novel oral anticoagulants</td>
</tr>
<tr>
<td>OAT</td>
<td>oral anticoagulation therapy</td>
</tr>
<tr>
<td>PV</td>
<td>pulmonary vein</td>
</tr>
<tr>
<td>PVI</td>
<td>pulmonary vein isolation</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RF</td>
<td>radiofrequency</td>
</tr>
<tr>
<td>RFA</td>
<td>radiofrequency ablation</td>
</tr>
<tr>
<td>RRAA</td>
<td>rapid repetitive atrial activity at initiation of atrial fibrillation</td>
</tr>
<tr>
<td>SA</td>
<td>surgical ablation</td>
</tr>
<tr>
<td>SR</td>
<td>sinus rhythm</td>
</tr>
<tr>
<td>TIC</td>
<td>tachycardia induced cardiomyopathy</td>
</tr>
<tr>
<td>TOE</td>
<td>transoesophageal echocardiography</td>
</tr>
<tr>
<td>TS</td>
<td>transseptal</td>
</tr>
<tr>
<td>TTE</td>
<td>transthoracic echocardiography</td>
</tr>
<tr>
<td>VKA</td>
<td>vitamin K antagonists</td>
</tr>
</tbody>
</table>
Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1 Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia with a complex aetiological background involving multiple mechanisms. AF not only causes individual suffering but it is also a major public health issue since it is associated with increased mortality, increases risk of stroke, causes repeat hospitalisations and requires individual therapeutic approaches. The health care costs linked to AF are substantial because of the prevalence of AF, the need for repeated clinical evaluation, long-term therapies, hospitalisations and sick leaves (Ericson et al. 2011, January et al. 2014).

AF may present without symptoms but patients with AF still require repeated evaluation and interventions. Asymptomatic AF is not associated with any better outcome than symptomatic AF (Flaker et al. 2005). Identification of underlying causes and prevention of complications are always required. Heart rate may be optimised during AF (rate control) or normal rhythm reinstated (rhythm control).

There is no question about the benefit of restoring normal rhythm in patients with AF. The question is whether the available methods of rhythm control are sufficiently efficient and/or safe enough. The current mainstream strategies for long term rhythm management are antiarrhythmic drug (AAD) therapy and percutaneous left atrial (LA) catheter ablation (CA). AAD therapy has been associated with undesirable clinical events and poor efficacy in AF rhythm control (Lafuente-Lafuente et al. 2012). CA is an invasive procedure where areas triggering and/or sustaining AF are eliminated or isolated in order to prevent the recurrence of arrhythmias. CA is a complex procedure and carries a risk for life-threatening complications (Calkins et al. 2012). The selection of rate or rhythm control is mainly driven by symptoms, AF duration and comorbidity, because there is evidence indicating that rhythm control should be mainly used to alleviate symptoms because currently there is no evidence that antiarrhythmic therapy achieves any reduction in hard clinical endpoints. A longer AF duration is associated with poorer efficacy and comorbidity with an increase of complications (January et al. 2014). However, it has been claimed that early rhythm control may be able to prevent disease progression (Van Gelder et al. 2011).

Despite intensive research, several aspects about the mechanisms of AF have remained unclear (Calkins et al. 2012). Clarification of these mechanisms is the key for better application of the currently available therapies as well as for the development of novel treatment options.
This study focuses on CA of AF. Its main aim was to acquire new information about the efficacy and safety of AF ablation, AF episode properties and prognostic markers associated with therapy outcome. The goal was to clarify the role of ablation therapy in patients with symptomatic AF and to evaluate new methods for selecting appropriate therapy.
2 Review of the literature

2.1 General aspects of cardiac function and AF

Normally cardiac contraction is triggered by the spontaneous electrical activation of the sinus node and transmitted by the myocardial fibres and specialised cells of the conduction system to the other parts of the heart. This creates a regular, yet adaptive heart rate, which is controlled by neural signalling and humoral messages (Anderson et al. 1981, Hammond & Froelicher 1985). Moreover, the normal function of atrioventricular (AV) node synchronizes the contraction of cardiac chambers so that an atrial contraction improves ventricular filling during diastole (Meijler & Fisch 1989).

Atrial fibrillation is a common sustainable cardiac arrhythmia. It is characterized by rapid, irregular, fibrillatory electrical activity and asynchronous atrial contractions. Irregular atrial activity and heterogenic AV nodal conduction results in uneven, unpredictable and often undesirable ventricular contractions (pulse) where the upper rate is limited by the AV node refractory period (Bootsma et al. 1970). Furthermore, AF results in a loss of atrial contraction (and relaxation) and AV synchrony. Beat-to-beat variations in stroke volume and contractility further reduce left ventricular (LV) function (Brookes et al. 1998, Muntinga et al. 1999, Viswanathan et al. 2001).

The incidence of AF increases with age. Complex, individual and clinically important interactions occur when the changes in the function of the heart by AF interact with other aspects of cardiovascular health. AF has been shown to increase the risk of stroke and to be associated with increased mortality (Brand et al. 1985, Jouven et al. 1999). The loss of atrial contraction decreases atrial blood flow and increases the risk of clot formation and thromboembolic complications, especially in patients with other risk factors (Morley et al. 1996). A constantly high heart rate of more than 100 per minute may cause tachycardia-induced cardiomyopathy (TIC) (Shinbane et al. 1997, Umana et al. 2003), and patients with pre-existing heart failure or its risk factors are generally much more vulnerable to AF (Wang et al. 2003). Subjects with an accessory AV pathway with rapid antegrade conduction carry a significant risk of sudden cardiac death if AF occurs (Pietersen et al. 1992).
2.2 Definition and types of AF

Atrial fibrillation is generally classified according to the duration of the AF episodes. AF can also be classified according to presence of underlying diseases or the risk factors associated with AF. The subtypes of AF are summarised in table 1 (January et al. 2014).

**Table 1. Definitions of AF.**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF duration</strong></td>
<td></td>
</tr>
<tr>
<td>First diagnosed AF</td>
<td>AF diagnosed for the first time regardless of symptoms or duration of episode</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>Recurrent AF episodes that spontaneously terminate within one week, or are cardioverted within 2 days of onset</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>AF that lasts more than one week or is cardioverted 2 to 7 days after onset</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>Continuous AF that has lasted for more than one year when rhythm control is desired</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>AF when rhythm control is not attempted/desired</td>
</tr>
<tr>
<td><strong>Other clinical subtypes</strong></td>
<td></td>
</tr>
<tr>
<td>Lone AF</td>
<td>AF in patient without known risk factors</td>
</tr>
<tr>
<td>Silent AF</td>
<td>AF without symptoms, regardless of duration</td>
</tr>
<tr>
<td>Nonvalvular AF</td>
<td>AF without rheumatic mitral stenosis or previous mitral valve operation</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation

2.3 Epidemiology of AF

2.3.1 Prevalence and lifetime risk of developing AF

Atrial fibrillation is the most common sustained arrhythmia and it poses considerable therapeutic challenges to the clinician. The lifetime risk for developing AF after the age of forty is about one in four for both men and women (Lloyd-Jones et al. 2004). The prevalence of AF increases with age. At the age of 50–59 years, the estimated prevalence is 0.5% and thereafter it doubles in every decade, reaching about 9% in octogenarians (Kannel et al. 1998). Furthermore, the prevalence of atrial fibrillation has increased during the last two decades. This may be caused by several reasons. The most likely explanations include aging of the population, awareness and better diagnosis and improved prognosis of the
underlying diseases (e.g. heart failure, coronary artery disease or stroke) (Chugh et al. 2014).

2.3.2 Risk factors

Numerous risk factors for atrial fibrillation have been described. The “classical” risk factors are advancing age, congestive heart failure (HF), valve disease, diabetes, hypertension and previous myocardial infarction (Benjamin et al. 1994). More recently discovered risk factors include higher birth weight, obesity, sleep apnoea, increased pericardial fat, nonhypertensive blood pressure (systolic blood pressure ≥130 mmHg), diastolic heart failure, genetic variations, subclinical coronary artery disease (CAD), low or high physical activity and chronic kidney disease. In addition, some biomarkers seem to be associated with AF (Rienstra et al. 2012). The risk factors for AF are summarised in table 2 (January et al. 2014).

Table 2. AF risk factors.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ageing</td>
<td>Age related remodelling</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Systolic or diastolic dysfunction or heart failure</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Type II diabetes, long duration or poor glycaemic control add risk</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systolic blood pressure ≥130 mmHg, high pulse pressure</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Previous myocardial infarction, subclinical coronary artery disease, ischaemia</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>Cardiomyopathy, valvular or congenital heart disease, ventricular hypertrophy</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Reduced kidney function and albuminuria</td>
</tr>
<tr>
<td>Family history</td>
<td>Parental history of AF</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>9 loci susceptible to AF identified in genome wide association studies</td>
</tr>
<tr>
<td>Height</td>
<td>High adult height</td>
</tr>
<tr>
<td>Birth weight</td>
<td>High birth weight</td>
</tr>
<tr>
<td>Obesity</td>
<td>High body mass index, excess pericardial fat</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Smoking</td>
<td>Former or current smoking</td>
</tr>
<tr>
<td>Exercise</td>
<td>High-level endurance training or low physical activity</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Binge drinking, moderate or high alcohol consumption</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Hyperthyreosis, thyreotoxicosis, low serum thyrotropin level</td>
</tr>
<tr>
<td>Left atrial dilatation</td>
<td>Left atrial diameter above 40 mm</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Elevated C-reactive protein or B-type natriuretic peptide levels</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation
2.4 Clinical manifestation of AF

2.4.1 Symptoms

AF causes several symptoms, which may vary from mild to disabling in their intensity. Patients with symptomatic AF have often asymptomatic episodes as well (Page et al. 1994). It is assumed that most patients have experienced asymptomatic AF episodes before the actual diagnosis (Camm et al. 2010). In the Registry of the German Competence NETwork on atrial fibrillation, 75% of the patients with AF were symptomatic. In the general population, the proportion of asymptomatic AF patients is probably much larger (Rho & Page 2005). Common symptoms related to AF include palpitations, fatigue, dyspnoea, chest pain and dizziness (Nabauer et al. 2009). The absence of symptoms is not associated with a better prognosis (Flaker et al. 2005). Several clinical scores have been developed to help in the classification of AF symptoms. The European Heart Rhythm Association (EHRA) score is presented in table 3 (Camm et al. 2010).

Table 3. EHRA score of AF symptoms.

<table>
<thead>
<tr>
<th>EHRA class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHRA I</td>
<td>No symptoms</td>
</tr>
<tr>
<td>EHRA II</td>
<td>Mild symptoms, normal daily activity</td>
</tr>
<tr>
<td>EHRA III</td>
<td>Severe symptoms, normal daily activity affected</td>
</tr>
<tr>
<td>EHRA IV</td>
<td>Severe symptoms, normal daily activity no longer possible</td>
</tr>
</tbody>
</table>

2.4.2 Consequences

Although AF was first considered to be a benign phenomenon, the results of several large population based studies have repeatedly shown that AF exerts a significant impact on an individual’s health. Some studies have estimated that AF doubles mortality (Jouven et al. 1999, Kannel et al. 1998), but the effect of associated cardiovascular risk factors and AF therapy is hard to evaluate. The risk of stroke is fivefold higher in patients with AF (Wolf et al. 1991). AF is the leading cause of thromboembolic stroke and it is estimated to account for 20% of all strokes (Camm et al. 2010). Heart failure and AF are common coexisting conditions. It is estimated that AF is associated with a three times higher risk of developing HF (Krahn et al. 1995). Symptomatic heart failure is present in about 30% of patients with AF (Nabauer et al. 2009). AF has been also linked to an
increased risk of cognitive dysfunction and dementia (Kalantarian et al. 2013). The quality of life (QoL) is impaired and the risk of both depression and anxiety is increased (Dorian et al. 2000, Thrall et al. 2007).

Since AF is a common clinical condition with significant health impacts, it is not surprising that it is associated with substantial healthcare costs. In a Swedish nationwide study, the annual costs related to AF were estimated as about 7000 € per patient. The majority of the costs were related to complications like HF and stroke (54%) followed by hospitalisation (18%) and loss of production (12%) (Ericson et al. 2011). There has been a clear increase in AF related hospitalisations and AF has been shown to prolong hospital stay regardless of the fundamental reason for admission (Christiansen et al. 2013, Wong et al. 2012).

2.5 Diagnosis of AF

Diagnosis of AF should always be documented by electrocardiography (ECG). Its characteristic ECG features are irregular R-R intervals, the absence of P waves and irregular and/or multiform fast atrial activity (atrial cycle length usually <200 ms). Moreover, it has been proposed that some ECG features during normal sinus rhythm (SR) (e.g. long or short P wave duration, prolonged PR interval and frequent atrial premature beats; APBs) are associated either with diagnosed or future AF (Chong et al. 2012, Fukunami et al. 1991, Nielsen et al. 2013), but none of them has proven accurate enough to be introduced into clinical practice.

2.5.1 Electrocardiographic methods and screening

Although the classic 12 lead ECG is excellent for confirming the diagnosis, longer rhythm monitoring is often required for AF detection (Camm et al. 2012a, Kirchhof et al. 2007). Patients with a documented arrhythmia characteristic of AF lasting for at least 30 seconds or for the duration of the recording should be diagnosed as having AF (Calkins et al. 2012). There is a strong relationship between the intensity of monitoring and the ability to diagnose AF (Ziegler et al. 2006). In the presence of suspected AF related symptoms, monitoring strategy may be selected according to symptom duration and interval between symptoms. In certain clinical situations (e.g. cryptogenic stroke), the detection of AF is valuable regardless of whether or not they are accompanied by symptoms as it helps to guide therapy (Gladstone et al. 2014).
There are a number of devices and methods for long-term rhythm monitoring, the 24–48 hour Holter monitoring is most commonly used. However, a seven day Holter recording is superior to shorter recordings in detecting AF (Charitos et al. 2012). Telemetry possesses similar qualities and is commonly used for hospitalised patients, although some applications allow for longer term remote monitoring (Mittal et al. 2011).

