**UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF**

Klinik und Poliklinik für Kardiologie

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# Catheter ablation for atrial fibrillation in octogenarians: Acute success, complications and follow-up

**Dissertation**

zur Erlangung des Grades eines Doktors der Medizin

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# 1. Introduction

## 1.01 Definition and diagnosis

Atrial fibrillation (AF) is defined as a supraventricular tachyarrhythmia characterised by uncoordinated and fast atrial electrical activity, consequently leading to an ineffective atrial contraction (Van Gelder *et al.*, 2024). The electrocardiographic characteristics of AF include irregular R-R intervals, absence of repeating P waves and irregular atrial activation (Van Gelder et al., 2024, **Figure 1**). To establish a diagnosis, an electrocardiogram (ECG) recording that is interpreted by a physician is required, preferably a 12-lead ECG (Van Gelder *et al.*, 2024).

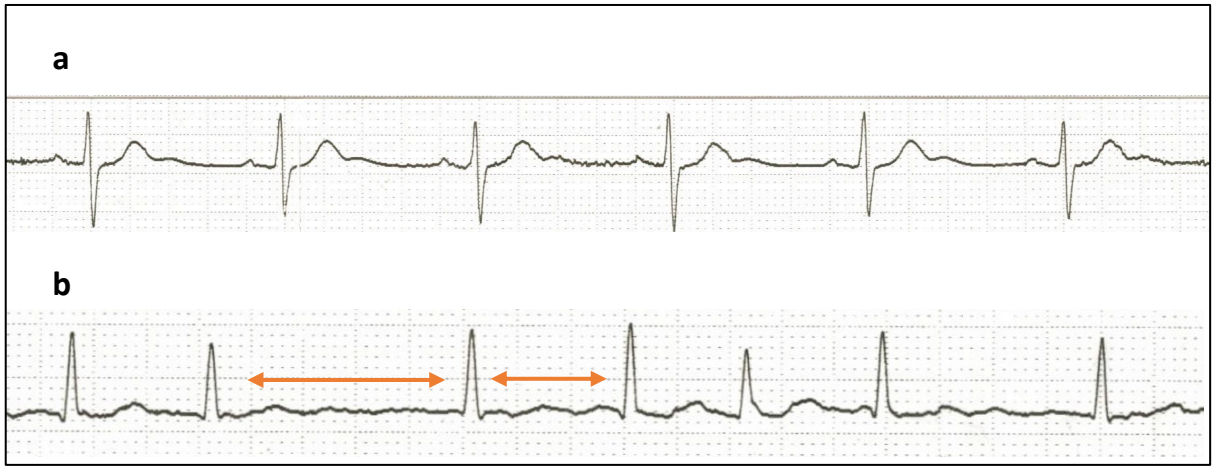


**Figure 1 a** An ECG rhythm strip (25 mm/s) showing normal sinus rhythm **b** An ECG strip showing AF with typical irregular R-R intervals (orange arrows), missing p-wave, and irregular atrial activation

## 1.02 Epidemiology

AF represents the most common sustained arrhythmia in adults worldwide (Emelia J. Benjamin *et al.*, 2019). Currently, it is estimated that the prevalence of AF lies between 2% and 4% in adults with an expected 2.3 - fold rise (Chugh *et al.*, 2014; Emelia J. Benjamin *et al.*, 2019). The risk for AF increases progressively with age with 5% of the population between the ages of 65 to 69 suffering from AF, 11% from 75 to 79 years and ultimately rising to 15% between the ages of 85 and 89 years (Wilke *et al.*, 2013). In addition, males are more commonly affected than woman and Caucasians more commonly than non-Caucasians (Emelia J. Benjamin *et al.*, 2019). At an index age of 55 years the lifetime risk is one in three individuals of European ancestry (Hindricks *et al.*, 2020).

## 1.03 Pathophysiology

AF is thought of as being multi-factorial and complex in terms of its causes. Modifiable and non-modifiable risk factors are associated with AF. The central non-modifiable risk factors for incident AF are genetic factors, increasing age, ethnicity, and male sex ( Emelia J Benjamin et al., 2019, Figure 2).

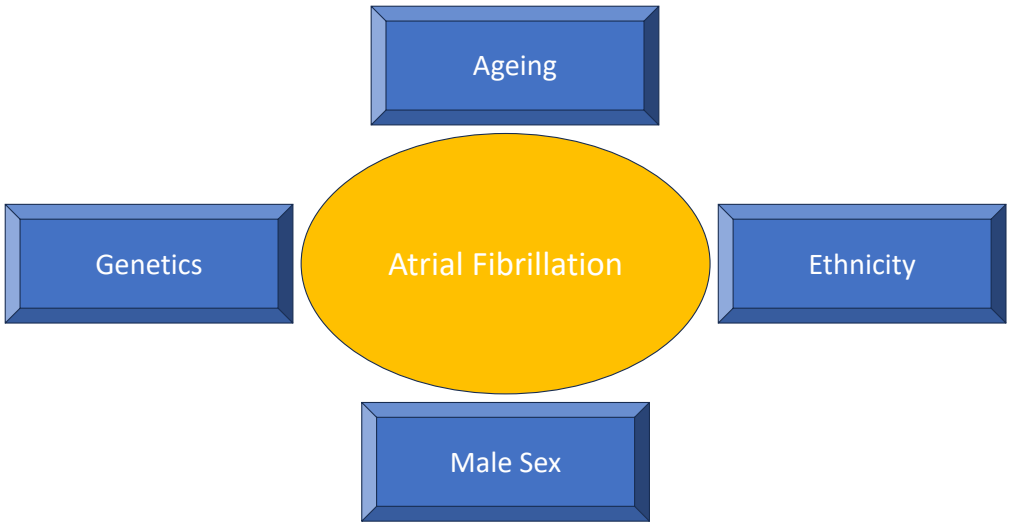


**Figure 2** The central, non-modifiable risk factors for AF, adopted from the 2020 ESC Guidelines for the diagnosis and management of Atrial Fibrillation, Hindricks et al., 2020

In addition, many other risk factors have been identified such as coronary artery disease (CAD), hypertension, heart failure, heart valve disease, chronic kidney disease (CKD), lung disease such as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea but also modifiable risk factors such as alcohol consumption, smoking, and obesity (Allan *et al.*, 2017; Aune *et al.*, 2018; Emelia J. Benjamin *et al.*, 2019). All the above factors can contribute to atrial structural remodelling and what is known as atrial cardiomyopathy (atrial, structural, architectural, contractile, and electrophysiological changes) ultimately leading to AF and the progression of AF (Wijffels *et al.*, 1995; Goette, Honeycutt and Langberg, 1996). A summary of co-morbidities and risk factors is shown in **Table 1** below.

| Non-modifiable risk factors | Modifiable risk factors | Cardiac Comorbidities | Other Comorbidities |
|---|---|---|---|
| Ageing | Physical inactivity | Coronary artery disease | Vascular disease |
| Genetics | Lipid profile | Heart failure | Chronic kidney disease |
| Male sex | Alcohol consumption | Heart valve disease | Diabetes |
| Ethnicity | Smoking | Hypertension | COPD |
| | Obesity | | Obstructive sleep apnoea |
| | | | Inflammatory diseases |

**Table 1** Risk factors associated with atrial fibrillation, adopted from the ESC guidelines (Hindricks et al., 2020)

## 1.04 Clinical features and classification

Clinical presentation of AF is highly individual and may vary from patient to patient. Patients can even be asymptomatic despite AF. If symptomatic, patients may experience the following symptoms (Van Gelder *et al.*, 2024) :

- palpitations
- dyspnoea
- fatigue
- angina pectoris
- dizziness
- syncope

More severe presentation may include hypotension, acute heart failure, pulmonary oedema, myocardial ischaemia, or even cardiogenic shock (Hindricks *et al.*, 2020). With regards to AF-related outcomes, it is well established that AF is associated with a 1.5-3.5 - fold increase in mortality (Benjamin *et al.*, 1998; Stewart *et al.*, 2002; Wang *et al.*, 2003; Andersson *et al.*, 2013). Moreover, 20-30 % of all ischaemic strokes are caused by cardiac emboli on the basis of AF (Boriani *et al.*, 2015). Due to excessive ventricular rate and irregular ventricular

contraction, 20-30% of AF patients suffer from left ventricular dysfunction leading to heart failure (Wijesurendra and Casadei, 2015; Kotecha *et al.*, 2016) . AF can also have a severe negative impact on cognitive decline, the development of dementia, depression, and a general decline in quality of life (Schnabel *et al.*, 2013; Freeman *et al.*, 2015). Overall, the annual hospitalisation rate lies between 10-40% due to the above-mentioned factors (Meyre *et al.*, 2019).