Event recorders enable good linkage between symptoms and arrhythmia provided that the duration of the arrhythmias and compliance are sufficient. Seven day Holter recordings compared with scheduled and symptom triggered event recordings have both been estimated to identify AF in about 70% of patients (Kirchhof et al. 2007), but sensitivity is strongly dependent on the characteristics of the patient population (Camm et al. 2012a, Ziegler et al. 2006). External loop recorders are capable of undertaking a few weeks of ECG monitoring, but are somewhat inconvenient to the patient and require good motivation and a relatively short inter-symptom interval.

Implantable loop recorders provide long-term automatically triggered and patient initiated arrhythmia evaluation. They have been shown to efficiently reveal AF episodes in high risk patients (Bloch Thomsen et al. 2010, Hindricks et al. 2010). Patients with pacemakers may have atrial high rate episodes or automatic mode switching episodes, which indicate the probability of AF and warrant further clinical evaluation (Glotzer et al. 2003, Healey et al. 2012).

Quite recently, there has been increasing interest in AF screening. Novel innovations include smartphone or mobile phone linked ECG detection, automatic blood pressure machines with AF diagnostic algorithms, single lead portable ECG analysers and facial videos recordings. It is probable that these applications will be helpful in the diagnosis of silent AF. However, further studies will be needed to evaluate the use of novel screening methods in real life populations and to demonstrate that they confer additional benefits over contemporary methods in guiding therapy and reducing complications (Couderc et al. 2015, Lowres et al. 2014, Moran et al. 2013, Quinn & Gladstone 2014, Tieleman et al. 2014). Pulse palpation, when achievable, is recommended for subjects ≥65 years in the European AF guidelines (Camm et al. 2012b).

2.5.2 Differential diagnosis

Atrial fibrillation usually presents as an irregular narrow complex tachycardia. Narrow complex AF is most commonly confused with atrial flutter (AFL) or atrial
tachycardia (Shiyovich et al. 2010). AV nodal or AV re-entrant tachycardias are regular and may respond to vagal manoeuvres. It may be challenging to differentiate ventricular tachycardia (VT) from supraventricular tachycardias or AF in cases where there is a permanent or functional bundle branch block or in case of antegrade conduction over an accessory pathway (Wolf Parkinson White syndrome, WPW). Ventricular tachycardia is more likely to occur in the absence of BBB morphology, in the presence of extreme electrical axis deviation or extremely wide QRS complex (>160 ms). AV dissociation, capture or fusion beats or discordant complexes in ECG precordial leads (V1–V6) are diagnostic for VT (Alzand & Crijns 2011, Wellens 2001). The characteristics of narrow complex arrhythmias which are important in the differential diagnosis of AF are shown in figure 1.

![Fig. 1. Simple flow chart for differential diagnosis of atrial fibrillation. AF, atrial fibrillation; AT, atrial tachycardia; AFL, atrial flutter; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; IST, inappropriate sinus tachycardia.](image)

### 2.6 Pathophysiological mechanisms of AF

Our current understanding of the mechanisms of AF has been formed over several decades of active research, but there are still some gaps in our understanding. AF is a complex arrhythmia with a varied aetiological background and a very variable response to therapy (January et al. 2014, Kappenberger 2013, Rienstra et al. 2012, Rienstra et al. 2012). The fast and irregular electrical activity, complex
cellular level actions, unpredictable onset and duration of AF cause significant problems for conducting mechanistic studies in humans. Different mechanisms of AF may exist between patients and even in a single patient. Furthermore, the provision of any antiarrhythmic therapy results in changes in the underlying atrial pathophysiology (January et al. 2014, Nattel S & Harada M 2014).

2.6.1 Initiation

The mechanisms of AF initiation have been studied by body surface mapping, epicardial and endocardial electrocardiographic methods, in isolated atrial myocytes, in animal models and in humans. The earliest report that AF could be initiated in anesthetised dogs by programmed atrial stimulation was already published in 1948 (Scherf et al. 1948). However, later reports which demonstrated that AF could persist without ectopic activity, questioned the clinical role of triggered initiation (Bennett & Pentecost 1970, Moe & Abildskov 1959). It took several decades before the concept of AF triggers and their key role for catheter ablation therapy were recognized. In the landmark study of Haissaguerre et al., spontaneous ectopic atrial beats that initiated AF were most often (94%) recorded in pulmonary veins by endocardial multipolar electrode mapping. Furthermore, ablation of these focuses by radiofrequency energy was able to suppress AF in many of these patients (Haissaguerre et al. 1998). The pulmonary vein (PV) triggers are located in atrial myocardial sleeves that extend distally as far as 3 cm from PV ostia. It is thought that the electrophysiological characteristics of these muscular sleeves account for the frequent ectopic activity initiating AF. The discrete muscle fibres tend to be separated from the surrounding tissues similarly to cardiac nodal tissue. Spontaneous electrical activity is therefore favoured if there is a poor connection to inactive myocardial tissue during diastole. Myocardial fibres also show a complex fibre orientation, favouring conduction slowing, unidirectional block and re-entry. At the cellular level, a higher resting potential, greater predisposition to depolarisation, abnormal calcium handling, shorter action potential and slower conduction are thought to predispose to spontaneous activity and re-entry (Chen & Chen 2006, Nattel 2013).
2.6.2 Perpetuation

It is believed that arrhythmogenic vulnerable substrates play a key role in perpetuation of AF. Unfortunately, the nature of the substrate is less clear, more complex and has proved harder to directly demonstrate than that of the PV triggers. Different mechanisms have been proposed and may coexist in a single patient (January et al. 2014).

One of the earliest hypotheses that remained predominant for decades was that AF was perpetuated by multiple re-entrant wavelets. It was postulated that these independent wavelets randomly propagated in the atria and that this was attributable to heterogenic cellular changes in refractory period and conduction velocity (Moe & Abildskov 1959, Workman et al. 2008).

Later works have questioned the role of re-entry in AF maintenance and suggested that AF is maintained by rapid firing local drivers (automatic foci or re-entrant circuit) most often located in or close to the pulmonary veins (Waldo 2003). The pathological activity is due to abnormal automaticity or triggered activity. Abnormal automaticity may be promoted by autonomic nervous system activity. Triggered activity is thought to be caused by early or delayed afterdepolarisations related to prolonged action potentials or cellular calcium overload (January et al. 2014, Workman et al. 2008). In a recent investigation where AF was simultaneously recorded with 512 atrial electrograms it was demonstrated that 2–5 rapid focal drivers were sustaining AF until autonomic nervous system (ANS) stimulation was terminated (Lee et al. 2013). Other works have questioned the stability of such drivers (Lee et al. 2014).

Recently it has been proposed that it was an electric dissociation between endocardial and epicardial layers that was sustaining AF via an electrical breakthrough between layers producing new fibrillation waves (double layer hypothesis). This hypothesis has been tested with simultaneous dual layer recordings in instrumented goats and it was hypothesized that transmural breakthroughs would be more common than focal discharges (Eckstein et al. 2013).

2.6.3 Remodelling

There is strong evidence that changes in atrial cellular function and structure lead to AF and vice versa (Wijffels et al. 1995). Changes occur in response to different stress factors including cardiac and systemic diseases, aging and AF itself. Atrial
size was the earliest reported and is still a clinically significant sign of atrial remodelling (Henry et al. 1976, Vaziri et al. 1994). In pathological studies, atrial enlargement was claimed to result from profound changes in both cardiac myocytes and interstitium. Whereas myocytolysis and dedifferentiation have been observed in atrial myocytes, it has been reported that there are varying levels of interstitial collagen deposition forming thick connective tissue fibres around myocyte bundles (Boldt et al. 2004, Corradi 2014); of these changes, atrial fibrosis is probably the least reversible (Ausma et al. 2003, Corradi 2014).

2.6.4 Genetics

A family member of an AF patient is estimated to have about a 40% higher risk of suffering AF (Fox et al. 2004). This finding suggests that in addition to the rare familial forms of AF, there are genetic risk factors that account for AF risk at the population level. Genome-wide association studies have been able to identify 9 loci related to AF (Tucker NR & Ellinor PT 2014). Future studies may be able to identify new loci and genetic variants related to AF, specify genetic mechanisms that lead to AF and ultimately use them as treatment targets (Lubitz et al. 2014, Tucker NR & Ellinor PT 2014). According to international AF guidelines, genetic testing may be considered in patients with a multigenerational AF family history but this kind of testing does not currently provide prognostic benefits or have any clear therapeutic implications (January et al. 2014).

2.7 Management of AF

2.7.1 Initial evaluation and follow-up

Atrial fibrillation therapy calls for individual considerations and shared decision making (Seaburg et al. 2014). The underlying conditions that contribute to development of AF have to be recognized and managed. The risk of stroke (and bleeding) needs validation and therapeutic considerations. Arrhythmia symptoms and type of arrhythmias should be evaluated and antiarrhythmic therapy considered together with the patient (Camm et al. 2012b).

The initial evaluation should include medical history, review of symptoms (EHRA score), evaluation of conditions predisposing to AF and its complications. Patients should be subjected to a basic examination including ECG and
echocardiography to detect structural heart disease, LA size, basic heart rate, conduction disturbances and possible signs of an arrhythmia syndrome.

Follow-up is essential for determining newly developed underlying conditions, re-evaluating symptoms, assessing therapy efficacy and safety and evaluating disease progression (Camm et al. 2010).

2.7.2 Treatment of underlying diseases and conditions

Patients with AF often have one or several risk factors that predispose to the arrhythmia. It is important to diagnose these conditions and to optimize their treatment. It has been shown that patients initially diagnosed with lone AF may develop cardiovascular diseases during follow-up (Weijs et al. 2013). The treatment of underlying conditions is important not only to reduce AF recurrences or progression but also to diminish the risk of complications.

Recent studies have evaluated the value of lifestyle modification as a part of AF therapy. Weight loss has been linked to better symptom control, reduced AF burden and reverse remodelling (Abed et al. 2013). In another study, exercise training was associated with increased exercise capacity, lower resting heart rate and better QoL in AF patients (Osbak et al. 2011). Recently, aggressive risk factor modification has been shown to reduce AF relapses after CA (Pathak et al. 2014, Pathak et al. 2015).

2.7.3 Prevention of thromboembolic complications

Risk stratification

Most patients with AF benefit from oral anticoagulation therapy (Calkins 2015). An essential part of AF management is an evaluation of the risks of thromboembolic complications. Strokes caused by AF have a poor prognosis. Presently, there are several validated risk scores for individual evaluation of stroke risk in patients with AF. The use of the CHA₂DS₂-VASc score (table 4), which is recommended by the international guidelines, covers the most commonly confronted clinical risk factors. It has been demonstrated to identify patients with a truly low thromboembolic risk, whereas antithrombotic therapy is generally indicated in other patient groups. Individual bleeding history and risk should also be evaluated. There are several bleeding risk scores that have been
validated in AF patients; the HAS-BLED score (table 4) has been recommended by the European Society of Cardiology. However the American guidelines indicate that the accuracy and clinical utility of none of the existing bleeding scores is sufficient and their use is not recommended in the guidelines (Camm et al. 2012b, Friberg et al. 2012, January et al. 2014, Pisters et al. 2010).

Table 4. Thromboembolism and bleeding risk stratification with currently recommended risk scores.

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>Score</th>
<th>HAS-BLED</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>Hypertension (SBP &gt;160 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>Abnormal renal and liver function*</td>
<td>1 or 2 (1 point each)</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>2</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>Bleeding tendency/predisposition*</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td>Labile INRs with VKA therapy*</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disease*</td>
<td>1</td>
<td>Elderly (age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>1</td>
<td>Drugs or alcohol*</td>
<td>1 or 2 (1 point each)</td>
</tr>
<tr>
<td>Sex (female*)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Maximum score | Maximum score | 9 |
| Annual risk (score 1 to 9) | 0%–15.2% | Annual risk (score 0 to >5) | 1.0%–12.5% |

*Vascular disease indicates prior myocardial infarction, peripheral artery disease or aortic plaque. Female gender as a lone risk factor is not considered to necessitate antithrombotic therapy. Abnormal renal function indicates dialysis, renal transplantation or elevated creatinine (>200 mmol/L) and abnormal liver function indicates significant hepatic disease or derangement of hepatic function tests. History of bleeding or anaemia. Labile INR (high or unstable) or less than 60% of time in therapeutic range. Antiplatelet drugs, nonsteroidal anti-inflammatory drugs or excessive use of alcohol. TIA, transient ischaemic attack; TE, thromboembolic; SBP, systolic blood pressure; INR, international normalised ratio; VKA, vitamin K antagonists.

**Antiplatelet therapy**

The efficacy of stroke prevention with aspirin is modest in AF. In AF population studies, aspirin has been able to prevent strokes of non-cardioembolic origin (Hart et al. 2007). However in elderly patients, the bleeding risk with aspirin is similar to that encountered with oral anticoagulation therapy (Camm et al. 2012b). The combination of aspirin and clopidogrel provides better stroke prevention than aspirin, but the bleeding risk is higher than with oral anticoagulation therapy (Connolly et al. 2009b, Dogliotti et al. 2014). According to the international AF guidelines, antiplatelet therapy is recommended for stroke prevention only in selected cases (Camm et al. 2012b, January et al. 2014). Finally, the results of a
recent European survey indicated that the commonly used combination of antplatelet and anticoagulant therapy was often unjustified and increased the risk of bleeding (De Caterina et al. 2014).

**Oral anticoagulants**

Oral anticoagulation is the cornerstone in the prevention of thromboembolic complications in AF. Although vitamin K antagonists (VKA) have been available for decades, they have several limitations; narrow therapeutic window and individual adjusted dosing, food and drug interactions and frequent need for laboratory testing. It also seems that VKA initiation is related to an increased risk of thromboembolic complications (Azoulay et al. 2014, Granger et al. 2015).

There are several novel oral anticoagulants (NOAC) which have been evaluated in large randomized controlled trials e.g. the direct thrombin inhibitor, dabigatran (Connolly et al. 2009a) as well as factor Xa inhibitors, rivaroxaban (Patel et al. 2011), apixaban (Granger et al. 2011) and edoxaban (Giugliano et al. 2013). In a pooled analysis of 12 studies and 54,875 patients, NOACs were superior to VKA in terms of reduced mortality, cardiovascular mortality, thromboembolic complications and the incidence of intracranial haemorrhage (Dentali et al. 2012). Recent European registry data indicates that anticoagulation therapy was being prescribed to 80% of eligible patients and its use has increased with time (Kirchhof et al. 2014).

**Left atrial appendage closure**

Left atrial appendage (LAA) is the predominant site of thrombus formation in nonvalvular AF (Blackshear & Odell 1996, Mahajan et al. 2012). Therefore, several techniques have been designed to remove or occlude LAA. Percutaneous techniques include endocardial application of an occluder device or suture ligation combining endocardial and epicardial approaches. Although the safety and long term efficacy of the currently available devices have been questioned, LAA occlusion is an attractive therapeutic option, especially in patients with a high bleeding risk or an inability to tolerate oral anticoagulation (Ko & Hylek 2015).

Surgical approaches have been available for years, but they require open heart surgery and have failed to achieve any consistent results and therefore they are not routinely recommended (Kanderian et al. 2008).
2.7.4 Rate control

The optimisation of ventricular rate is essential for all patients with AF. This is beneficial for several reasons including symptom control, better exercise capacity and prevention of tachycardia-induced cardiomyopathy. However, strict rate control in permanent AF targeting resting heart rate of less than 80 beats per minute has not been found to be beneficial even in patients with heart failure. This approach more often requires multiple clinical evaluations, a higher number and higher doses of rate control drugs (Mulder et al. 2013, Van Gelder et al. 2010). It may be that a higher heart rate compared to sinus rhythm is required during AF in order to maintain cardiac output (Daoud et al. 1996).

Pharmacological rate control

Beta-blockers, non-dihydropyridine calcium channel blockers (CCB) and digoxin (alone or in various combinations) are the most commonly used drugs for rate control in patients with AF. Beta-blockers reduce ventricular rate at rest and during exercise, but may also reduce exercise capacity (Atwood et al. 1987, Boriani et al. 2003). They are the treatment of choice in patients with established structural heart disease. In paroxysmal AF, beta-blockers may prevent AF recurrences (Camm et al. 2010).

CCBs reduce heart rate both at rest and exercise. They may provoke AF recurrence in paroxysmal AF. Recently, CCBs have been proposed to be the first-line option in patients with permanent AF and no-to-minimal structural heart disease because of their ability to improve the exercise capacity (Ulimoen et al. 2014).

Recently, many reports have raised concern about the safety of digoxin in rate control. In the analysis of SPORTIF III and IV studies, that were designed to compare ximelagatran and warfarin, digoxin use was independently associated with increased mortality (Gjesdal et al. 2008). A similar finding was reported in two large retrospective cohorts evaluating the association of digoxin use to mortality (Freeman et al. 2015, Turakhia et al. 2014, Vamos et al. 2015).

Among the other AADs, only amiodarone is recommended for ventricular rate control in patients with permanent AF, but its long term use is limited by potential serious side effects (January et al. 2014). Sotalol has been shown to reduce heart rate in AF (Kochiadakis et al. 2001), but its use is not recommended because of the significant risk of proarrhythmia (MacNeil et al. 1993).
Dronedarone was anticipated to provide benefits in permanent AF, but in the PALLAS study, its use was associated with an increased risk of arrhythmic death and this drug is now contraindicated in rate control (Connolly et al. 2011).

The current evidence indicates that strict rate control in AF does not improve outcome or symptom status (Van Gelder et al. 2010). A resting heart rate of below 110 beats per minute is therefore recommended. Whether or not the neutral effect of strict rate control is related to the adverse effects of rate control medications, digoxin use should be limited more to patients with heart failure.

**Atrioventricular node ablation**

AV node ablation is a valuable option in patients with drug refractory AF and severe symptoms or tachycardia induced cardiomyopathy. This procedure has been shown to improve symptoms, quality of life, exercise capacity and left ventricular ejection fraction (LVEF) in patients with drug refractory tachycardic AF (Wood et al. 2000). In younger patients with AF, rhythm control strategy is usually preferred. Patients must be informed about permanent pacemaker dependency after AV node ablation (Camm et al. 2010, January et al. 2014). After AV nodal ablation, biventricular pacing is recommended for patients with symptomatic HF and reduced LVEF (<35%). It should also be considered for patients with less severe LV dysfunction and in those who develop HF during right ventricular pacing (Brignole et al. 2012).

### 2.7.5 Rhythm control

Rhythm control strategy aims to restore and maintain normal sinus SR. Many studies have evaluated the benefits of rhythm control compared to a rate control strategy but mostly with AAD therapy (Al-Khatib et al. 2014, de Denus et al. 2005). It is reasonable to assume that if SR is maintained, there would be a clear benefit not only in quality of life but also in survival. So far, pharmacological rhythm control has shown no benefits in hard clinical endpoints (*i.e.* all-cause mortality, cardiac mortality and stroke). Therefore, rhythm control is mainly recommended for symptom relief (Camm et al. 2010, January et al. 2014). Early rhythm control therapy may prevent AF progression (Avitall et al. 2008). There are several clinical situations in which rhythm control is preferable. Inadequate rate control or tachycardia induced cardiomyopathy, young age and patient preference are some of the factors that support rhythm control. Unfortunately, the
efficacy and safety of the currently available antiarrhythmic drugs are far from ideal.

**Cardioversion**

Cardioversion (CV) is a common clinical procedure where AF termination is attempted either with direct current shock or with AADs. The most important considerations in CV are the related risk of stroke, the probability of future rhythm control and possible haemodynamic instability during AF. The last of these options represents a rare clinical condition, whereas estimation of stroke risk, anticoagulation therapy and rationale of CV need to be evaluated every time.

There is increasing evidence about the importance of anticoagulation during CV even in patients with a short duration of AF. The first analyses of the FinCV population which examined 7660 acute cardioversions showed that in patients without oral anticoagulation or periprocedural heparin, thromboembolic complications were increased in the presence of thromboembolic risk factors shortly after CV (Airaksinen et al. 2013). The second analysis showed that if CV was performed between 12 to 48 hours after symptom onset, there was a significant increase in the thromboembolic risk compared to earlier CV (Nuotio et al. 2014). A recent report from a Danish retrospective cohort also detected an increased risk related to CV in patients without prior or subsequent anticoagulation (Hansen et al. 2015). These findings highlight the need of oral anticoagulation after CV and because of their rapid onset of action, NOACs may be the preferable choice (Airaksinen et al. 2013, Azoulay et al. 2014, Mayor 2013).

Electrical CV is highly effective in restoring normal SR. However, it may increase thromboembolic risk via “atrial stunning” after the procedure and it requires anaesthesia. However, atrial stunning is also present after spontaneous or pharmacologically induced transition to SR (Khan 2003). New agents for pharmacological CV are being studied. Rapid onset of action, efficacy and safety would be desired features but none of the currently available agents can be considered as ideal. The properties and efficacy of the currently available options for cardioversion are summarized in table 5 (Bash et al. 2012, Kirchhof et al. 2005, Rashba et al. 2004).
Table 5. Currently available methods for cardioversion of AF.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Usability</th>
<th>Conversion rate</th>
<th>Potential adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2h</td>
<td>8–24h</td>
</tr>
<tr>
<td>Placebo*</td>
<td>Peroral or intravenous, also “pill in the pocket”, not in SHD.</td>
<td>12%</td>
<td>Hypotension, AFL with 1:1 conduction, proarrhythmia</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Peroral or intravenous, also “pill in the pocket”, not in SHD.</td>
<td>64%</td>
<td>Hypotension, AFL with 1:1 conduction, proarrhythmia</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Peroral or intravenous, also “pill in the pocket”, not in SHD.</td>
<td>51%</td>
<td>Hypotension, AFL with 1:1 conduction, proarrhythmia</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>Intravenous, rapid effect.</td>
<td>52%</td>
<td>Hypotension, QT prolongation.</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Rapid effect, requires intensive monitoring, proarrhythmic.</td>
<td>50%</td>
<td>Hypotension, QT prolongation, TdP</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Peroral or intravenous, slow effect.</td>
<td>16%</td>
<td>Hypotension, phlebitis, bradycardia</td>
</tr>
<tr>
<td>DC energy</td>
<td>Requires anaesthesia</td>
<td>83–100%, higher</td>
<td>Hypotension, hypoventilation, with biphasic current thromboembolism, arrhythmias</td>
</tr>
</tbody>
</table>

*Placebo as compared with pharmacological cardioversion. AFL, atrial flutter; TdP, torsades de pointes; SHD, structural heart disease

**Long term antiarrhythmic drug therapy**

Atrial fibrillation is the most common indication for AAD therapy. Flecainide, propafenone, amiodarone, dronedarone and sotalol are the most extensively used antiarrhythmic agents today. Cardiac comorbidities and cardiac conduction properties must be evaluated before initiation and during AAD treatment.

Two Vaughan-Williams class IC agents, flecainide and propafenone, are fast sodium channel blockers that have been shown to slow the velocity of atrial conduction and to prolong the atrial effective refractory period in rate-dependent manner (Wang et al. 1995). They may also increase the excitable gap (Wijffels et al. 2000). Today, class IC agents are the mainstream of AAD therapy due to their relatively good efficacy and good safety profile in selected patients. They should however be avoided in patients with CAD, HF or structural heart disease.

Amiodarone and dronedarone are multichannel blockers with properties which encompass all Vaughan Williams classes. Dronedarone causes fewer adverse events than amiodarone, but it is also less effective (Piccini et al. 2009a). In indirect comparisons, its efficacy has also been postulated to be lower than that of class IC agents (Freemantle et al. 2011). Its use has also been limited due to suspected liver toxicity (Friberg 2014) and uncertainties followed by reported excess mortality in patients with permanent AF in the PALLAS trial (Connolly et
Amiodarone is the most effective AAD for the maintenance of SR and is also usable in the presence of structural heart disease. On the downside, it has a number of potential extra-cardiac adverse side effects. Sotalol is a class III antiarrhythmic agent which also blocks beta-adrenergic receptors. It can be used in patients with CAD, but it prolongs QT interval and may cause torsades de pointes. Most studies in AF patients have been underpowered to evaluate the association of sotalol or amiodarone use and mortality, but an association to increased mortality has been reported for both agents (Piccini et al. 2014, Singh et al. 2005).

AFFIRM trial is probably the most influential trial comparing AADs to rate control. This trial included a large number of patients with all AF subtypes. The on-treatment analysis suggested that patients in SR had a better survival, but this was offset by excess mortality related to use of AADs (Corley et al. 2004). The most commonly used drugs in the AFFIRM trial were amiodarone and sotalol. Since then, the selection of patients and AADs has probably evolved and the proportion of patients being treated with AADs declined (Andersen et al. 2009, Andrade et al. 2010, Reiffel et al. 2010).

Table 6 summarises the efficacy of AADs in the maintenance of SR (Freemantle et al. 2011).

Table 6. Efficacy of antiarrhythmic drugs in the maintenance of sinus rhythm.

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of studies/patients*</th>
<th>AF recurrence rate vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>3/149</td>
<td>42% vs. 72%</td>
</tr>
<tr>
<td>Propafenone</td>
<td>6/1425</td>
<td>48% vs. 73%</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>2/1507</td>
<td>68% vs. 78%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>6/771</td>
<td>36% vs. 78%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>10/2471</td>
<td>60% vs. 65%</td>
</tr>
</tbody>
</table>

* No. of studies and patients in trials comparing drug therapy against placebo. AF, atrial fibrillation

Catheter ablation

Catheter ablation currently aims to isolate AF triggering areas (usually pulmonary veins) and/or to modify the arrhythmogenic atrial substrate in order to prevent AF initiation and perpetuation. AF ablation is a complex procedure with constantly evolving methods and technology (Calkins et al. 2012).

AF ablation has been evaluated for all AF subtypes and in the presence or absence of cardiac comorbidities. CA has been compared to AAD therapy after
the initial failure of AAD therapy in several randomised trials. Meta-analyses from these studies have shown that CA has superior efficacy, but reported adverse events were more serious compared to AAD therapy (Bonanno et al. 2010, Calkins et al. 2009, Nair et al. 2009, Piccini et al. 2009b). AF ablation indications and techniques are discussed in detail in the following pages.

**Surgery**

Surgical ablation (SA) appeared several years prior to CA originating from experimental AF models and experiences with surgical treatment of other cardiac arrhythmias. This evolved into the Cox maze procedure where the possibility of macroentrant circuits was abolished by cut and sew compartmentation of the atria while still maintaining internodal conduction. This technique was however both challenging and time consuming (Cox 2011, Prystowsky 2008).

Less invasive surgical methods including radiofrequency or cryoablation have later been studied. FAST investigators compared CA and stand-alone thoracoscopic SA in patients with previously unsuccessful antiarrhythmic therapy (AADs or CA). At the 12 months’ follow-up, the efficacy of surgical ablation was superior to CA but serious adverse events were common with SA (Boersma et al. 2012). SA is feasible in selected patients during concomitant cardiac surgery whereas stand-alone SA may be conducted in highly symptomatic patients, who have shown a poor response to AAD and/or CA therapy (Calkins et al. 2012, January et al. 2014).