The classification of AF includes first diagnosed AF, paroxysmal (AF that terminates spontaneously or with intervention within 7 days of onset), persistent (AF that is sustained beyond 7 days including AF terminated by interventions after 7 days) and permanent (AF that is accepted by patient and physician and no attempts to restore and maintain sinus rhythm are undertaken) (Van Gelder *et al.*, 2024). AF classification according to the current European Society of Cardiology (ESC) guidelines is summarised in **table 2** below.

| AF pattern | Definition |
|---|---|
| First-diagnosed AF | AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms |
| Paroxysmal AF | Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. AF episodes that are medically or electrically cardioverted within 7 days should be considered paroxysmal. |
| Persistent AF | AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or direct current cardioversion, after 7 days or more. |
| Permanent AF | AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patient with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as “long-standing persistent AF”. |

**Table 2** Classification of atrial fibrillation adopted from the 2024 ESC guidelines for the management of AF (Van Gelder et al., 2024).

## 1.05 Clinical assessment

In patients with a first diagnosis of AF, a complete medical history and a thorough assessment of concomitant conditions, AF pattern, stroke risk, symptoms and left ventricular dysfunction should be established (Van Gelder *et al.*, 2024). Further work up should include laboratory

tests including thyroid and kidney function, electrolytes, and full blood count. Furthermore, transthoracic echocardiography to assess left ventricular (LV) size and function, left atrial size, valve disease and right heart function should be performed to guide treatment (Van Gelder *et al.*, 2024). To assess symptoms and quality of life, the modified European Heart Rhythm Association (mEHRA) symptom scale is used in clinical practice and summarised in the following illustration (**Table 3**).

| Score | Symptoms | Description |
|---|---|---|
| 1 | None | AF does not cause any symptoms |
| 2a | Mild | Normal daily activity not affected by symptoms related to AF |
| 2b | Moderate | Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms |
| 3 | Severe | Normal daily activities affected by symptoms related to AF |
| 4 | Disabling | Normal daily activities discontinued |

**Table 3** Modified European Heart Rhythm Association (mEHRA) symptom scale of AF adopted from the ESC 2024 Guidelines for the Diagnosis and Management of Atrial Fibrillation (Van Gelder et al., 2024)

## 1.06 Management of patients with atrial fibrillation: AF-CARE Pathway

The management of AF can be challenging and requires a coordinated and patient-individualised care-pathway. This includes an interdisciplinary approach and a focus on patient education and adherence to treatment. Integrated management of AF should be based on a holistic approach proposed by the ESC Guidelines known as the AF-CARE pathway (**Figure 3**).

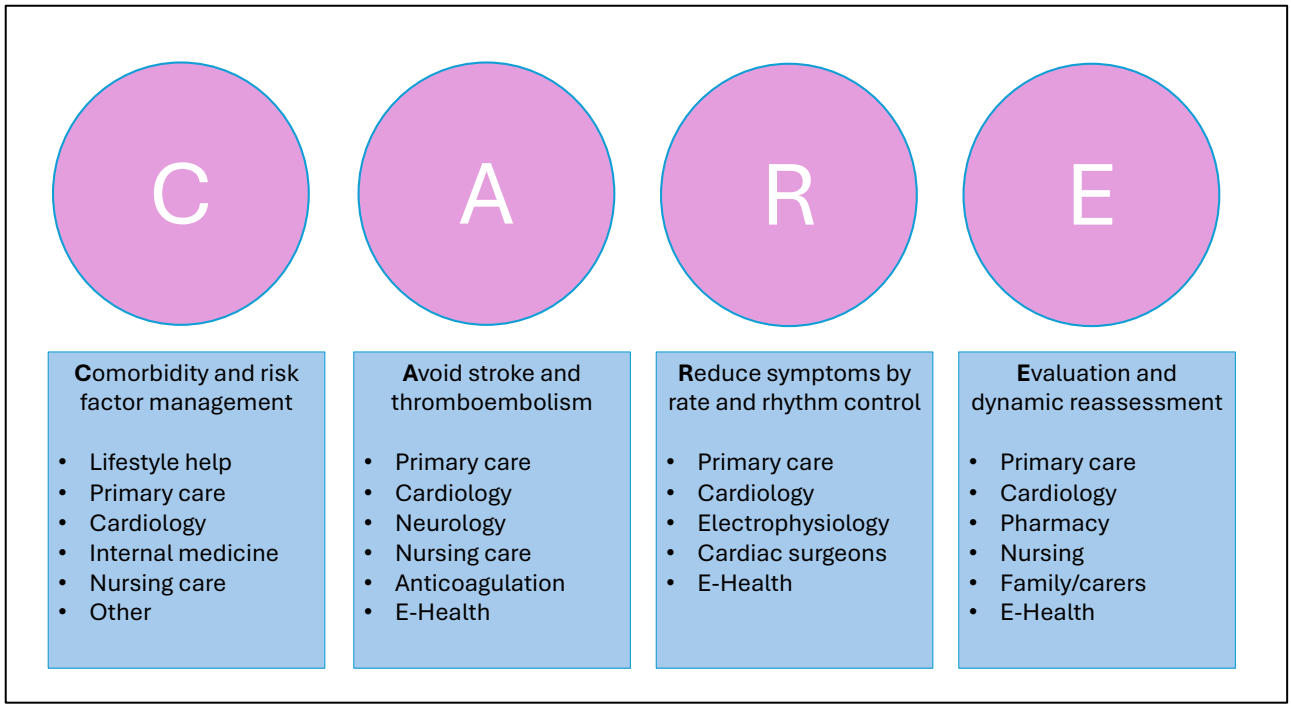


**Figure 3** The CARE pathway as recommended adopted from the 2024 ESC Guidelines (Van Gelder et al., 2024)

This pathway underlines the recommended patient-centred, multidisciplinary approach with the support of validated technology to achieve the goals of comorbidity management, avoiding stroke, reducing symptoms and evaluation/reassessment (Van Gelder *et al.*, 2024)

### 1.06.1 Comorbidity and risk factor management ("C")

As mentioned earlier, AF is multifactorial in its cause but also in terms of drivers of the disease progression. Comorbidities and lifestyle factors play a central role in the development and progression of AF and therefore should be considered in treating AF using a holistic approach.

***Obesity***

Obesity increases the risk for AF and is a well-established cardiovascular risk factor (Overvad, Rasmussen, Skjøth, Overvad, Lip, *et al.*, 2013). The Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort (LEGACY) - trial showed significantly lower AF burden in patients with adequate weight reduction of 10% (Pathak *et al.*, 2015). With regards to catheter ablation, obesity has been identified as factor increasing recurrence rates after catheter ablation (Providência *et al.*, 2019). In addition, it has been linked to higher complication rates after catheter ablation in some studies (Shoemaker *et al.*, 2013).

### *Alcohol and caffeine consumption*

Another important risk factor and driver for AF is alcohol consumption with an additional risk for adverse events such as thromboembolism, bleeding and death (Overvad, Rasmussen, Skjøth, Overvad, Albertsen, *et al.*, 2013; Lim *et al.*, 2021). Vosokoboinik et al. showed a significant reduction in AF burden in drinkers under alcohol abstinence compared to patients with continuous consumption in a prospective, randomised multi-centre trial (Voskoboinik *et al.*, 2020) on the basis of which alcohol reduction to 3 standard drinks per week is recommended as a maximum (Van Gelder et al., 2024). Interestingly, caffeine on the other hand unlikely contributes to AF, provided it is a habitual consumption. A state-of-the art review by Voskoboinik et al. analysed 11 different trials showing no effect of caffeine consumption on AF-incidence (Voskoboinik, Kalman and Kistler, 2018).

### *Physical activity*

When it comes to physical activity, several studies have shown a protective effect of moderate activity on cardiovascular health in general, including incident AF (Lavie *et al.*, 2009; Mont, 2010). In more than moderate sports, such as seen in professional athletes, however, higher rates of AF are observed (Calvo *et al.*, 2016). Calvo et al. showed a U-shaped relationship between lifetime physical activity and AF-risk, meaning an increased AF-risk after a total of >2000 hours of physical activity (Calvo *et al.*, 2016). Therefore, in clinical practice, moderate physical exercise is recommended. (Van Gelder et al., 2024).

### *Arterial Hypertension*

Hypertension represents a significant risk factor and its co-existence with AF is associated with a higher risk of stroke, heart failure, major bleeding and mortality (Lopes *et al.*, 2014; Noubiap *et al.*, 2021). The target blood pressure as recommended by current guidelines is 120-129 mmHg (McEvoy *et al.*, 2024).

### *Heart failure*

Heart failure also represents a key comorbidity in AF patients with an impact on recurrence and arrythmia prognosis (Kotecha and Piccini, 2015). In AF patients, the incidence of heart failure is associated with higher stroke risk and mortality (Atrial Fibrillation Investigators, 1998). Therefore, adequate guideline-recommended heart failure medication, such as betablockers, sacubitril/valsartan, aldosterone-receptor antagonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors are warranted (McDonagh *et al.*, 2023).

***Diabetes Mellitus***

Type 2 diabetes mellitus is observed in 25% of AF patients with an associated for worse prognosis and excess mortality (Alijla et al., 2021). Adequate management of diabetes has been shown to reduce AF symptoms, burden and improved rhythm stability (Pathak *et al.*, 2014; Middeldorp *et al.*, 2018), therefore strict glycaemic control using diet and medication is recommended (Van Gelder et al., 2024).