### 2.8 Catheter ablation of atrial fibrillation

#### 2.8.1 Indications

Catheter ablation is an invasive procedure that carries a risk of serious complications. There is a large body of evidence that CA reduces AF related symptoms and improves QoL. Therefore, the fundamental reason to perform ablation is to alleviate AF related symptoms (Calkins et al. 2012).

CA is most efficient in young patients with paroxysmal AF and low comorbidity (Leong-Sit et al. 2010). Moreover, the possible exposure to several decades of AAD therapy is not desirable in these patients. Advanced age itself however, is not a contraindication for CA. In selected populations, the efficacy of
CA has remained even in elderly subjects (Corrado et al. 2008). The risk of periprocedural complications is higher than in younger patients, but it should not be overlooked that elderly people are also more vulnerable to risks of AAD therapy (Blandino et al. 2013, Deshmukh et al. 2013).

Current evidence does not support the use of CA as a means to reduce the risk of thromboembolic complications or to eliminate the need for anticoagulation therapy. Hence, CA should not be performed in asymptomatic patients because of the unclear benefit, procedural risk, expenses and resource utilisation (January et al. 2014, Kochhauser & Verma 2015).

When CA is planned, the patient must be informed about the individual risks and benefits of the procedure compared to other therapeutic approaches. The recommended indications for AF ablation according to international AF guidelines are summarised in table 7 (Calkins et al. 2012, January et al. 2014).

Table 7. Indications of AF ablation.

<table>
<thead>
<tr>
<th>Indication</th>
<th>COR and LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA is recommended in symptomatic patients with drug-refractory or drug intolerant paroxysmal AF</td>
<td>I/C</td>
</tr>
<tr>
<td>CA is reasonable as the first-line therapy in symptomatic patients with paroxysmal AF after weighing the risks and benefits of the therapy</td>
<td>IIa/B</td>
</tr>
<tr>
<td>CA is reasonable in symptomatic patients with drug-refractory or drug intolerant persistent AF</td>
<td>IIa/A</td>
</tr>
<tr>
<td>CA may be considered as the first-line therapy in symptomatic patients with persistent AF after weighing the risks and benefits of the therapy</td>
<td>IIb/C</td>
</tr>
<tr>
<td>CA may be considered in symptomatic patients with long standing persistent AF</td>
<td>IIb/B</td>
</tr>
<tr>
<td>CA of the accessory pathway is recommended in symptomatic patients with pre-excited AF</td>
<td>I/C</td>
</tr>
</tbody>
</table>

CA, catheter ablation; COR, class of recommendation; LOE, level of evidence AF, atrial fibrillation

2.8.2 Techniques

Basics of AF ablation

Diagnostic catheters are usually advanced to the heart via the femoral veins in order to obtain intracardiac electrograms, enable pacing and to act as anatomical references. Transseptal (TS) puncture is performed with a long needle inserted inside a TS sheath. After advancing the sheath into left atrium (LA), the needle
and the dilator are replaced with an ablation catheter. Navigation inside LA is
guided by 3D electroanatomical mapping, fluoroscopy and/or intracardiac
echocardiography (ICE). Energy is transmitted with an ablation system to the LA
endocardial surface in order to produce a scar that isolates the PVs, eliminates
other triggers or modifies the atrial arrhythmogenic substrate.

**Pulmonary vein isolation**

Pulmonary vein isolation (PVI) forms the basis for virtually all CA techniques. The evolution of the PVI technique is presented in figure 2.

A. Focal ablation  
B. PVP elimination  
C. Anatomic isolation

![Fig. 2. The evolution from the initial discovery and ablation of focal pulmonary vein (PV) triggers (red stars) into the current application of wide circumferential PV isolation. (A) The initial strategy involved intracardiac mapping of spontaneous AF triggers and ablation to the site of earliest ectopic activity inside PVs (Haissaguerre et al. 1998). (B) It was noted that ectopic activity was inconsistent and often occurred in ostial PV areas and in multiple PVs. Therefore, ostial ablation was performed with the goal of completely isolating the PVs (Haissaguerre et al. 2000a). A method of segmental ostial ablation combining mapping with a circular decapolar catheter and ablation with a separate catheter was introduced (Haissaguerre et al. 2000b). (C) Early on, a method of creating a continuous ablation line around PVs guided by electroanatomical mapping was introduced (Pappone et al. 1999) and was later found to be more effective than segmental ostial ablation in a randomised trial (Arentz et al. 2007).](image-url)
Ablation of non-pulmonary vein triggers

Several investigators have reported on the initiation of AF from non-PV foci. These foci include superior and inferior vena cava, LA posterior wall, crista terminalis, coronary sinus, fossa ovalis, ligament of Marshall and tricuspid and mitral annulus. Some researchers have claimed that elimination of these non-PV triggers alone may eliminate AF (Chen & Tai 2005, Lin et al. 2003). Others have proposed that these non-PV triggers may be a sign of more advanced disease and predict a worse treatment outcome (Chang et al. 2013, Usui et al. 2015). Several manoeuvres have been used to provoke and identify non-PV triggers (Calkins et al. 2012).

Substrate ablation

Additional ablation beyond PV isolation is used especially in persistent AF (Parkash et al. 2011). This strategy aims to locate and eliminate the arrhythmogenic substrate that maintains AF. Some centres have proposed a stepwise ablation strategy where additional substrate ablation strategies are applied until AF is terminated (O'Neill et al. 2009, Scherr et al. 2015). Since there are a number of technical approaches and procedural end points for substrate modification, it is not surprising that there is variability in outcomes and controversy about the use of the different approaches. It has been reported that intensive ablation strategy is associated with an increase of procedure duration and complications (Scherr et al. 2015).

Linear ablation was the earliest form of AF ablation. It was initially considered ineffective as a stand-alone procedure. Subsequently, acceptable long term results for pure linear ablation in persistent atrial fibrillation have been reported (Wu et al. 2014). Usually linear ablation is performed after PVI. The most common linear ablation lesions include LA roof line connecting left and right PV encircling lesions, mitral isthmus line connecting the mitral annulus to left sided PV encircling line, anterior line connecting the mitral annulus to the roof line or either PV encircling line. Cavotricuspid isthmus ablation may be conducted if typical atrial flutter has been documented. It is always recommended to verify complete block over the ablation lines, because there is a report that an incomplete linear lesion increases the risk of LA flutter and LA tachycardia (Sawhney et al. 2010). A recent meta-analysis has postulated that PVI combined with LA linear ablation achieves the most favourable outcome compared to other
approaches in patients with persistent AF (Wynn et al. 2014). The use of linear ablation has not been found to be beneficial in paroxysmal AF (Arbelo et al. 2014, Kim et al. 2014, Mun et al. 2012) and a recent article by Verma et al. also questioned its role in persistent AF (Verma et al. 2015).

Another method was introduced in 2004, this involved the ablation of complex fractionated electrogram (CFAE) areas (Nademee et al. 2004). These areas are thought to have poor intercellular connections which may produce uncoordinated and slow depolarisation patterns. Alternatively they may represent regions of wavelet pivot points, wave collisions, fibrillatory conduction or rotor meandering (Viles-Gonzalez et al. 2013). The intracardiac signals at the CFAE areas are characterised by low voltage multipotential signals and short cycle lengths. The CFAE sites were first defined by the operator and heterogeneity in their detection was considerable. Later automated softwares have been used to unify classification of the CFAE, but their adoption has not been universal (Caldwell & Redfearn 2012). CFAE areas have been shown to associate with locations on ganglionated plexi and are possibly linked to autonomic nervous system function (Lin et al. 2009). Ablation of CFAE areas has been noted to terminate AF. Some meta-analyses have detected some benefits from CFAE ablation (Hayward et al. 2011, Kong et al. 2011), but recent evidence suggests that CFAE ablation does not improve outcome in persistent AF in comparison to PVI (Verma et al. 2015) and subjecting large areas to ablation potentially increases the risk of complications.

Ganglionated plexi (GP) have also been used as an ablation target in both CA and SA. There are four major GP embedded in pericardial fat around human atria. GP have been ablated by either empiric ablation of anatomical areas of normal GP locations or by locating them by applying high frequency endocardial stimulation to provoke a vagal response in order to locate areas adjacent to GP. Nonetheless this method has been surrounded by considerable controversy. First, experimental models have suggested that partial or even complete GP ablation may itself provoke AF (Hirose et al. 2002, Mao et al. 2014). Secondly, a higher ablation power and duration may be needed to indirectly target GP, thus increasing the risk of complications (Chugh 2013).

Dominant frequency (DF) analysis is performed by recording intracardiac signals at different LA sites and after computerised processing, the signal with the highest amplitude frequency is defined. The concept is to identify the high frequency sites that potentially perpetuate AF. It is assumed that those sites with the highest frequency represent local sources where AF is maintained and because
of variations in both conduction and refractoriness, the frequency is lower elsewhere in the atria. Ultimately, the areas with the highest dominant frequencies are postulated to represent AF sustaining rotors and ablation targets. The first report of DF site ablation was published in 2005 (Sanders et al. 2005). This approach has been also combined to CFAE ablation in some studies (Kumagai et al. 2013). Nonetheless, the use of DF mapping and ablation in AF is still at the experimental level.

Recently, a procedure called rotor ablation has been a focus of increasing enthusiasm. It is based on the hypothesis of focal sources sustaining AF (Sahadevan et al. 2004). DF analysis aims to reveal in an indirect manner the presence of rotor(s). In this technique, the rotors that perpetuate AF are mapped by single or biatrial multipolar endocardial basket catheters, which allow for simultaneous recordings around the atria. This data is then computerised and presented as movies of AF activation cycles in order to identify the focal rotor(s) (Narayan et al. 2012). Rotor ablation has been used in all types of AF (Zaman et al. 2015) and has been demonstrated to be superior to PVI alone (Narayan et al. 2014). Noninvasive panoramic mapping has also been used to locate rotor activity. In this technique, multiple skin electrode recordings are spatially integrated into the atrial geometry with computed tomography (CT) image integration (Haissaguerre et al. 2013).

Energy sources and ablation catheters

Two alternative methods are predominantly used in CA; radiofrequency (RF) and cryoablation. Radiofrequency energy is low voltage, high frequency alternating current electricity that is delivered through the metal tip of the ablation catheter to adjacent tissue. The temperature of around 50°C causes permanent tissue damage and the lesion size is dependent on the duration of energy delivery. Three types of catheters have been used; closed tip, cooled tip and open irrigated catheters. Cooled catheters allow a deeper lesion; open irrigation has been demonstrated to reduce thrombus formation and steam pops (Thomas et al. 2004). Recent innovations include contact force sensing catheters (Natale et al. 2014), decapolar circular RF ablation catheters (Zellerhoff et al. 2014) and balloon RF ablation catheters (Sohara et al. 2009).

In cryoablation, liquid nitrous oxide is circulated to the distal end of the ablation catheter to produce tissue cooling. This causes the formation of extravascular and intra-cellular ice, leading to a vascular injury and the cessation of blood flow.
When tissue rewarms, the hyperaemia and increased capillary permeability result in vascular occlusion and cell death (Piccini & Daubert 2011). This technique was first used in SA. Point by point cryoablation has limited efficacy in PVI. Cryoablation with a deflectable balloon, which is delivered to the PV antral area is now mostly used (Sarabanda et al. 2005). The efficacy of lesion formation depends on the warming effect of the circulating blood and tissue contact. PV occlusion with balloon catheter at ablation is therefore necessary. It has been stated that cryoablation has similar efficacy and safety outcomes compared to RF ablation (Jourda et al. 2015).

Other energy sources for AF ablation include high intensity focused ultrasound (HIFU) and laser ablation. HIFU ablation has been withdrawn from clinical use due to high risk of the development of atrio-oesophageal fistula (Neven et al. 2010). Endoscopic laser balloon ablation has been approved in Europe. In this technique, a laser beam is targeted under endoscopic visual guidance through a compliant balloon to the PV antrum (Schmidt et al. 2010). Preliminary studies have reported good acute PV isolation rates and similar results in freedom from AF recurrence compared to PVI by RFA (Dukkipati et al. 2013).

**Periprocedural imaging**

Electroanatomic mapping systems are commonly used to guide point by point circumferential PVI. These approaches allow good spatial resolution and reduce radiation exposure (Sporton et al. 2004). The catheter position is either calculated in relation to electromagnetic fields or electrical signals between skin electrodes. Computed tomography, magnetic resonance imaging (MRI) or ICE images may be merged with the electroanatomic maps during ablation (Dong et al. 2006).

Intracardiac echocardiography has been used to guide TS puncture, to identify PV ostia, oesophagus and pericardium, to guide catheter placement, to guide energy titration and to detect thrombus formation (Camm et al. 2012b).

Rotational or PV angiography may be used in order to identify LA or PV structure, to locate PV ostia or to assess PV stenosis (Camm et al. 2012b).
2.8.3 Outcomes

Efficacy

The vast majority of studies have compared CA to AAD therapy in symptomatic and mainly in patients with paroxysmal AF after ineffective or intolerated AAD therapy. There are at least six meta-analyses estimating the efficacy of CA which have evaluated from 4 to 63 trials (Bonanno et al. 2010, Calkins et al. 2009, Ganesan et al. 2013, Nair et al. 2009, Noheria et al. 2008, Piccini et al. 2009b). In the largest meta-analysis, the single procedure success was estimated to be 57% and the multiple procedure success was higher, 71%, without the need for AAD therapy during a mean follow-up of 14 months (Calkins et al. 2009).

There are only three randomised studies that have compared RFA and AAD as first-line therapy. RAAFT-1 was published in 2005. It included 70 patients and concluded that CA was effective as a first-line therapy (Wazni et al. 2005). MANTRA-PAF was the largest trial; it examined 294 patients and concluded that cumulative AF burden and complications were similar between RFA and AAD therapy. However 36% of patients in AAD treatment group underwent PVI (Cosedis Nielsen et al. 2012). The RAAFT-2 study included 127 patients and reported that CA resulted in fewer atrial tachyarrhythmias during the two year follow-up. Almost every second patient (48%) in the AAD group subsequently underwent ablation during the follow-up (Morillo et al. 2014). Overall, there has been a high rate of crossover (i.e. to receive the alternative therapy) during follow-up in the studies comparing AAD and ablation therapy. These studies will be considered in more detail.

In general, the proportion of patients with non-paroxysmal AF has been relatively low in most CA studies. Furthermore as described above, the methods adopted to achieve CA in persistent AF have been complex and variable between individual studies. The efficacy of CA (or any antiarrhythmic therapy) is lower in persistent AF (Oral et al. 2002). In a recent meta-analysis of 46 studies and 3819 patients, CA was found to have superior efficacy over AADs in persistent AF (Wynn et al. 2014). However, as demonstrated by a recent study, freedom from AF after a single procedure in persistent AF is low (35% at 1 year and 17% at 5 years), but improved significantly after multiple procedures (65% at 5 years) (Scherr et al. 2015).

The efficacy of CA is reduced with advanced age and comorbidity. AF is clearly associated with HF, resulting in a poor outcome. In fact the presence of
HF limits the choices of AAD therapy (Trulock et al. 2014). Therefore, some trials have compared CA to rate control in patients with HF. In this setting, CA often restored SR, reduced symptoms, improved functional capacity and LVEF (Hunter et al. 2014, Jones et al. 2013). In a recent meta-analysis of 26 studies, CA was able to maintain SR in 60% of the patients during two years, the efficacy of a single procedure was less *i.e.* 40% (Anselmino et al. 2014). Overall, the studies of CA in patients with HF represent selected populations and more studies will be needed before it will be possible to establish guidance on when and how to apply CA in this setting (Trulock et al. 2014).

**Safety**

Catheter ablation of AF is a complex procedure and carries a risk of serious complications. On the other hand, antiarrhythmic therapy is not risk free. After the initial findings of PV stenosis, stroke and oesophageal damage, a determined and still on-going effort was made to develop new methods and improved techniques to minimise complications. Table 8 summarises common AF ablation complications detected in the larger international surveys and meta-analyses (Cappato et al. 2010, Gupta et al. 2013, Hoyt et al. 2011).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate,%</th>
<th>Complication</th>
<th>Rate,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.06–0.15</td>
<td>Femoral haematoma</td>
<td>1.53</td>
</tr>
<tr>
<td>Tamponade/perforation</td>
<td>1.0–1.31</td>
<td>Arteriovenous fistula</td>
<td>0.04–0.43</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0.80–1.1</td>
<td>Femoral pseudoaneurysm</td>
<td>0.43–0.93</td>
</tr>
<tr>
<td>Diaphragmatic paralysis</td>
<td>0.17–0.30</td>
<td>Sepsis</td>
<td>0.01–0.14</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1.22</td>
<td>Myocardial infarction</td>
<td>0.07</td>
</tr>
<tr>
<td>Significant PV stenosis</td>
<td>0.08–0.50</td>
<td>Pneumothorax</td>
<td>0.07–0.20</td>
</tr>
<tr>
<td>Atrio-oesophageal fistula</td>
<td>0.08–0.54</td>
<td>Haemothorax</td>
<td>0.02–0.22</td>
</tr>
<tr>
<td>Valvular damage</td>
<td>0.07–0.20</td>
<td>Serious bleeding</td>
<td>0.36–0.80</td>
</tr>
</tbody>
</table>

TIA, transient ischaemic attack; PV, pulmonary vein

**Prevention of procedure related thromboembolic complications**

Several advances in procedural techniques have led to a reduction in the numbers of procedural complications. Prior to CA procedure, attention should be paid to the anticoagulant therapy and imaging should be conducted. Anticoagulation therapy (if not contraindicated) should be at a therapeutic level for at least 3
weeks before the procedure in order to reduce thromboembolic complications. Transoesophageal echocardiography (TOE) is often performed prior to the ablation procedure. It has been reported that a higher thromboembolic risk score, a longer AF duration and AF at presentation all carry a higher risk of the development of an LAA thrombus (Camm et al. 2012b). Some centres prefer using bridge therapy in patients using vitamin K antagonists i.e. VKA is interrupted before the procedure and instead heparin or low molecular weight heparin (LMWH) is used for anticoagulation during the periprocedural time. However, recent evidence has suggested that bridging therapy is associated with more bleeding and thromboembolic complications (Di Biase et al. 2014, Santangeli et al. 2012).

During the ablation procedure, heparin is administered before and/or immediately after TS puncture. The sheaths and the open-irrigated ablation catheters are flushed with heparinised saline to prevent thrombus formation during mapping and ablation. Repeated measurements of activated clotting time (ACT) are recommended and heparin boluses given to maintain ACT >300ms during the procedure (Camm et al. 2012b).

Recent meta-analyses and multicentre studies have compared the efficacies of VKA, dabigatran, rivaroxaban and apixaban as periprocedural anticoagulation. No difference was noted in efficacy or safety between the drugs (Aryal et al. 2014, Di Biase et al. 2015, Stepanyan et al. 2014). Since the transition between NOACs and VKA carries an increased thromboembolic and bleeding risk (Granger et al. 2015), it seems that there may be no reason for this practice. However, before antagonists for NOACs are introduced into common clinical practice, the risk of severe bleeding related to CA may limit their use. At least 2–3 months of oral anticoagulation therapy should be maintained after the procedure and thereafter as clinically indicated (January et al. 2014).

### 2.8.4 Challenges

There are several challenges related to AF ablation. PV reconnection is a common phenomenon; this may develop acutely in up to 50% and later in up to 80% of the patients (Cappato et al. 2003, Sauer et al. 2006). However the mechanisms underpinning this reconnection are far from clear. They may be caused by imperfect ablation lines, anatomical individual variation or reformation of conductive tissue (Rajappan et al. 2008). Contact-force sensing catheters may offer better lesion formation (Providencia et al. 2015). Some studies have
indicated that long term relapses are mostly due to causes other than PV reconnection (Usui et al. 2015).

Another important question is whether the arrhythmogenic substrate should be modified and if so, how this should be achieved. At the moment, there is no evidence to support additional substrate modification in paroxysmal AF. In non-paroxysmal AF, additional substrate modification may be necessary but the best means to undertake this procedure remain to be established. Recently, rotor ablation and isolation of fibrotic areas have displayed some promise but it seems that an individual strategy tailored to each patient will still likely be required in the future (Kottkamp et al. 2015).

CA is currently a feasible approach for a limited proportion of patients with AF. It will be essential to improve both its efficacy and safety if CA is to become the mainstream of AF therapy. Even in selected patient groups, the results are somewhat unpredictable. Many studies have addressed the important question of whether there are any factors that can be determined that could predict the efficacy of AF ablation (Calkins et al. 2012). The single most important advance has been the discovery of a fibrotic process behind AF. It was recently reported that the extent of atrial tissue fibrosis, as determined with preprocedural MRI, seems to predict CA outcome in repeated settings (Marrouche et al. 2014). However, the MRI technique is demanding and costly and thus new methods for better patient selection need to be developed.
3 Aims of the study

The purpose of this study was to provide new information about the role of ablation therapy in AF. The focus was on the efficacy and safety, the role of first-line therapy and prognostic factors. The specific aims of the study were:

1. To evaluate the efficacy and safety of first-line RF ablation compared to standard antiarrhythmic drug therapy (I, II).
2. To determine the safety of RF ablation in patients with ongoing oral anticoagulation with warfarin (III).
3. To investigate the electrocardiographic changes related to initiation of AF and their relation to outcome of antiarrhythmic therapy (IV).
4. To examine the relationship between echocardiographic variables and RF ablation outcome (V).
4 Materials and methods

4.1 Meta-analysis (I)

4.1.1 Literature search

PubMed, Scopus, Cochrane, ClinicalTrials.gov and Google search engines were used to search for published, unpublished and ongoing studies. Trials were collected on 13th of August 2014. The following search terms were used: ‘atrial fibrillation’, ‘ablation’, ‘isolation’, ‘drug*’, ‘antiarrhythmic’, ‘medica*’, and ‘random*’. Reference lists of relevant articles were further inspected.

4.1.2 Data extraction

Search results were screened by two reviewers. Prospective, randomised, controlled trials comparing the efficacy and safety of first-line AAD and RFA therapy in paroxysmal AF were selected.

Pre-defined study design and baseline characteristics were included. Primary outcome measures were freedom from AF recurrence and proportion of patients without symptomatic AF relapse. Secondary outcome measures were the proportion of crossover to control therapy, reablation and adverse events related to therapy.

4.2 MANTRA-PAF data analyses (II, IV)

The Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) was a prospective randomized study conducted in nine centres in Denmark, Finland, Sweden and Germany. The study was approved by the local ethics committee and patients gave their written informed consent. An on-treatment analysis and baseline Holter recording analysis was performed on the MANTRA-PAF data.

4.2.1 Inclusion, exclusion and randomisation

A total of 294 patients with at least 2 documented episodes of symptomatic paroxysmal AF during the past 6 months and an indication for antiarrhythmic
therapy were included the MANTRA-PAF trial which ran between June 2005 and March 2009. Patients of age more than 70 years and those with previous antiarrhythmic drug therapy with class I or class III agents, severe LA dilatation (>50 mm), severe heart failure (LVEF <40% or NYHA III–IV), significant structural heart disease or secondary AF were excluded. Stratified block randomization was used to assign patients to either AAD or RFA therapy.

The baseline investigations included transthoracic echocardiography (TTE), 7 day Holter recording, evaluation of quality of life and symptom severity assessment.

4.2.2 Antiarrhythmic drug therapy

The first-line AADs were class IC antiarrhythmic agents, flecainide and propafenone. When there was a contraindication to their use, a class III agent, i.e. amiodarone or sotalol, was prescribed. Recommended AAD dosages were 100 mg twice a day (BID) for flecainide, 300 mg BID for propafenone, 200 mg per day for amiodarone and 80–120 mg BID for sotalol. AV conduction slowing drugs were recommended with class IC agents. If the initial AAD failed, it was recommended to try another AAD or to consider RFA if it was clinically indicated and the use of other AADs was not feasible.

4.2.3 Radiofrequency catheter ablation

Effective oral anticoagulation therapy (OAT) for at least 3 weeks before ablation was recommended. TOE was performed to rule out LAA thrombus. Anticoagulation during the procedure was performed according to institutional standards. Electroanatomical mapping was used to guide PVI with either a 3.5 mm irrigated tip or an 8 mm solid tip catheter. Additional ablation of LA roof and mitral isthmus were optional. Successful elimination of high frequency electric activity >0.2 mV inside the encircled area was documented either by electroanatomical mapping or by a circular mapping catheter. Cavotricuspid isthmus ablation was performed if a typical AFL had been documented previously or during the procedure.

Antiarrhythmic drugs were allowed during the 3 month “blanking period” after CA during which relapses are common and do not necessarily indicate treatment failure. If there were AF relapses and reablation was not feasible, supplementary AAD therapy was provided.
4.2.4 Follow-up

Clinical controls together with 7 day Holter monitoring were performed 3, 6, 12, 18 and 24 months after the first antiarrhythmic therapy. Patient log-books were used to collect information about AF relapses, health care contacts and sick leave periods. TTE and QoL assessments were repeated after 12 and 24 months.

4.2.5 On-treatment analysis (II)

On-treatment analysis of the MANTRA-PAF data was performed to compare three groups of patients:

1. Patients that received only RFA therapy.
2. Patients that received only AAD therapy.
3. Patients that received the assigned therapy and also the alternative therapy after the 3 month blanking period.

Primary endpoints were cumulative and per visit AF burden in 7 day Holter recordings. Secondary endpoints were freedom from all AF and symptomatic AF, differences in QoL assessments and all adverse events during the follow-up. AF episodes lasting for at least 60 seconds (duration defined in study protocol) after the blanking period were counted as relapse and included in AF burden.

4.2.6 Baseline Holter recording analysis (IV)

All available baseline Holter recordings of the MANTRA-PAF study were analysed in order to evaluate the impact of baseline AF episode characteristics on the long-term efficacy of the assigned antiarrhythmic therapy.

In the final analysis, 124 patients with documented AF episode(s) in their baseline Holter recordings were included. Holter analysis was performed by the same physician without knowledge of treatment outcome. All AF episodes were analysed and care was taken to differentiate between AF and AFL. The duration and the interval between episodes were noted. The episode onset was analysed with help of preceding rhythm analysis if necessary. Atrial premature beat coupling interval and R-R interval were measured at AF initiation as illustrated in figure 3. Any subsequent electrical activity following APB was analysed. The number of atrial and ventricular premature beats and all other rhythm disturbances occurring during the 60 minutes preceding AF initiation were
documented. Digitised Holter recordings were manually analysed at 50 mm/s sweep speed.

Patients were divided into two groups based on AF recurrence(s) (≥60 s) during follow-up. Atrial fibrillation episode characteristics were compared between the groups.

Fig. 3. ECG measurements at AF initiation. APB, atrial premature beat.

4.3 Safety of uninterrupted anticoagulation therapy in AF ablation (III)

4.3.1 Study population

In this observational study, all 228 AF ablation procedures conducted in 193 patients treated from 2006 to 2008 at Oulu University Hospital were included. Patients were classified into two groups according to the level of anticoagulation at the time of the ablation procedure. If there was the presence of LA thrombus in preprocedural TOE or values of the international normalised ratio (INR) were above 3.5, then the procedure was postponed.