***Obstructive sleep apnoea***

Obstructive sleep apnoea (OSA) is a particular prevalent condition in AF patients and screening in AF patients may be reasonable (Kadhim *et al.*, 2021). However, data regarding an improvement in outcome of AF when treating OSA with continuous positive airway pressure (CPAP) are inconclusive (Hunt *et al.*, 2022; Nalliah *et al.*, 2022), nevertheless guidelines recommend treatment of OSA to prevent/reduce AF burden with a class IIb recommendation (Van Gelder et al., 2024).

## 1.06.2 Avoiding stroke and thromboembolism (“A”)

AF increases the risk of stroke five-fold, depending on several risk factors (Boriani *et al.*, 2015). In AF, the most common location (≥ 90 %) for thrombi is in the left atrial appendage (LAA) (Blackshear and Odell, 1996). Thrombi in this area can lodge and enter the systemic circulation via the left ventricle and the aorta, leading to stroke and/or ischaemia of the mesenterial area or limbs. The common stroke risk factors are summarised in the clinical risk-factor-based $CHA_2$-$DS_2$-VA (previously $CHA_2$-$DS_2$-VASc) score including the following factors: Congestive heart failure, hypertension, Age ≥75, diabetes mellitus, stroke, vascular disease, age 65 – 74 years (and sex category, female, however this factor was removed) (Lip *et al.*, 2010; Van Gelder *et al.*, 2024).

| $CHA_2DS_2$-VA risk factor | Points |
|---|---|
| **C**ongestive heart failure<br>• Signs/Symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction | +1 |
| **H**ypertension<br>• Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment | +1 |
| **A**ge 75 years or older | +2 |
| **D**iabetes Mellitus<br>• Fasting glucose >125 mg/dl (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin | +1 |
| Previous **s**troke, transient ischaemic attack, or thromboembolism<br>• Previous myocardial infarction, peripheral artery disease or aortic plaque | +2 |
| **V**ascular disease | +1 |
| **A**ge 65-74 years | +1 |

**Table 4** $CHA_2$-$DS_2$-VA Score (previously $CHA_2$-$DS_2$-VASc, including sex category) definitions and points system (adopted from the 2024 European Society of Cardiology guidelines for the management of atrial fibrillation, Van Gelder et al., 2024)

The score previously included sex category ($CHA_2$-$DS_2$-VASc) including a point for female sex and was used a t the time of data collection, however this was removed and changed by the 2024 guidelines

Using the $CHA_2$-$DS_2$-VASc Score, the annual risk of stroke can be estimated (**Table 5**). For example, a score of one equals an annual stroke risk of 1.3%, while a score of nine increases the risk to 15.2% (Lip *et al.*, 2010).

| $CHA_2DS_2$-VASc Score | Adjusted Annual Stroke Rate |
|---|---|
| 0 | 0 % |
| 1 | 1.3 % |
| 2 | 2.2 % |
| 3 | 3.2 % |
| 4 | 4.0 % |
| 5 | 6.7 % |
| 6 | 9.8 % |
| 7 | 9.6 % |
| 8 | 6.7 % |
| 9 | 15.2 % |

**Table 5** Annual adjusted stroke risk according the $CHA_2$-$DS_2$-VASc Score (adopted from the 2020 European Society of Cardiology Guidelines for the Diagnosis and Management of AF)

According to updated guidelines, based on the $CHA_2$-$DS_2$-VA Score, stroke prevention using oral anticoagulation (OAC) should be guided. Anticoagulation is recommended with a $CHA_2$-$DS_2$-VA score ≥2 (Van Gelder *et al.*, 2024). In the case of a score of 1 oral anticoagulation for stroke prevention should be considered based on net clinical benefit (Van Gelder *et al.*, 2024).

### 1.06.2.1 Vitamin K antagonists (VKAs)

Traditionally, vitamin K antagonists (VKAs) were used as the gold standard anticoagulation for stroke prevention in AF. VKAs reduce stroke risk by 64% and mortality by 26% (Hart, Pearce, and Aguilar, 2007). Currently, VKAs are the only treatment with a proven safety profile in patients with rheumatic heart disease and/or an artificial heart valve (Connolly *et al.*, 2022). The main limitation of VKAs is the narrow therapeutic index, requiring frequent assessment of international normalised ration (INR) and dose adjustments according to INR. When used, a target INR of 2.0 – 3.0 is recommended for adequate stroke prevention in most patients – this

may vary in patients with mechanical valve prothesis. It is established that VKAs are only effective and safe with a time in therapeutic range of >70% (Hindricks *et al.*, 2020).

### 1.06.2.2 Direct oral anticoagulants (DOACs)

More recently, four randomised controlled trials (RCTs) showed the non-inferiority to VKAs in stroke prevention of so called direct oral anticoagulants (DOACs), namely apixaban, dabigatran, edoxaban and rivaroxaban (Connolly *et al.*, 2009; Granger *et al.*, 2011; Patel *et al.*, 2011; Giugliano *et al.*, 2013). A meta-analysis of these RCTs showed a 19% significant stroke reduction, a 51% reduction in haemorrhagic stroke and a similar ischaemic stroke risk reduction compared to VKA (Ruff *et al.*, 2014). Importantly, DOACs were associated with a significant 10% reduction in all-cause mortality (Ruff *et al.*, 2014). However, DOACs were also associated with a 25% increase in gastrointestinal bleeding when compared to VKA (Ruff *et al.*, 2014). Given this overwhelming data regarding DOACs, patients should favourably be started on DOACs when AF is newly diagnosed according to current guidelines (Van Gelder *et al.*, 2024). One major limitation of DOACs are the existing uncertainty in patients with end-stage kidney disease. While dose adjustments are possible in severe kidney disease, only the RENAL-AF trial has recently shown similar bleeding and stroke risk for apixaban when compared to warfarin (Pokorney *et al.*, 2022). Given the available data, the 2024 ESC guidelines recommend DOACs in preference to VKAs except in patients with rheumatic heart disease and/or mechanical heart valves (Van Gelder *et al.*, 2024). In clinical practice, a full dose of DOACs and a reduced dose are available in selected patients, as illustrated below (**Table 6**). AF patients with contraindications for long-term oral anticoagulation, such as patients with a history of intracranial bleeding pose a significant challenge in clinical practice. As mentioned earlier, most (≥ 90%) thrombi seen in AF patients are formed within the left atrial appendage (LAA) and can ultimately dislodge and lead to stroke by entering the arterial circulation. In patients with AF and contraindications for anticoagulation, interventional occlusion of the LAA may be considered according to the ESC Guidelines for the diagnosis and management of AF (Van Gelder *et al.*, 2024) .

| DOAC | Standard full dose | Criteria for dose reduction | Reduced dose |
|---|---|---|---|
| **Apixaban** | 5 mg twice daily | Two out of three needed:<br>- Age ≥80 years<br>- Body weight≤60 kg<br>- Serum creatinine >133mmol/L | 2.5 mg twice daily |
| **Dabigatran** | 150 mg twice daily | If any of these apply:<br>- Age 80 years<br>- Receiving concomitant verapamil | 110 mg twice daily |
| **Edoxaban** | 60 mg once daily | If any of these apply:<br>- Moderate/severe renal impairment (creatinine clearance 15-50 mmol/L<br>- Body weight ≤60 kg<br>- Concomitant ciclosporin, dronedarone, erythromycin or ketoconazole | 30 mg once daily |
| **Rivaroxaban** | 20 mg once daily | Creatinine clearance 15-49 ml/min | 15 mg once daily |

**Table 6** DOAC dosing overview and criteria for dose reduction, adopted from the current ESC guidelines (Van Gelder *et al.*, 2024)

### 1.06.2.3 Assessment of bleeding risk

Like assessment of stroke risk, bleeding risk assessment should also be performed before initiating OAC in every patient. The score-system most used is the HAS-BLED score which entails uncontrolled hypertension (SBP >160 mmHg), abnormal renal and /or hepatic function, previous stroke, bleeding history, labile INR, elderly and drugs or excessive alcohol drinking **(Table 7)** (Pisters *et al.*, 2010). Important to note, the current guidelines stress, that a high bleeding risk should not lead to the withholding of OAC, as the clinical benefit is even more evident in these patients (Van Gelder *et al.*, 2024). This means, bleeding risk factors should be addressed and if possible treated (e.g. blood pressure control).

| Clinical characteristic | Points |
|---|---|
| **H**ypertension<br>• Uncontrolled, >160 mmHg systolic | 1 |
| **A**bnormal renal and liver function<br>• Dialysis, transplant, Cr >200 umol/L, Cirrhosis, bilirubin 2x normal, AST/ALT >3x normal | 1 point each |
| **S**troke history | 1 |
| **B**leeding or predisposition to bleeding | 1 |
| **L**abile INR<br>• Unstable high INRs, time in therapeutic range <60% | 1 |
| **E**lderly<br>• Age >65 | 1 |
| **D**rugs or alcohol<br>• Antiplatelet agents, NSAIDs, ≥ 8 alcoholic drinks/week | 1 or 2 |

**Table 7** HAS-BLED Score with definitions and points (adopted from the 2020 European Society of Cardiology Guidelines for the Diagnosis and Management of Atrial Fibrillation)

## 1.06.3 Reduce symptoms by rate control (“R”)

In general, to treat AF-related symptoms, two strategies are available – rate control and/or rhythm control, lastly with the goal to restore a stable sinus rhythm.