4.3.2 AF ablation procedure

Access to the right heart was obtained via the femoral veins. One or two TS punctures were performed under fluoroscopic guidance to access LA. A 3D electroanatomical map of the LA and PVs was constructed using the Carto system (Biosense Webster, Inc., Diamond Bar, CA, USA). PV ostia were carefully
identified by PV angiography or integration of previously acquired CT or MRI image with the 3D electroanatomical map. A wide circumferential PVI was performed around right and left-sided veins with an open-irrigated 3.5 mm tip ablation catheter. PVI was confirmed by electroanatomical mapping or by a circular mapping catheter. Additional linear ablation was performed in patients with longstanding persistent AF or cavitricuspid isthmus dependent AFL.

4.3.3 Anticoagulation protocol

At least 3 weeks of therapeutic OAT before ablation procedure was required unless contraindicated. During the procedure, all the patients were heparinised. Following TS puncture a 5000 IU bolus of unfractionated heparin was given. Heparinised saline was continuously infused through the sheath and ablation catheter. Heparin was infused at a fixed speed of 600 IU per hour during electroanatomical mapping and 6000 IU per hour during RFA. Activated clotting time was not measured. Protamine was administered before removing catheters and introducers if more than 14 000 IU of heparin had been infused during the procedure. Subcutaneous LMWH was administered for patients with subtherapeutic INR levels at the time of the procedure until therapeutic anticoagulation level was reached during clinical follow-up. OAT was prescribed for at least 3 months after the procedure.

4.3.4 Follow-up and safety outcomes

Punction sites were manually compressed and patients remained supine for at least 4 hours after the procedure. Patients were monitored by telemetry until the following day. Patients were repeatedly evaluated by nurses and a physician when necessary. A clinical examination was routinely performed on the following day and before discharge. In case of cardiac or neurological symptoms or suspected bleeding, further examinations were ordered at a low threshold.

Patients were advised to contact the hospital after discharge in case of any suspected complication(s). Clinical control and physical examination were carried out three months after the procedure. Any complication was enquired and verified from patient records. Any thromboembolic event was considered a major complication. Intracranial haemorrhage, cardiac tamponade or bleeding requiring intervention was defined as major bleeding. Bleeding that did not require interventions was considered minor.
4.4 Impact of echocardiographic variables on AF ablation outcome (V)

4.4.1 Study population

In this study, 49 patients scheduled for AF ablation were recruited to undergo more detailed baseline and follow-up examinations. The study was approved by the local ethics committee and patients gave their written informed consent.

4.4.2 Inclusion and exclusion criteria

Patients with drug refractory or intolerant symptomatic AF referred for ablation were included. Patients with previous AF ablation or cardiac surgery, significant structural heart disease or comorbidity or large LA (>50 mm) were excluded.

4.4.3 Antiarrhythmic therapy

If patient had ongoing AAD therapy, this was continued until the ablation procedure and thereafter according to the physician’s discretion during the blanking period. AAD therapy was subsequently discontinued unless clinically necessary. The CA ablation procedure was conducted as in study III.

4.4.4 Transthoracic echocardiography

TTE was performed by two experienced cardiologists. Cardiac dimensions, volumes, systolic and valvular function were assessed according to the guidelines of American Society of Echocardiography. A detailed examination of diastolic function was performed by combining transmitral flow, propagation velocities and PV flow tracings. Cardiac cycle loops from apical four chamber views were recorded for later offline analysis. Philips Sonos 7500 ultrasound system (Philips Medical Systems, Eindhoven, The Netherlands) was used for all examinations and QLAB (Philips Medical systems) imaging analysis software was used for offline analysis of septal tissue Doppler velocities.
4.4.5 Follow-up and outcome

The clinical evaluation, ECG and 24 hour Holter monitoring were performed at 3, 6 and 12 months after the procedure. Additional ECG and Holter recordings were obtained in cases with symptom recurrence. AF episodes after the 3 month blanking period were counted as a relapse. Successful therapy was defined as freedom of either recurrent symptoms or any documented atrial tachyarrhythmias without AAD therapy.

4.5 Statistical Methods

4.5.1 Meta-analysis (I)

Statistical heterogeneity was measured by $I^2$ to estimate percentage of variability between studies. $I^2 <40\%$ was considered as not important. A random-effects model was used and the weight of each study was derived from the inverse of its squared standard error and inter-trial variance. The risk of bias was assessed in 6 pre-defined categories for each study. Continuous variables were compared as mean and 95% confidence interval (CI). Dichotomous variables and outcome endpoints were compared as odds ratio or risk ratio (RR) with 95% CI. A generic inverse variance analysis was carried out to estimate pooled RR for freedom from recurrent arrhythmias. A P value <0.05 was considered statistically significant. Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all analyses.

4.5.2 On-treatment analysis (II)

Differences in baseline characteristics were analysed by Chi-square test and Mann-Whitney test. Categorical endpoints were compared by Chi-square test. The AF burden was compared by Mann-Whitney, Kruskal-Wallis and Wilcoxon signed rank tests. Adverse events were compared with Kruskal-Wallis test. Changes in symptom index (SF-36) were measured by two-way repeated measures analysis. A P value <0.05 was considered statistically significant. SPSS/PASW version 19, BMDP release 8.1 and STATA version 11 were used for analyses.
4.5.3 Studies III–V

Nominal variables were expressed as numbers and percentages and compared by Chi-square test and Fisher’s exact test. Ordinal variables were presented as mean and standard deviation and compared with Chi-square test or Wilcoxon rank sum test. Continuous variables are presented as mean and standard deviation and compared with independent samples t-test. Multivariable analysis was further performed for variables with a P value ≤0.1 in a univariable analysis using Cox regression analysis (IV) or logistic regression analysis (V). All tests were two-sided and a P value of <0.05 was considered statistically significant.
5 Results

5.1 Catheter ablation as first-line therapy for paroxysmal AF

5.1.1 Meta-analysis of AAD vs. RFA therapy (I)

Literature search

The literature search produced 1233 potential studies. After cursory screening, 70 studies were reviewed more in detail. Subsequently, review articles, editorials, letters and duplicates were removed. Out of the 20 remaining publications, most were excluded because of a second-line study setting or because they had endpoints other than arrhythmia recurrence. Three articles ultimately fulfilled the pre-specified criteria.

Patients

Three randomized multicentre trials (RAAFT-1, MANTRA-PAF and RAAFT-2) with 491 patients were included in the analysis. These studies included antiarrhythmic therapy naïve patients with symptomatic PAF. Inclusion and exclusion criteria are reported in table 9. There were no significant differences in baseline characteristic of the patients. Mean age was 53 to 55 years.

Table 9. Inclusion and exclusion criteria of the trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>RAAFT-1</th>
<th>MANTRA-PAF</th>
<th>RAAFT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF duration ≥3 months</td>
<td></td>
<td>≥6 months</td>
<td>≥6 months</td>
</tr>
<tr>
<td>Number of episodes monthly episodes</td>
<td></td>
<td>≥2</td>
<td>1–4</td>
</tr>
<tr>
<td>Age &lt;18 or &gt;75 years</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Previous AF ablation</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Contraindication to OAT</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Left atrial diameter &gt;50 mm</td>
<td></td>
<td>&gt;55 mm</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH &gt;15 mm</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Secondary AF</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; OAT, oral anticoagulation therapy; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy
**Differences between studies**

Overall, the risk of bias was considered low in MANTRA-PAF and RAAFT-2. There were differences in the use antiarrhythmic therapy, follow-up methods and endpoints. These differences are reported in detail in original publication I.

**Primary clinical outcome**

RFA was associated with significantly higher freedom from recurrent AF ($P=0.02$, RR 0.63, 95% CI 0.44–0.92, $I^2$ 38%) as shown in figure 4. There was also a trend toward fewer symptomatic AF recurrences with RFA ($P=0.09$, RR 0.57, 95% CI 0.30, 1.08, $I^2$ 74%) but statistical significance was not reached (figure 5).

**Secondary clinical outcomes**

The numbers of complications, hospitalisations and crossovers and their risk are presented in table 10. Tamponade was the most frequent complication related to RFA (7/212 vs. 0/209 patients, $P=0.05$, RR 7.83, 95% CI 0.99–62.09, $I^2$ 0%). One
patient had severe PV stenosis (>70%) related to RFA (P=0.53). Symptomatic bradycardia was more frequent with AAD therapy than with RFA (0/172 vs. 8/181 patients, P=0.04, RR 8.33, 95% CI 1.05–0.50, I² 0%). The frequency of crossover was about 4 times higher in the AAD than in the RFA group (19/238 vs. 80/242, P<0.0001, RR 0.24, 95% CI 0.15–0.38, I² 0%).

Table 10. Complications, hospitalisations and crossover in patients treated with RFA or AADs.

<table>
<thead>
<tr>
<th>Outcome end-points</th>
<th>Number of studies</th>
<th>Participants</th>
<th>RFA 238 pts</th>
<th>AAD 242 pts</th>
<th>P value</th>
<th>RR (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamponade</td>
<td>2</td>
<td>413</td>
<td>7</td>
<td>0</td>
<td>0.05</td>
<td>7.83 (0.99, 62.09)</td>
<td>0%</td>
</tr>
<tr>
<td>PV stenosis</td>
<td>3</td>
<td>480</td>
<td>1</td>
<td>0</td>
<td>0.53</td>
<td>2.78 (0.12, 66.88)</td>
<td>-</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2</td>
<td>372</td>
<td>0</td>
<td>8</td>
<td>0.04</td>
<td>0.12 (0.02, 0.95)</td>
<td>0%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
<td>480</td>
<td>1</td>
<td>0</td>
<td>0.48</td>
<td>3.13 (0.13, 76.14)</td>
<td>-</td>
</tr>
<tr>
<td>AFL with 1:1 AV conduction</td>
<td>2</td>
<td>413</td>
<td>0</td>
<td>3</td>
<td>0.22</td>
<td>0.25 (0.03, 2.25)</td>
<td>0%</td>
</tr>
<tr>
<td>Syncope</td>
<td>2</td>
<td>413</td>
<td>0</td>
<td>3</td>
<td>0.21</td>
<td>0.25 (0.03, 2.23)</td>
<td>0%</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>2</td>
<td>372</td>
<td>89</td>
<td>99</td>
<td>0.92</td>
<td>0.98 (0.64, 1.50)</td>
<td>87%</td>
</tr>
<tr>
<td>Crossover</td>
<td>3</td>
<td>480</td>
<td>19</td>
<td>80</td>
<td>&lt;0.0001</td>
<td>0.24 (0.15, 0.38)</td>
<td>0%</td>
</tr>
</tbody>
</table>

PV, pulmonary vein; AFL, atrial flutter; AV, atrioventricular; RFA, radiofrequency ablation; AAD, antiarrhythmic drug

5.1.2 On-treatment analysis of MANTRA-PAF data (II)

Patient groups

Initially, 294 patients without prior antiarrhythmic therapy were randomized to RFA (n=146) or AAD (n=148) therapy. Eight patients did not receive the therapy to which they had been assigned.

Out of the patients randomized to ablation therapy, 140 patients (96%) underwent RFA. The mean number of ablations per patient was 1.6 ± 0.7. After the blanking period, 30 patients (21%) received AAD therapy (crossover).

AAD therapy was initially prescribed to 146 patients (99%) randomised to AAD treatment. They used a mean 1.3 ± 0.5 AADs per patient. Fifty-four patients (37%) underwent RFA after the blanking period (crossover).

A total of 84 patients received the alternative therapy (AAD or RFA) after the blanking period (crossover group). The use of therapies and the formation of the patient groups are illustrated in figure 6.
Fig. 6. The cascade of therapy and formation of patient groups in the on-treatment analysis.

**Baseline characteristics**

The baseline characteristics were rather similar between the patient groups. Hypertension was the most common comorbid condition. It was more common in the AAD group than in either the RFA or the crossover group (43% vs. 29% vs. 26%, P=0.03). There was no difference in age (56 ± 10 vs. 56 ± 10 vs. 54 ± 9 years), body mass index (27 ± 4 vs. 27 ± 4 vs. 26 ± 3) or LA size (40 ± 5 vs. 40 ± 5 vs. 41 ± 5 mm) in the RFA, AAD and crossover group.

**Efficacy of antiarrhythmic therapy**

The AF burden significantly decreased in all groups during the follow-up. In contrast to the situation in the AAD group, the AF burden displayed a continuous reduction during follow-up in the RFA group. At the end of the 2 year follow-up, both the burden of AF (90th percentile, 1% vs. 10% vs. 18%, P=0.0017) and symptomatic AF (0% vs. 2% vs. 5%, P=0.0017) were significantly lower in the RFA group than in the AAD and the crossover groups. The cumulative AF burden was significantly higher in the crossover group than in the other groups.
(P<0.001). The timeline of AF burden (90th percentile) in each group is illustrated in figure 7.

Fig. 7. Atrial fibrillation burden at baseline and during follow-up.

In each group, significantly more patients were free of AF at follow-up compared to baseline. At the end of follow-up, the proportion of patients free of AF (89% vs. 73% vs. 74%, P=0.006) and symptomatic AF (95% vs. 86% vs. 83%, P=0.016) was significantly higher in the RFA group than in the AAD and crossover groups.

The physical and mental QoL components of the SF-36 improved significantly in all groups during follow-up. There were no significant differences between the groups at baseline or during follow-up.

Safety of antiarrhythmic therapy

Serious adverse events occurred in 21 (19%) patients in the RFA group, 7 (8%) patients in the AAD group and 19 (23%) patients in the crossover group (P=0.10).
There was one procedure-related stroke leading to death in the RFA group. Many events reported as serious adverse events during follow-up were not related to the therapy (e.g. cancer, rotator cuff rupture, knee arthroscopy). Table 11 shows the most prominent serious adverse events occurring during the follow-up.