### 1.06.3.1 Pharmacological rate control

Rate control aims to reduce ventricular rate to control symptoms of AF, which usually are caused and intensified by tachycardia. Rate control should be an implemented strategy in all patients to control heart rate when in AF. The optimum target rate for rate control in AF has

been investigated in clinical studies. When comparing strict rate control (≤80 beats per minute) and lenient rate control (≤110 beats per minute), the RACE (rate control efficacy in permanent atrial fibrillation) II randomized controlled trial showed no difference in dyspnoea and hospitalisation (Groenveld *et al.*, 2013). Therefore, a lenient rate control with a target rate ≤110 beats per minute is acceptable if symptoms are controlled. Pharmacological agents used to achieve rate control are beta-blockers, non-dihydropyridine calcium channel blockers, digoxin, or amiodarone as a last resort (Van Gelder *et al.*, 2024).

#### 1.06.3.2 Non-pharmacological rate control: Pace and ablate

A non-pharmacological approach, when medication fails, involves the ablation of the atrioventricular (AV) node after previous pacemaker/cardiac resynchronisation therapy (CRT) implantation. This approach aims to stop the conduction of AF from the atria onto the ventricles, making patients dependant on the rate set by the pacemaker. Complication rates and long-term mortality of this procedure are low and have shown to improve if pacemaker implantation occurred weeks prior to ablation and if the pacing rate was set between 70 – 90 bpm (Wang *et al.*, 2013). The device chosen (pacemaker or CRT-system) should be based on patient characteristics. In patients with permanent AF and a narrow QRS complex, Brignole et al. were able demonstrate superiority of ablation combined with CRT with regards to mortality when compared to pharmacological rate control (Brignole *et al.*, 2021), however more extensive data in this regard is lacking. Additionally, the role of conduction system pacing in this regard needs to be awaited in further studies.

### 1.06.4 Reduce symptoms by rhythm control

Contrary to rate control, rhythm control aims to restore and maintain sinus rhythm. Available therapies include cardioversion, antiarrhythmic drugs (AADs), and catheter ablation. Currently, the main indication for rhythm control found in the ESC guidelines is to reduce symptoms and improve quality of life as available trials available at that time had failed to show a prognostic benefit. Recently, however, the large, randomised Early Rhythm Control for Atrial Fibrillation (EAST-AFNET 4) trial was able, for the first time, to show superiority of rhythm control compared to rate control with regards to cardiovascular death, stroke, and hospitalisation, however this was limited to early (≤1 year) diagnosed AF with risk factors only (Kirchhof *et al.*, 2020).

### 1.06.4.1 Antiarrhythmic drugs

AADs are used to convert AF into sinus rhythm or to maintain sinus rhythm once it has been established successfully. The choice of agents depends mainly on concomitant cardiac disease. Class Ic AADs involve flecainide and propafenone. These drugs are not recommended in patients with structural heart disease, as increased mortality was demonstrated for flecainide in the CAST study (Cardiac Arrhythmia Suppression Trial) (Echt *et al.*, 1991). Class III AADs involve sotalol, dofetilide and amiodarone. Amiodarone has demonstrated superiority to other antiarrhythmic agents in both cardioversion (Khan, Mehta and Gowda, 2003) and maintenance of sinus rhythm (Freemantle *et al.*, 2011). It is classified as a Class III antiarrhythmic agent due to its major effect of blocking potassium channels to prolong cardiac action potentials, also leading to prolongation of the QT-Interval and sinus bradycardia. Importantly, the main concern that limits the use of amiodarone are its non-cardiac toxicities. The resulting metabolite can accumulate in lungs, thyroid, liver, and the nervous system, leading to several severe side-effects (Gelfman, 2022). Due to the limitation of class Ic drugs in heart failure, hypertrophy and coronary artery disease, amiodarone may be given in these patients. There are newer Class III Drugs such as dronedarone and vernakalant. Dronedarone is a newer derivative of amiodarone, designed to reduce amiodarone-related non-cardiac toxicities, however, the antiarrhythmic efficacy of dronedarone is inferior to amiodarone (Freemantle *et al.*, 2011).

### 1.06.4.2 Electrical cardioversion

Cardioversion is a quick and safe method of achieving sinus rhythm under sedation and can be performed electively or as an acute therapy. In haemodynamically unstable patient, direct current cardioversion is recommended, as it is more effective than pharmacological cardioversion (Hindricks *et al.*, 2020). Monitoring of oxygen saturation and blood pressure are carried out routinely. The main complications include skin burning or bradycardia, making the availability of atropine, isoproterenol, or transcutaneous pacing mandatory. Important to not, long term success is moderate with studies showing recurrence in 50% of patients within one year (Kuppahally *et al.*, 2009). Cardioversion does not offer curative treatment but can be helpful to improve symptoms or evaluate presence of arrhythmia-induced cardiomyopathy.

### 1.06.4.3 Catheter ablation of atrial fibrillation

Today, catheter ablation for AF is well established and has been shown to be superior to AADs for maintaining sinus rhythm and controlling symptoms in patients with paroxysmal AF (Calkins *et al.*, 2009; Hakalahti *et al.*, 2015; Packer *et al.*, 2019). The main clinical benefit of catheter ablation is the reduction of arrhythmia-related symptoms. The improvement of symptoms was demonstrated in the large CABANA (Catheter ablation vs. Antiarrhythmic Drug therapy for Atrial Fibrillation) – Trial (Packer *et al.*, 2019). However, the primary endpoint of death, disabling stroke, severe bleeding or cardiac arrest when compared to medical therapy was not met (Packer *et al.*, 2019). Previously, a reduction in mortality and hospitalisation was shown only in patients with heart failure (with reduced left ventricular ejection fraction) and AF in the CASTLE-AF (Catheter Ablation vs. Standard conventional Treatment in patients with left ventricular dysfunction and Atrial Fibrillation) trial (Marrouche *et al.*, 2018). Contrary to these results however, the AMICA (Atrial fibrillation Management In Congestive heart failure with Ablation) trial, which investigated patients with reduced ejection fraction failed to show a benefit of catheter ablation at one-year follow up (Kuck *et al.*, 2019). More recently, a significant benefit of catheter ablation/rhythm control was shown for end-stage heart failure patients in the randomized CASTLE-HTx Trial for the endpoints of preventing heart-transplantation, left ventricular assist devices and mortality (Sohns *et al.*, 2023). Another important consideration should be made in AF patients with a cardiomyopathy due to the arrhythmia itself (tachycardia-induced cardiomyopathy). In these patients, the irregular and rapid activity of the atria leads to a dysfunction of the ventricle and subsequent heart failure. If suspected, catheter ablation is recommended to restore the left ventricular ejection fraction (Van Gelder *et al.*, 2024). As far as which modality of rhythm control to choose, according to the 2024 ESC guidelines for the diagnosis and management of atrial fibrillation, catheter ablation is recommended in paroxysmal and persistent AF after antiarrhythmic drug therapy failure or intolerance (Van Gelder *et al.*, 2024). In addition, ablation is recommended as first-line therapy for rhythm control in patients with paroxysmal AF to reduce symptoms, recurrence and disease-progression (Van Gelder *et al.*, 2024). Here, an informed patient choice and preference is highlighted.

#### 1.06.4.3.1 Pulmonary vein isolation (PVI)

Haïssaguerre et al. demonstrated in 1998, that the initiation of atrial fibrillation is triggered by ectopies from the pulmonary veins (PVs) (Haïssaguerre *et al.*, 1998). Over the years creating circumferential lesions at the PV antra around the ipsilateral PVs, a procedure known as pulmonary vein isolation (PVI), has become the cornerstone of catheter ablation for atrial

fibrillation (**Figure 4**). In terms of techniques and technologies, point-by-point radiofrequency (RF) ablation or single shot devices (for example cryoballoon) or non-thermal energy sources such as pulsed field ablation (PFA) can be used to perform PVI.

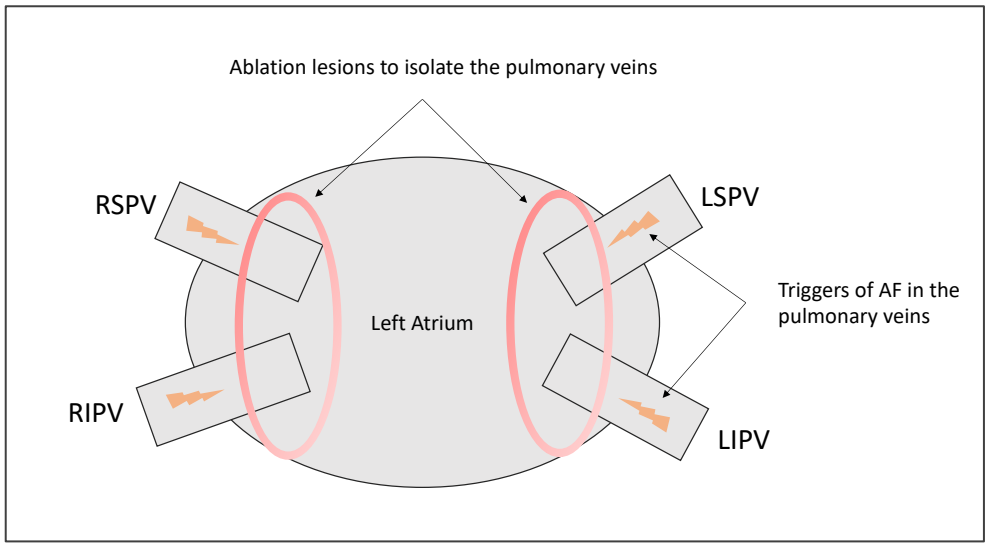


**Figure 4** Pulmonary veins as the trigger for atrial fibrillation and the theoretical idea behind electrical isolation of the pulmonary veins from the left atrium for the basis of catheter ablation. LSPV indicates left superior pulmonary vein; LIPV, left inferior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein

### 1.06.4.3.2 Energy sources for catheter ablation

***Radiofrequency ablation***

Traditionally, point-by-point ablation using RF as an energy source was used and was the gold standard for many years. In this procedure, the ipsilateral pulmonary veins are electrically isolated from the left atrium by creating circular lesions around their antrum using thermal radiofrequency current as an energy source (Hindricks *et al.*, 2020). Nowadays, various 3D-mapping systems are used, to visualise anatomy and catheters to help guide ablation but also provide electroanatomic information such as tissue voltage and local activation of signals (Borlich *et al.*, 2018) . An example of such 3D map is shown in **Figure 5**.

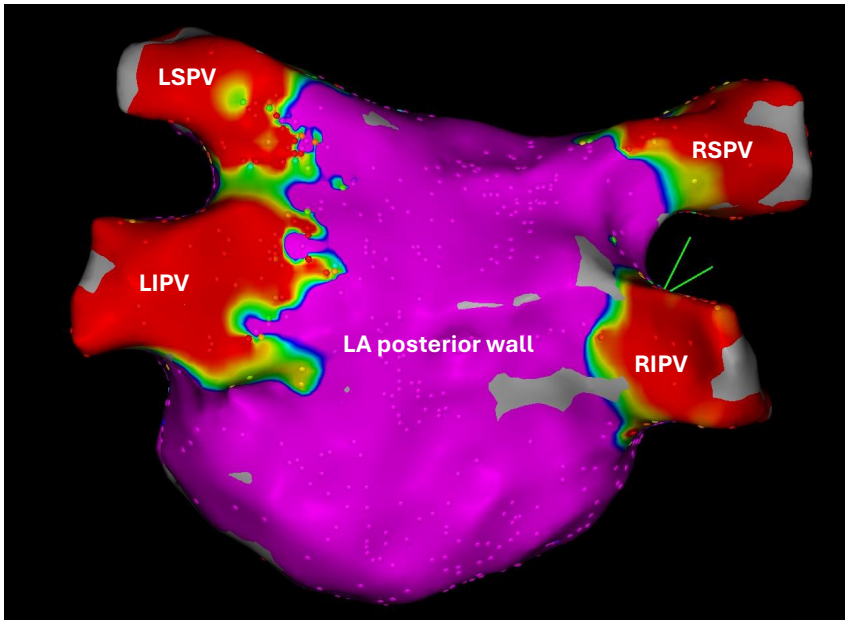


**Figure 5** Carto3 voltage map of the left atrium with a posterior-anterior view showing a healthy posterior wall (purple mass indicating normal voltage with no areas of fibrosis). LA= left atrium LSPV= left superior pulmonary vein LIPV= left inferior pulmonary vein RSPV= right superior pulmonary vein RIPV= right inferior pulmonary vein

Variations of RF ablation exist with so-called high-power-short-duration (HPSD) RF applications. Recently, protocols with a maximum of up to 50 W and very HPSD with a maximum of 90 W have been evaluated and shown to shorten procedure times compared to standard RF ablation (Bourier *et al.*, 2018; Kottmaier *et al.*, 2020).

***Cryoballoon ablation***

Contrary to the point-by-point RF ablation guided by 3D mapping, requiring multiple ablation lesions and tactile catheter movements, the cryoballoon (CB) is a balloon-based system aiming to isolate the pulmonary veins by a "single-shot" (Kuck *et al.*, 2016). CB ablation works in theory by cell injury due to the application of cryoenergy (Altmann *et al.*, 2012). With regards to effectivity, a multicentre, randomised trial comparing both energy sources for paroxysmal, drug – refractory atrial fibrillation showed non – inferiority and similar safety of the CB when compared to RF ablation in 762 patients (Kuck *et al.*, 2016). Compared to RF ablation, CB ablation is slightly shorter but associated with longer fluoroscopy time (Heinroth *et al.*, 2022).

***Pulsed Field Ablation (PFA)***

More recently, PFA has been used for catheter ablation of AF. PFA is a nonthermal ablative modality, whereby ultrarapid electrical fields are applied to the targeted myocardial tissue (Reddy *et al.*, 2019). A recent multicentre trial, MANIFEST-PF, showed 99.9% acute effectiveness (Ekanem *et al.*, 2022). There were no oesophageal complications or phrenic nerve injuries persisting past hospital discharge. Major complications (1.6%) were pericardial tamponade (0.97%) and stroke (0.4%); one stroke resulted in death (0.06%) (Ekanem *et al.*, 2022). A main clinical benefit of PFA appears to be the specificity for cardiac tissue, thereby reducing the damage to surrounding tissue, also enabling to target more vulnerable areas in the left atrium such as the posterior wall of the left atrium. In addition to PVI, PFA has also been used to treat non-pulmonary vein triggers of AF and AT (Gunawardene *et al.*, 2022). Die ADVENT-trial was the first RCT comparing PFA to CB and RF ablation, showing non-inferiority with regards to arrhythmia-free survival and safety in a total of 607 patients (Reddy *et al.*, 2023).

### 1.06.4.3.3 Concomitant atrial tachycardias and ablation beyond PVI

***Atrial tachycardia***

After previous PVI, linear ablation or substrate modification, atrial surgery or in progressive scaring due to AF, left atrial tachycardia (AT) may develop due to abnormal substrate or conduction gaps (Mountantonakis and Gerstenfeld, 2010). An example of AT as seen on lead V1 in a 12-lead ECG is shown in **Figure 6**.

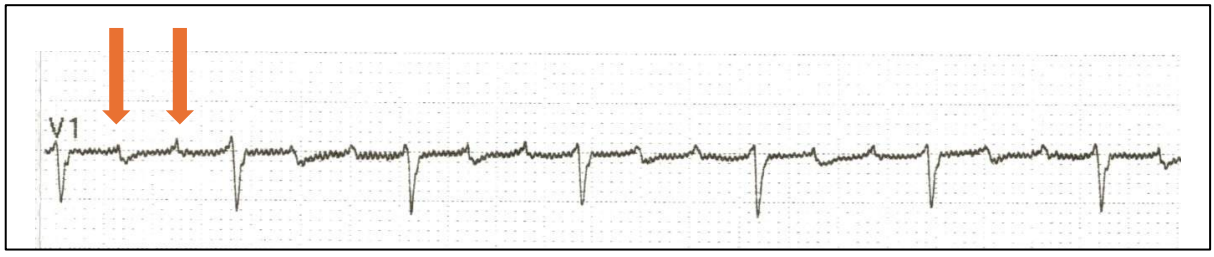


**Figure 6** Lead V1 in a 12-lead ECG (25mm/s) showing an AT (regular QRS-complexes and multiple p-waves highlighted by the orange arrows)

In general, ATs can be classified according to their electrophysiological mechanism as either focal, microreentrant and marcoreentrant (Saoudi *et al.*, 2001).

Focal atrial tachycardia usually arises from a distinctive location and spreads within the rest of the atrium (Hung *et al.*, 2020).

Microreentrant tachycardia, also called localized re-entries, first described by Jais et al., are localized circuits within smaller atrial segments (Jaïs *et al.*, 2009).

Macroreentrant ATs are the most common form of AT after previous AF ablation and spread around structures such as the mitral valve in perimitral flutter, the most common location for macroreentrant tachycardia after previous ablation followed by circuits involving the roof (Chugh *et al.*, 2005). Other sites include the PVs, left atrial septum, anterior LA or the LAA (Hindricks *et al.*, 2020). Presence of AT often warrants re-ablation, as ATs are not well controlled by AADs and AT can be more symptomatic (Knecht *et al.*, 2009).