Table 11. Serious adverse events

<table>
<thead>
<tr>
<th>Complication</th>
<th>RFA (n=110)</th>
<th>AAD (n=92)</th>
<th>Crossover (n=84)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0.55</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0.45</td>
</tr>
<tr>
<td>Pulmonary vein stenosis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>Atrial flutter or atrial tachycardia</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0.85</td>
</tr>
<tr>
<td>Bradycardia with need for a pacemaker</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.30</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0.18</td>
</tr>
</tbody>
</table>

RFA, radiofrequency ablation; AAD, antiarrhythmic drug

Rate and temporal trends of crossover

In the RFA group, crossover most often occurred 3 to 6 months after randomisation and was rare thereafter. At the end of follow-up, only 13 patients (9%) initially assigned to RFA therapy were on AADs. Among patients initially randomised to AAD therapy, the cross-over rate was constant during the follow-up. A survival curve of crossover to control therapy is displayed in figure 8.
5.2 Safety of AF ablation during therapeutic OAT (III)

5.2.1 Characteristics of ablation procedures

Ablation therapy was evaluated during continuous and interrupted OAT. Out of the 228 consecutive ablation procedures, INR at the time of the procedure was subtherapeutic (1.6 ± 0.3, group 1) in 103 procedures and therapeutic (2.4 ± 0.4, group 2) in 125 procedures. The mean age was 54 ± 9 years in both groups. Hypertension was the most common morbid condition and the average CHA2DS2-VASc score was 0.9 ± 0.9 in group 1 and 1.0 ± 1.1 in group 2 (P=0.66). Mean HAS-BLED scores were 0.9 ± 0.9 and 0.7 ± 0.8 in groups 1 and 2, respectively.

There were no differences in total procedure or RFA duration between the groups. The use of heparin during the procedure was similar between the groups (10 552 ± 1506 vs. 10 486 ± 1750 IU in groups 1 and 2 respectively, P=0.78).
5.2.2 Complications

In both groups, there was one case of major bleeding because of damage to the femoral artery wall caused by the introducers. They were detected and surgically repaired after introducer removal. There was one problematic TS puncture where contrast media was found to be entering the pericardial space and the procedure was discontinued and performed later. No difference in bleeding complications was found between the groups. There was one thromboembolic stroke in group 2 that occurred 16 days after the procedure during AF and at a prolonged subtherapeutic INR level. It was successfully treated with thrombolysis eventually leading to full recovery. The complications are summarised in table 12. No complications were related to continuous OAT during TS punctures guided by fluoroscopy.

Table 12. Complications during the three month follow-up in patients with subtherapeutic (group 1) and therapeutic (group 2) oral anticoagulation therapy.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group 1 (n=103)</th>
<th>Group 2 (n=125)</th>
<th>Total (n=228)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>0 (0%)</td>
<td>1 (0.8%)</td>
<td>1 (0.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1 (1.0%)</td>
<td>1 (0.8%)</td>
<td>2 (0.9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>11 (10.7%)</td>
<td>14 (11.2%)</td>
<td>25 (11.0%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1 (1.0%)</td>
<td>0 (0%)</td>
<td>1 (0.4%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Complicated transseptal puncture</td>
<td>1 (1.0%)</td>
<td>0 (0%)</td>
<td>1 (0.4%)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

5.3 AF episode characteristics and ablation outcome (IV)

Patient characteristics

In a MANTRA-PAF substudy, AF episode characteristics were evaluated before the initiation of antiarrhythmic therapy. Evidence of AF was found in 124 patients in their baseline Holter recordings. Forty-five of them were free of AF during the follow-up (group 1). AF relapse was detected in 76 patients (group 2). Three patients did not receive their allocated therapy. There were some differences in the baseline clinical characteristics between the groups (i.e., history of thyroid disease, LVEF and LV hypertrophy). These are presented in table 13
Table 13. Baseline characteristics in patients with (group 2) and without (group 1) AF recurrence.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=45)</th>
<th>Group 2 (n=71)</th>
<th>Total (n=124)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53 ± 10</td>
<td>56 ± 8</td>
<td>55 ± 9</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex, male</td>
<td>33 (73%)</td>
<td>60 (79%)</td>
<td>96 (77%)</td>
<td>0.48</td>
</tr>
<tr>
<td>SBP</td>
<td>132 ± 15</td>
<td>134 ± 20</td>
<td>133 ± 18</td>
<td>0.58</td>
</tr>
<tr>
<td>DPB</td>
<td>81 ± 9</td>
<td>82 ± 11</td>
<td>82 ± 10</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 3</td>
<td>27 ± 4</td>
<td>27 ± 3</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (29%)</td>
<td>22 (29%)</td>
<td>35 (28%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2 (4%)</td>
<td>1 (1%)</td>
<td>3 (2%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (4%)</td>
<td>2 (3%)</td>
<td>5 (4%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>4 (9%)</td>
<td>0</td>
<td>4 (3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lung disease</td>
<td>2 (4%)</td>
<td>3 (4%)</td>
<td>5 (4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>2 (4%)</td>
<td>1 (1%)</td>
<td>3 (2%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>0</td>
<td>4 (5%)</td>
<td>4 (3%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0</td>
<td>4 (5%)</td>
<td>4 (3%)</td>
<td>0.30</td>
</tr>
<tr>
<td>LVEF</td>
<td>60 ± 9</td>
<td>63 ± 9</td>
<td>62 ± 9</td>
<td>0.06</td>
</tr>
<tr>
<td>LA diameter</td>
<td>40 ± 5</td>
<td>41 ± 6</td>
<td>41 ± 6</td>
<td>0.19</td>
</tr>
<tr>
<td>LVH</td>
<td>0</td>
<td>6 (8%)</td>
<td>6 (5%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

SPB, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TIA, transient ischaemic attack; LVEF, left ventricular ejection fraction; LA, left atrial; LVH, left ventricular hypertrophy

Characteristics of AF episodes

A total of 2317 AF episodes were documented and analysed. The most common mechanism initiating AF was APB (1924 episodes, 83%). AF had converted from AFL in 155 episodes (7%). AT initiated AF in 2 episodes. The mechanism of initiation could not be analysed in 10% of the episodes because of the presence of some artefact (9%) or if the episode initiation was invisible (1%). In a significant proportion of AF episodes (30%), initiation was characterised by subsequent rapid repetitive atrial activity (RRAA) following APB. This electrocardiographic activity has not previously been described. It was more common in patients with AF recurrence during follow-up (15/45 vs. 39/71 in group 1 and 2 respectively, P=0.013). Examples of this activity are shown in figures 9 and 10.
Fig. 9. Example of rapid repetitive atrial activity (RRAA) at AF initiation.

Fig. 10. Example of repetitive RRAA before episode onset.

There were no differences in the number of premature atrial or ventricular beats or other arrhythmias prior to episode onset between the groups. The AF episode characteristics in both patient groups are presented in table 14.
Table 14. Characteristics of AF episodes in patients with (group 2) and without (group 1) AF recurrence.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (50)</th>
<th>Group 2 (71)</th>
<th>Total (124)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of episodes</td>
<td>719</td>
<td>1486</td>
<td>2317</td>
<td></td>
</tr>
<tr>
<td>AF episode number per patient</td>
<td>3 (1–15)</td>
<td>4 (2–19)</td>
<td>3 (2–17)</td>
<td>0.37</td>
</tr>
<tr>
<td>AF episode duration (min)</td>
<td>189 (38–683)</td>
<td>136 (35–829)</td>
<td>141 (35–689)</td>
<td>0.83</td>
</tr>
<tr>
<td>AF burden %</td>
<td>12 (4–20)</td>
<td>13 (3–28)</td>
<td>12 (3–24)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean RR interval at initiation (ms)</td>
<td>538 ± 116</td>
<td>538 ± 145</td>
<td>538 ± 134</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean APB coupling time (ms)</td>
<td>420 ± 54</td>
<td>427 ± 70</td>
<td>424 ± 64</td>
<td>0.59</td>
</tr>
<tr>
<td>Subsequent RRAA (patients)</td>
<td>15 (35%)</td>
<td>39 (59%)</td>
<td>54 (44%)</td>
<td>0.01</td>
</tr>
<tr>
<td>RRAA cycle length (ms)</td>
<td>196 ± 23</td>
<td>189 ± 22</td>
<td>191 ± 23</td>
<td>0.18</td>
</tr>
<tr>
<td>APB number preceding 30 min</td>
<td>28 (6–50)</td>
<td>19 (6–44)</td>
<td>21 (6–48)</td>
<td>0.43</td>
</tr>
<tr>
<td>APB number preceding 60 min</td>
<td>35 (10–69)</td>
<td>31 (8–73)</td>
<td>34 (9–71)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Values presented as n (%), mean ± SD or median (interquartile range). AF, atrial fibrillation; APB, atrial premature beat; RRAA, rapid repetitive atrial activity.

All variables with a P value ≤0.1 in univariable analysis were entered into the Cox regression multivariable analysis. RRAA (RR 1.67, 95% CI 1.01–2.74, P=0.044) was independently associated with AF relapses. A further subgroup analysis was performed in patients treated with RFA or AAD therapy. In patients treated with RFA, a higher age (51 vs. 59 in group 1 and 2, P<0.001) was associated with AF recurrence. In patients treated with AADs, the presence of RRAA was associated with AF recurrence (P=0.006).

5.4 Echocardiographic features and ablation outcome (V)

Baseline characteristics of patients with and without AF recurrence

A thorough echocardiographic examination was performed before AF ablation to reveal associations with therapy outcome. After the 3 month blanking period, 18 out of 49 patients (37%) were free of AF without supplementary AAD therapy (group 1), whereas 31 patients (63%) had symptom recurrence, documented AF relapse or AAD therapy (group 2) during the one year follow-up.

Female gender (7/31 vs. 0/18, P=0.038) and a history of cardioversion (22/31 vs. 7/18, P=0.032) were more common in group two compared to group 1. The mean age was 52 ± 8 and 54 ± 9 year in groups 1 and 2 respectively (P=0.47). The history of AF was 6.0 ± 4.7 years in group 1 and 8.0 ± 5.9 years in group 2.
(P=0.22). AF was paroxysmal in 56% in group 1 vs. 48% of patients in group 2, (P=0.63). The majority of the patients had no comorbidities (67%).

**AF ablation outcome and echocardiography**

Baseline TTE was performed in all patients. In the univariate analysis, the ratio of early diastolic mitral inflow velocity and septal mitral annular early diastolic tissue Doppler velocity (E/e’ ratio) was the only echocardiographic parameter related to outcome (6.9 ± 1.4 vs. 8.3 ± 2.2 in groups 1 and 2, P=0.034). The results of echocardiographic measurements are shown in table 15.

**Table 15. Echocardiographic parameters in patients with and without successful ablation therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n=49)</th>
<th>Group 1 (n=18)</th>
<th>Group 2 (n=31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>62 ± 8</td>
<td>62 ± 8</td>
<td>62 ± 7</td>
<td>0.97</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>50 ± 8</td>
<td>50 ± 5</td>
<td>50 ± 10</td>
<td>0.95</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>108 ± 37</td>
<td>123 ± 47</td>
<td>99 ± 28</td>
<td>0.076</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>42 ± 17</td>
<td>49 ± 21</td>
<td>38 ± 14</td>
<td>0.048</td>
</tr>
<tr>
<td>LVMI</td>
<td>116 ± 33</td>
<td>124 ± 32</td>
<td>112 ± 34</td>
<td>0.24</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>41 ± 5</td>
<td>41 ± 5</td>
<td>41 ± 5</td>
<td>0.97</td>
</tr>
<tr>
<td>RVDD (mm)</td>
<td>27 ± 5</td>
<td>29 ± 6</td>
<td>26 ± 5</td>
<td>0.12</td>
</tr>
<tr>
<td>E velocity (cm/s)</td>
<td>71 ± 15</td>
<td>68 ± 9</td>
<td>73 ± 17</td>
<td>0.19</td>
</tr>
<tr>
<td>E Deceleration time (ms)</td>
<td>149 ± 32</td>
<td>138 ± 29</td>
<td>157 ± 31</td>
<td>0.057</td>
</tr>
<tr>
<td>E/A velocity ratio</td>
<td>1.4 ± 0.5</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.5</td>
<td>0.85</td>
</tr>
<tr>
<td>e’ (cm/s)</td>
<td>9.4 ± 2.2</td>
<td>10 ± 1.8</td>
<td>9.0 ± 2.3</td>
<td>0.18</td>
</tr>
<tr>
<td>E/e’</td>
<td>7.8 ± 2.1</td>
<td>6.9 ± 1.4</td>
<td>8.3 ± 2.2</td>
<td>0.034</td>
</tr>
<tr>
<td>Vp (cm/s)</td>
<td>58 ± 21</td>
<td>51 ± 14</td>
<td>61 ± 23</td>
<td>0.13</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>90 ± 15</td>
<td>90 ± 15</td>
<td>90 ± 15</td>
<td>0.98</td>
</tr>
<tr>
<td>S velocity (cm/s)</td>
<td>53 ± 14</td>
<td>53 ± 11</td>
<td>52 ± 16</td>
<td>0.82</td>
</tr>
<tr>
<td>D velocity (cm/s)</td>
<td>54 ± 14</td>
<td>51 ± 14</td>
<td>56 ± 14</td>
<td>0.31</td>
</tr>
<tr>
<td>Ar velocity (cm/s)</td>
<td>28 ± 8</td>
<td>26 ± 6</td>
<td>29 ± 9</td>
<td>0.41</td>
</tr>
</tbody>
</table>

LVEF, left ventricular (LV) ejection fraction; LVEDD, LV end diastolic diameter; LVEDV, LV end diastolic volume; LVESV, LV end systolic volume; LVMI, LV mass index; LA, left atrial; RVDD, right ventricular diastolic diameter; E, early transmitral inflow; A, late transmitral inflow; e’, annular septum diastolic velocity; Vp, flow propagation velocity; IVRT, isovolumic relaxation time; S, systolic pulmonary venous (PV) flow; D, diastolic PV flow; Ar, end diastolic PV flow

In the multivariate analysis (logistic regression), a higher E/e’ ratio was the most powerful predictor of AF recurrence (OR 1.911; 95% CI 1.046–3.493, P=0.035).
6 Discussion

In this study, the efficacy and safety of CA in AF was approached from several directions. Randomised controlled trials are the golden standard in medical research. A meta-analysis of such trials provides strong clinical evidence and may overcome some of the weaknesses in a single trial. An on-treatment analysis was further performed to diminish the effect of crossover and to identify reasons why crossover was necessary. Although the on-treatment analysis breaks the randomisation, it may overcome some of the bias created with crossover. The safety of catheter ablation is often approached by conducting registry studies. While their weakness is the lack of randomisation, the strength of this kind of approach is that all patients are included in the analysis. The present studies analysing baseline examinations in relation to CA outcome are hypothesis creating, need later confirmation and should also be assessed with caution before making any wider clinical judgements.