After identification of the earliest activation and or entrainment mapping, catheter ablation of critical isthmuses is aimed for after identification of the underlying AT circuit (Ouyang *et al.*, 2002; Hung *et al.*, 2020). Regarding ablation strategies, focal AT can be treated by catheter ablation at the earliest activation site. (Hung et al., 2020). In the case of macroreantrant AT, linear ablations between anatomical or electrical barriers, which interrupt the circuit, remain the essential tool in the management of macroreentrant AT ablation (Ouyang *et al.*, 2002; Hung *et al.*, 2020). Here, as mentioned previously, perimitral ATs are the most common after AF ablation. The most common line of ablation for the mitral isthmus is from the lateral mitral anulus to the LIPV, however, in some cases, epicardial ablation via the CS is necessary to achieve an electrical block of the mitral isthmus (Hung *et al.*, 2020). An example of an 3D activation map of a perimitral AT is shown in **Figure 7**.

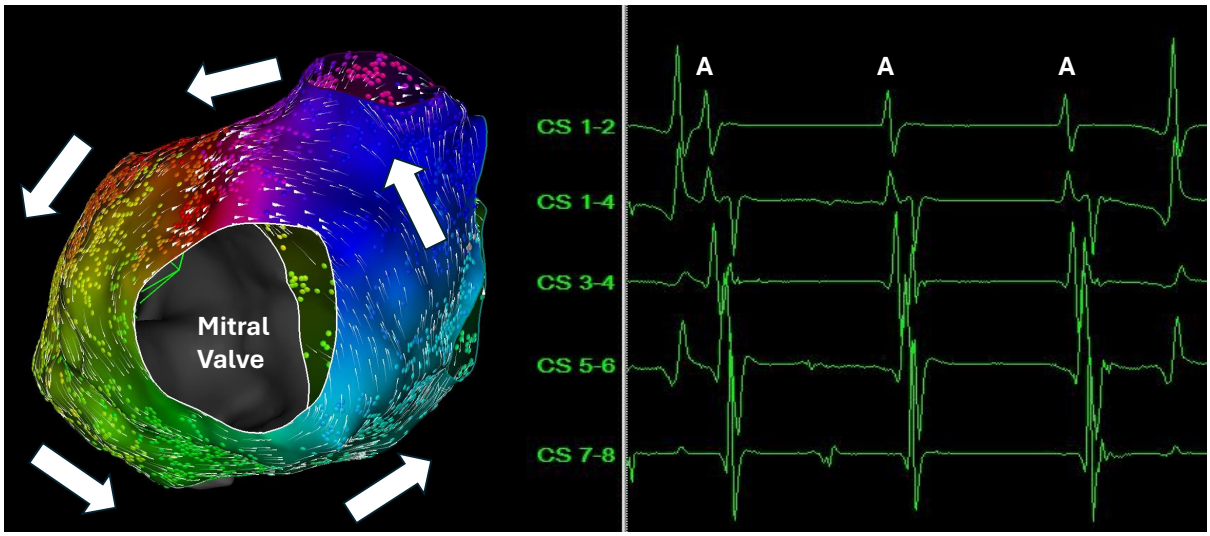


**Figure 7** Carto3 activation map showing a perimitral re-entry as highlighted by the white arrows (left image) and the according intracardiac electrograms as recorded within the coronary sinus A=atrial signal

The second most common ATs after previous AF ablation are roof-dependent (Hung *et al.*, 2020). Treatment usually involves a roof line, which is usually achieved by ablating a linear lesion between the left and right superior PVs. An example of intracardial electrograms and 3D activation map of a roof-dependent AT is shown in **Figure 8.**

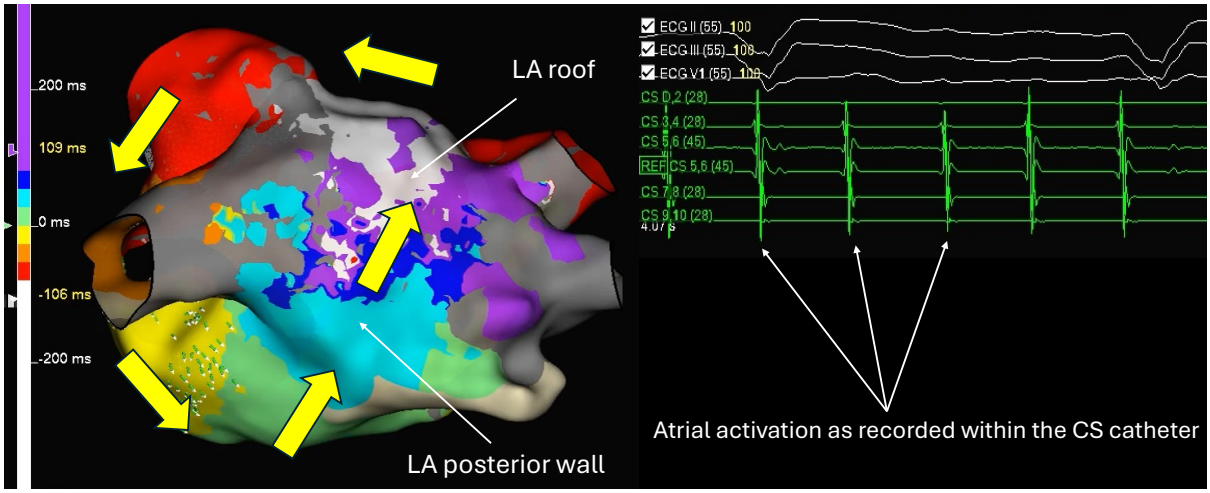


**Figure 8** EnsiteX 3D-activation map of a roof-dependent AT (tachycardia re-entry shown with yellow arrows in the left image) and corresponding intracardiac electrograms as recorded within the coronary sinus catheter in the right image

Another strategy of linear ablation is the anterior line, hereby the anterior mitral annulus is connected to a roof line or the RSPV (Jaïs et al., 2007). Examples of an anterior line and roof line are illustrated in **Figure 9**.

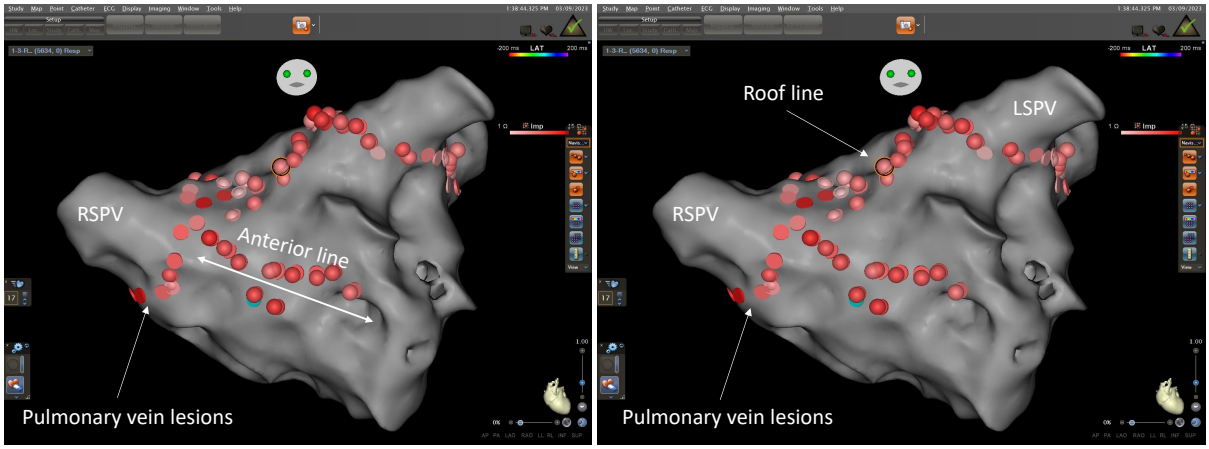


**Figure 9** Cardiac Mapping (Carto3) showing the LA with isolated PVs and additional anterior line (left image) and additional roof line (right image)

***Posterior wall isolation***

Furthermore, the left atrial posterior wall has also been suggested to play a role in the initiation and maintenance of AF and AT, as the posterior wall has the same embryological origin as the pulmonary veins, which means that both structures may equally contribute to AF (Sugumar *et al.*, 2018). Therefore, it is assumed, that targeting the posterior wall with ablation may modify the substrate involved in the initiation and progression of AF (Sugumar *et al.*, 2018). In terms of the ablation technique, a line joining the two superior pulmonary veins and a second line joining the two inferior pulmonary veins, is created. The lateral boundary of the lesion is formed by the circumferential lesions of the pulmonary veins ultimately leading to a so-called “box lesion”. A recent randomized study failed to show benefit of additional box lesions compared to PVI alone in patients with persistent AF (Kistler *et al.*, 2023). PFA has been proposed as an appropriate modality for the posterior all due to its specificity for cardiac tissue only, thereby avoiding oesophageal lesions, initial non- randomized data has yielded promising results (Gunawardene et al., 2023; Badertscher et al., 2024), however, randomized data is yet awaited.

***Right atrial flutter***

Cavotricuspid isthmus (CTI) - dependent atrial flutter is another arrhythmia, that commonly co-exists in AF patients and involves a macro-re-entry circuit around the tricuspid annulus. Diagnosis of atrial flutter can be achieved via a 12-lead ECG. Here, a characteristic “saw-tooth” appearance of the p-waves can be observed (**Figure 10**). As far as the treatment is concerned, catheter ablation is the most effective therapy and shown to be superior to AADs such as amiodarone (Natale *et al.*, 2000). Ablation includes ablation of the CTI with the achievement of a bidirectional block. Catheter ablation of CTI is recommended in symptomatic, recurrent episodes according to the 2019 ESC Guidelines for the management of patients with supraventricular tachycardia (Brugada *et al.*, 2020).

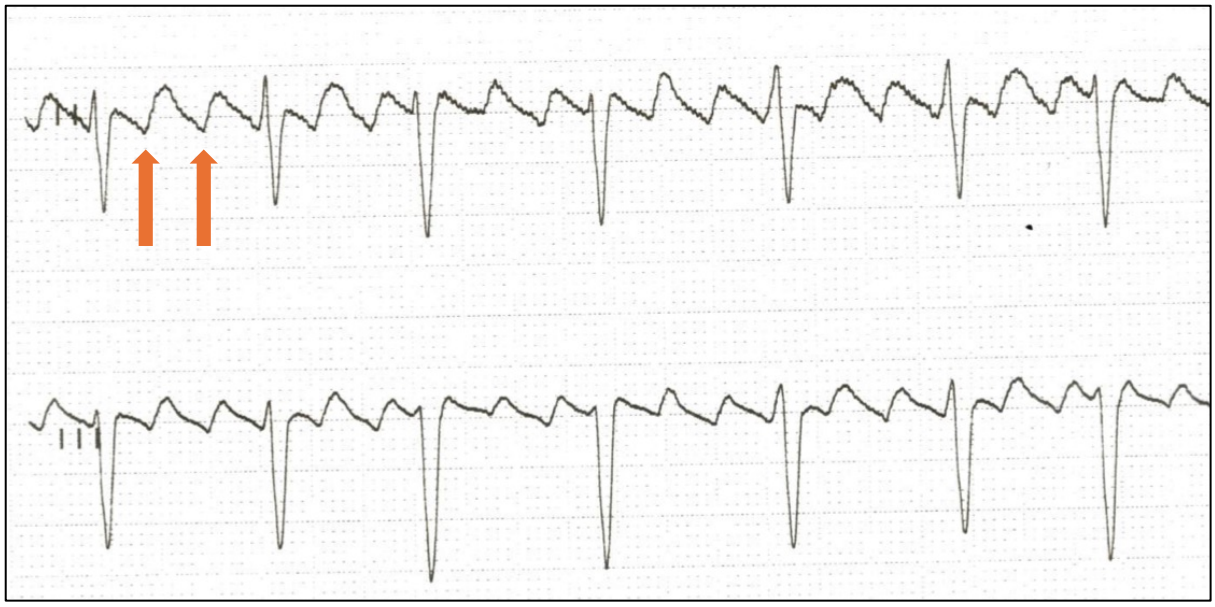

**Figure 10** 12-lead ECG (25mm/s) with inferior leads II and III showing typical atrial flutter with negative p-waves and the characteristic “saw-tooth” appearance as highlighted by the orange arrows

***Ablation of complex fractionated atrial electrograms (CFAE)***

Complex fractionated atrial electrograms (CFAE) have been linked to indicate slow conduction, a mechanism by which AF may be perpetuated (Jalife, Berenfeld and Mansour, 2002). CFAE are usually targeted for ablation in procedures where AF is persistent despite isolated pulmonary veins and in progressive atrial cardiomyopathy. Most trials, such as the CHASE-AF RCT comparing PVI alone to PVI with additional ablation of CFAE failed to show additional benefit in persistent AF (Vogler *et al.*, 2015). The only trial signalling an improved outcome was published recently in the ERASE-AF trial (Huo *et al.*, 2022), more extensive data showing a prognostic benefit are lacking as of now.

### 1.06.4.3.4 Success of rhythm control and catheter ablation

Success of catheter ablation is dependent on several factors such as AF type, duration, but also comorbidities such as sleep apnoea, metabolic syndrome, and hypertension. Risk factors for AF recurrence are LA size, AF duration, age, renal dysfunction, and an extensive atrial substrate as seen in imaging such as MRI (Hindricks *et al.*, 2020). Permanent isolation of the pulmonary veins is difficult to achieve with a significant number of patients requiring multiple procedures. In paroxysmal AF, sinus rhythm without symptomatic recurrence is seen in 70%, decreasing to 50% in patients with persistent AF (Kirchhof *et al.*, 2016). Especially in persistent and long-standing persistent AF, the atrial substrate may involve non-pulmonary vein foci such

as the atria, LAA, rotors, superior vena cava and CFAE) (Hindricks *et al.*, 2020). However, additional benefit of ablation outside the PVs compared to PVI alone is yet to be demonstrated and subject to current research.

#### 1.06.4.3.5 Complications of catheter ablation

In terms of complications of catheter ablation, rates of 4-14% are reported (Hindricks *et al.*, 2020). Complications can include thromboembolic events, cardiac tamponade, vascular complications, pulmonary vein occlusion, atrio-oesophageal fistula, heart block, lung injury, mitral valve injury, endocarditis, phrenic nerve injury, aspiration, and death (Overview in **Table 8**). Periprocedural death is rare with less than 0.2% und mostly due to cardiac tamponade (Arbelo *et al.*, 2014).

| Complication severity | Complication type | Complication rate |
|---|---|---|
| Life-threatening complications | Periprocedural death | <0.1% |
| | Oesophageal perforation/fistula | <0.5% |
| | Periprocedural thromboembolic event | <1.0% |
| | Cardiac tamponade | 1% |
| Severe Complications | Pulmonary vein stenosis | <1.0% |
| | Persistent phrenic nerve palsy | <1.0% |
| | Vascular complications | 2-4% |
| | Conversion to sternotomy | N/A |
| | Pneumothorax | N/A |

**Table 8** Classification of complications adopted according to the 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation (Hindricks *et al.*, 2020)

***Pulmonary vein stenosis***

Pulmonary vein stenosis is defined by a reduction in pulmonary vein diameter following ablation. According to the guidelines, it is categorised as a severe complication with a rate of <1.0% (Hindricks *et al.*, 2020). Symptoms may include cough, dyspnoea, haemoptysis, and recurrent pneumonia. CT or MRI can be performed to confirm the diagnosis. Balloon angioplasty or stenting are treatment options for severe pulmonary stenosis.

***Oesophageal perforation/fistula***

In the case of a fistula, the oesophageal lumen is connected to the left atrium or the pericardium due to the lesion created by ablation. It is also categorised as a life-threatening complication of catheter ablation with an overall incidence <0.5% and a very high mortality of more than 60-80% (Dagres *et al.*, 2006). Clinical manifestation occurs 2-4 weeks after ablation with symptoms including dysphagia, fever, sepsis, and neurological events due to air embolism (Tilz *et al.*, 2023). Urgent CT or MRI are recommended to confirm the diagnosis, urgent surgery is required after the diagnosis is made, however, even then mortality is 65.8% (Tilz et al., 2023). This particular complication has not yet been reported for PFA.

***Cardiac tamponade***

Cardiac tamponade is classed as a life-threatening complication of catheter ablation and is the most common cause of death associated with AF ablation (Arbelo *et al.*, 2014). In the case of tamponade, rapid percutaneous pericardiocentesis needs to be performed to restore haemodynamic stability. Alternatively, surgical treatment may be needed. An example of pericardial effusion as seen on transthoracic echocardiography is shown in **Figure 11**.