Since the volume of a single centre performing AF ablation is somewhat limited, multicentre studies should ideally be performed. Three out of the present evaluated five studies included patients from multiple centres. Finally, the evolution of AF ablation has been considerable over several years and studies may often include methodology that is partially outdated.

6.1 Efficacy of first-line AF ablation (I, II)

The meta-analysis of all currently published prospective randomised studies showed superior efficacy of CA strategy compared to AAD therapy in preventing AF recurrences in patients with paroxysmal AF. Furthermore, the results of the on-treatment analysis of the MANTRA-PAF data revealed that CA preserved its efficacy better than AAD therapy. These data provide further support for use of CA as a first-line therapy. Recent substudies of the MANTRA-PAF trial have shown that AF ablation is associated not only with significantly greater improvement in QoL measures (Walfridsson et al. 2015), but also that AF ablation as a first-line therapy is cost-effective in patients aged 50 years or younger although the cost-effectiveness is uncertain in older patients (Aronsson et al. 2015).

The present results are in line with the results of previous studies comparing CA and AAD therapy as a second-line therapy after the prior failure of AAD therapy (Bonanno et al. 2010, Calkins et al. 2009, Ganesan et al. 2013, Nair et al.
It is however probable that prior failure of AAD therapy selects patients in whom AAD therapy will be less effective and somewhat limits the choices in AAD therapy. The efficacy of first-line AAD therapy in the present studies was rather good, considerably better than in the previous reports mentioned above. However, the rate of crossover was up to 4 times higher with AAD therapy.

Early relapses following CA are common, but may resolve spontaneously or be managed by AADs or cardioversion. After the blanking period, reablation should be considered if AF relapses occur (Calkins et al. 2012, January et al. 2014) as this has been found to increase the success rate (Calkins et al. 2009, Pokushalov et al. 2013). The rate of reablation in trials included in the meta-analysis varied between 14 to 49%.

Operator experience and ablation technique are probably related to the efficacy of AF ablation. In the MANTRA-PAF study, there was considerable variance in patient volumes and in the degree of experience in AF ablation between centres. In contrast, only high volume centres were involved in RAAFT-2 (>200 procedures a year), however the rate of AF recurrence during follow-up was similar between the studies.

First-line CA may be further supported by prevention of disease progression. One aim of the present on-treatment analysis of the MANTRA-PAF data was to identify reasons for failure of antiarrhythmic therapy. Baseline variables were compared across treatment groups. The only baseline factor associated with crossover was the higher baseline AF burden (P=0.008). Slow atrial remodelling may precede first manifested AF episodes. AF on the other hand, further promotes remodelling. Thus, efficient treatment strategy is desirable if one wishes to avoid unnecessary delay and disease progression (Bunch et al. 2013, Corradi et al. 2014, Hooft van Huysduynen & Rienstra 2012, Van Gelder et al. 2011).

## 6.2 Safety of AF ablation (I–III)

AF ablation carries a risk of severe complications. There was one death related to periprocedural stroke in MANTRA-PAF, and the frequency of tamponade (6%) was high in RAAFT-2. Bradycardia was more common in patients treated with AADS. Otherwise, there were no differences in complications related to RFA and AAD therapy although the complications were more serious with RFA. Similar findings about the severity of complications have been reported earlier (Calkins et al. 2009). Therefore, while the efficacy of RFA is superior to AAD therapy,
potential complications must be considered when choosing the treatment strategy
best suited for each individual patient. Moreover, the operator experience and
centre volumes need to be taken into consideration since they have been
associated with complication rates (Deshmukh et al. 2013).

The complications of CA usually present during or shortly after the
procedure, whereas the potential risks of AAD therapy accumulate for the
duration of the therapy. There is a paucity of reliable data about the long term
safety of AAD therapy (Al-Khatib et al. 2014). In the clinical setting, long term
AAD therapy is often required and progression of AF and development of
underlying diseases may increase the risks of AADs (Connolly et al. 2011, Echt et
al. 1991). In AAD therapy, long-term monitoring for adverse events is always
needed.

6.2.1 Continuous VKA during ablation

The results of the observational study indicated that AF ablation during
uninterrupted warfarin with simple unmonitored heparinisation was safe. In
contrast, it has been reported that if bridge therapy with LMWH is used, then it is
essential to monitor ACT as thrombus formation on the sheaths or catheters has
been detected shortly after LA access (Bruce et al. 2008). Moreover, LA RFA
lesions are thrombogenic and thus therapeutic OAT is desirable early after
ablation. Novel oral anticoagulants were not used in the present study.

Several observational studies and one randomised study have confirmed the
safety of continuous VKA therapy during AF ablation and shown reduction of
thromboembolic complications with this strategy (Di Biase et al. 2014, Santangeli
et al. 2012). A recent European survey found that 70% of centres were using
continuous VKA therapy and routine ACT monitoring was also common (89% of
centres) (Chen et al. 2014). Although the use of heparin seems necessary during
ablation (Martinek et al. 2013), there is no conclusive evidence about the benefit
of ACT monitoring in patients with therapeutic OAT.
6.3 Preprocedural evaluations and AF ablation efficacy (IV, V)

6.3.1 AF initiation characteristics

The present data showed that RRAA following APB at AF initiation was associated with AF recurrence after the initiation of antiarrhythmic therapy. This was also shown in multivariate analysis. However, when examining the patients treated with RFA or AADs, this effect was only apparent in patients treated with AAD therapy. Altogether, these findings highlight the role of PVI and suggest that patients with RRAA respond poorly to AAD therapy and should instead be treated with RFA. This novel finding will have to be confirmed in future studies.

As far as is known, RRAA at AF initiation from surface ECG has not been reported before. RRAA was seen in 30% of AF initiations. It may be that this activity following APB is a second phase of AF initiation in some patients ultimately forcing the atria to adopt AF and it may also participate in AF maintenance. It is possible that sites with this kind of activity are isolated or disturbed by CA during PVI. Whether a poor AAD response is a consequence of different cellular mechanisms at AF initiation between patients with and without RRAA, needs further evaluation. A recent endocardial mapping study suggested rather similarly that AF was initiated by organised mechanisms, namely focal activity or a spiral wave (Schricker et al. 2014). Some patients exhibited both mechanisms. Whether RRAA in surface ECG is a consequence of a focal driver needs further evaluation.

6.3.2 Echocardiographic parameters

According to the present retrospective analysis, a higher E/e’ ratio was the most powerful predictor of outcome after a single AF ablation procedure during the 1 year follow-up. Patients in the study were young and had low comorbidity and E/e’ values were well below those encountered in patients with diastolic heart failure. Notably LA diameter was not associated with outcome, but patients with large LA (>50 mm) were excluded from the study. The E/e’ ratio has been shown to correlate to LV filling pressure and LA pressure, but simultaneous measurement of both variables may be required in patients currently in AF (Li et al. 2010).

Other studies have also reported the association between diastolic dysfunction and AF ablation efficacy (Cha et al. 2011, Ejima et al. 2013, Hirai et al. 2013).
al. 2014), but also negative results have been described (Hwang et al. 2009, Kohari et al. 2013). In one study, LA pressure was measured by a direct invasive technique; it was found to be related to ablation outcome in patients with a normal or slightly enlarged LA but not in patients with larger atria (Linhart et al. 2013).

Other novel echocardiographic measurements have been investigated to see whether they influence the outcome of AF ablation i.e. LA spontaneous echo contrast (Hartono et al. 2012), LA speckle tracking imaging (Hammerstingl et al. 2012, Loghin et al. 2014), LA wall ultrasound reflectivity (den Uijl et al. 2011), three dimensional LA size and function estimation (Montserrat et al. 2013).

It remains to be established whether any novel echocardiographic method is robust and universal enough to provide any significant aid in targeting AF ablation therapy. The diverse and dispersed changes in LA structure and function and the accuracy of echocardiographic imaging to directly evaluate LA have proved to be problems inherent with TTE. At present, the measurement of LA volume is the recommended method for evaluation of LA prior to CA (Bax et al. 2015, Kohari et al. 2013).

6.4 Future directions

The AF ablation procedure is constantly being developed and improved. The accuracy of preprocedural imaging, procedural mapping and navigation and catheter technology have conferred substantial benefits for patients and electrophysiologists (January et al. 2014). The number of CA procedures is still rising while the use of AAD therapy for AF has declined (Lip et al. 2014). One can predict that there will be a shift in the future towards first-line CA, especially in young patients. For CA, the next anticipated step would be to reveal benefits in hard clinical endpoints. Although there is some evidence that CA might reduce stroke and mortality (Nademane e et al. 2015, Pappone et al. 2003), this is still not proven. Whether currently available methods will be able to provide these kinds of benefits is being studied in the CABANA and the EAST trials. However, there is a very long way to go before AF ablation will become mainstream therapy since the efficacy and safety of CA is best in lone atrial fibrillation whereas most AF patients are elderly and have multiple comorbidities. Future studies are expected to provide more accurate information about individual AF mechanisms and the optimal ways to target these different mechanisms (Heijman et al. 2013, January et al. 2014).
New strategies for periprocedural anticoagulation are also evolving because of the introduction of NOACs. Antidotes for NOACs are under investigation and will allow for a rapid reversal of the anticoagulant effect should there be a bleeding complication.

6.5 **Strengths and limitations**

6.5.1 **Strengths of the thesis**

*Meta-analysis*

Meta-analysis was performed by searching several databases and it included only prospective randomised studies comparing first-line CA and AAD therapy with rather similar study designs. Most of the included studies had also reported that study design and bias of positive publication were unlikely. Methodological differences were assessed in detail and supplemental information used to further delineate study outcomes. The risk of bias in individual studies for specific endpoints was reported by examining only analyses without studies at risk of bias. The heterogeneity between studies was assessed and estimated by the use of a random effects model.

*On-treatment analysis*

Crossover to control therapy during follow-up is common in studies comparing CA and AAD therapy which causes challenges for intention to treat analyses. On-treatment analysis was able to reveal the differences in frequency and timing of crossover and outcome between patients treated with pure RFA and pure AAD.

*Study of procedural anticoagulation*

Although this study was observational, it provided data of consecutive patients treated during a three year period and validated the anticoagulation protocol used in our institution. Other studies have confirmed these present findings and now uninterrupted warfarin therapy is currently recommended for AF ablation.
Study of electrocardiographic features

The study material had unique features. This retrospective study used the largest available data of long duration high quality Holter monitoring performed just before initiation of the AAD or RFA therapy enabling analysis of arrhythmic mechanisms and efficacy of therapy. It also included intensive follow-up to detect long term arrhythmia recurrences.

Statistical analysis

It was decided to use the statistical methods most commonly applied in similar clinical settings. A statistician was part of the MANTRA-PAF study and meta-analysis was performed by a skilled and experienced analyst. Power calculations were performed for MANTRA-PAF study. Blinding of outcome assessment was also present in MANTRA-PAF as well as in most of the studies included in the meta-analysis.

6.5.2 Limitations

In all studies, patients were young with respect to the average age of AF patients. They also had low comorbidity and mostly paroxysmal AF. Therefore, the present results cannot be directly extrapolated to other patient populations. Because AF ablation is constantly evolving, it may be possible that different results would be obtained using currently available methods.

It has to be recognised that there are common limitations inherent in all meta-analyses, e.g. there were some differences between ablation technique, definitions and methods for arrhythmia recurrence monitoring in the included studies. On-treatment analysis breaks the effect of randomisation and the results of this analysis are therefore only suggestive. On the other hand, it was deemed important to perform this kind of analysis because frequent crossover during follow-up period is likely to affect treatment effects in an intention-to-treat analysis.

The analysis of ECG data has some limitations. First of all, it was not possible to evaluate the initiation of AF in some patients because they had no AF episodes in the baseline Holter recording. In addition, in some cases, the analysis of the AF initiation was not possible because of noise or artefacts.
The major limitations in the echocardiographic analysis were the relatively small sample size and heterogeneity in the type of AF. In some patients, measurements were performed during AF, which may have affected the results. Furthermore, interoperator variability was not measured. The intensity of monitoring for arrhythmia recurrences was also reasonably low.
7 Conclusions

The following conclusions can be made on the basis of this study:

1. First-line RFA in patients with symptomatic paroxysmal AF is more effective than AAD therapy in the prevention of AF recurrence. During long term follow-up, the effect of RFA ablation is more durable than that of AAD therapy. The rate of complications was similar for both therapies, although some complications associated with RFA were more severe.

2. RFA is safe during uninterrupted warfarin therapy and with a simplified procedural heparinisation protocol without the need for ACT monitoring.

3. At AF initiation, RRAA is associated with AF recurrence after the initiation of antiarrhythmic therapy. This effect was observed in patients treated with AAD therapy. The presence of RRAA may indicate a poor response to AAD therapy and the need for RFA therapy.

4. A higher septal E/e’ ratio is associated with a higher frequency of AF recurrence after RFA. It remains to be established whether the E/e’ ratio has any role in guiding RFA therapy.
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