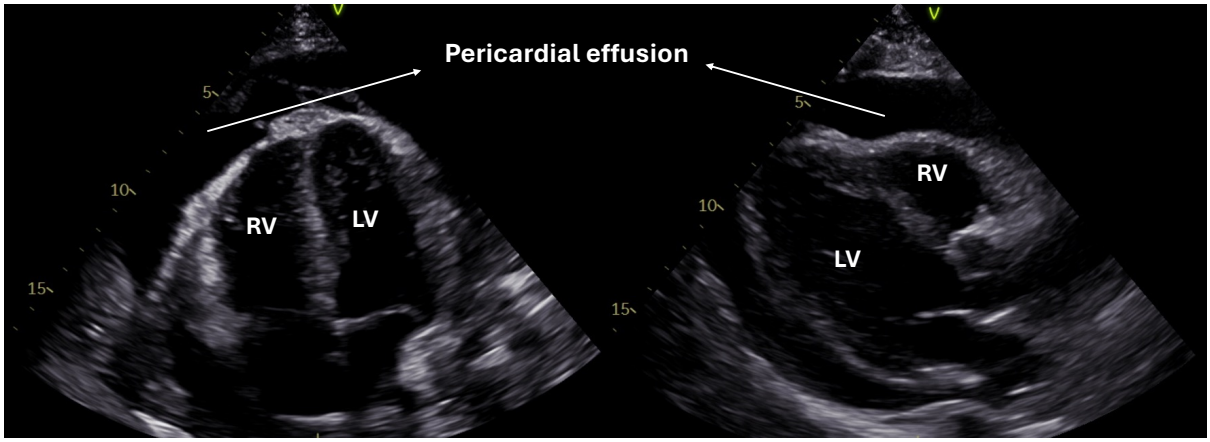


**Figure 11** Transthoracic echocardiography showing a large pericardial effusion in a four-chamber view (left image) and in a parasternal view (right image). LV= left ventricle RV= right ventricle

***Thromboembolism***

Systemic thromboembolism is reported in <1% of AF ablation (Berger *et al.*, 2019). It's nevertheless a serious and potentially life-threatening complication. The most significant risk factor is a previous stroke or transient cerebrovascular attack (TIA). The pathophysiology may involve persistent activation of the clotting cascade due to catheter placement, endothelial disruption from ablation and atrial stunning (Boersma *et al.*, 2020).

***Phrenic nerve injury***

Injury to the phrenic nerve can occur with thermal energy modalities and is explained by the anatomical proximity of the phrenic nerve to the right pulmonary veins, especially the right superior pulmonary vein (RSPV). A higher incidence of injury to the right phrenic nerve can be observed during CB ablation (Kuck *et al.*, 2016). A recent worldwide registry revealed a total recovery of 97% after 12 months with only 0.06% having a persistent and symptomatic phrenic nerve palsy (Heeger *et al.*, 2022). Similar to esophageal fistula, no permanent phrenic nerve palsy has been reported for PFA.

***Vascular complications***

Vascular complications are the most common complication of AF ablation (Berger *et al.*, 2019). Possible complications entail haematoma, pseudoaneurysm and arteriovenous fistula. A systemic meta-analysis by Triantafyllou et al. showed significantly reduced vascular complications in electrophysiological procedures with ultrasound-guided venous access compared to a landmark-guided approach (Triantafyllou *et al.*, 2022). Depending on the complication, management may involve compression, thrombin injection or surgery.

## 1.07 Evaluation and dynamic reassessment ("E")

The current guidelines for AF highlight, that AF is dynamic and progressive in its nature, therefore continuous reassessment is necessary to guide treatment (Van Gelder et al., 2024). The main aim of this aspect is to prevent progression of AF, heart failure, thromboembolism and bleeding complications (Van Gelder et al., 2024).

### 1.08 Management of atrial fibrillation in octogenarians

The treatment of AF in octogenarians poses a special challenge due to more frailty, comorbidities, and suspected higher complication rates. With a demographic change leading to an increase in life expectancy, more patients may require rhythm control, including catheter ablation, to maintain life quality. As for current clinical practice in the elderly population, rate control seems to be the preferred treatment strategy, however, there is insufficient evidence to support rate control over rhythm control and vice versa (Hindricks *et al.*, 2020). RCTs investigating outcomes of catheter ablation in octogenarians are lacking and in general data for this growing patient population is scarce. Because of the current demographic change with a significant increase in the number of elderly patients and the association of age with AF, the number of octogenarians presenting with AF will inevitably increase in the future. More efforts are required to generate data and investigate various treatment options in these patients.

### 1.09 Aim of this study

The aim of this work is to contribute to investigating catheter ablation, the most potent option for rhythm control, in octogenarian AF patients over the age of 80 years with regards to efficacy and safety in a single, large-volume centre for catheter ablation.

## 2 Methods

### 2.1 Study population

Consecutive patients aged 80 years and older, undergoing catheter ablation for symptomatic AF or AT (after previous AF ablation), including RF, CB and PFA ablation procedures, from January 2021 until January 2022, were retrospectively analysed. Patients receiving non-AF related procedures, such as ventricular tachycardia or supraventricular tachycardias were excluded. In addition, patients receiving ablation for procedures with the intention of rate control, such as AV-node ablation, were also excluded.

### 2.2 Procedure planning

Written consent was obtained prior to all ablation procedures. Transoesophageal echocardiography (TOE) was performed prior to all procedures to assess structural heart disease and to rule out intracardiac thrombi. Patients on DOACs omitted one dose on the day of the procedure. For patients on VKA, INR of 2.0 up to 2.5 was targeted.

## 2.3 Catheter ablation procedure

### 2.3.1 Sedation and monitoring

All patients were monitored using continuous oxygen saturation, non-invasive blood pressure measurements as well as 12-lead ECG. Analgosedation was achieved by a selection or combination of propofol, midazolam and sufentanyl.

### 2.3.2 Intraprocedural anticoagulation

All patients received intravenous, unfractionated heparin (UFH) after transseptal puncture according to their body weight (100 units of Heparin/kg). Activated clotting time (ACT) was measured regularly and additional heparin was given depending on the measured ACT with a target of > 300 seconds. Antagonization with protamine was not performed routinely.

### 2.3.3 Index procedures - Radiofrequency pulmonary vein isolation

Once sedation was achieved, the procedure would be initiated with three punctures of the femoral vein under palpation of anatomical landmarks. Ultrasound of the femoral vessels was only carried out in difficult punctures, if necessary, but not routinely. Following successful puncture three sheaths were placed in the vein using Seldinger technique. Next, the coronary sinus (CS) was intubated to record atrial and ventricular electrogram signals and to perform pacing manoeuvres. The next step involved accessing the left atrium via the right atrium, a step known as transseptal puncture, which is performed under fluoroscopic guidance. Once access into the left atrium was established, a 3D electroanatomic map of the left atrium was created. The mapping systems used were the following:

1. CARTO3 (Biosense Webster, Diamond Bar, CA, United States)
2. EnSite NavX (St. Jude Medical, St. Paul, MN, United States)
3. Rhythmia (Boston Scientific, Cambridge, MA, United States)

Now circumferential point-by-point ablation of the pulmonary veins as carried out until electrical isolation was achieved. Here a variety of power settings were used, from conventional RF ablation to HPSD-protocols up to 70 watts. Examples of fluoroscopy and 3D map during RF ablation is shown in **Figure 12**, intracardiac signals with live isolation of the pulmonary vein is shown in **Figure 13**.

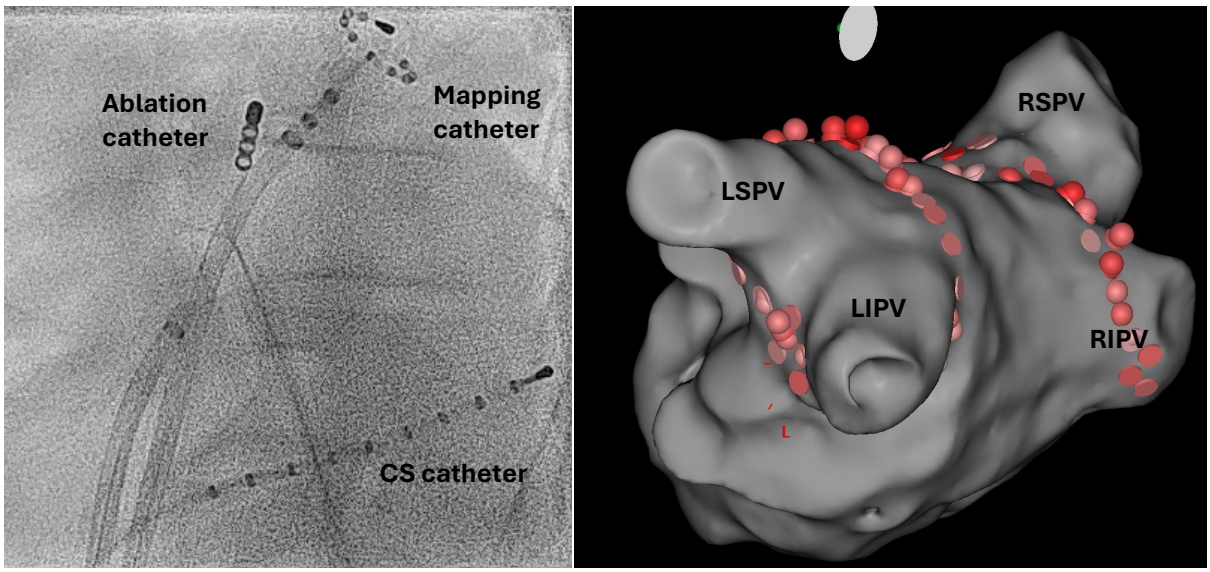


**Figure 12** Fluoroscopic image showing RF ablation of the left pulmonary veins with the ablation catheter and mapping catheter placed in the left atrium (left image) and the according Carto3 3D map with the lesions performed as shown by the red dots

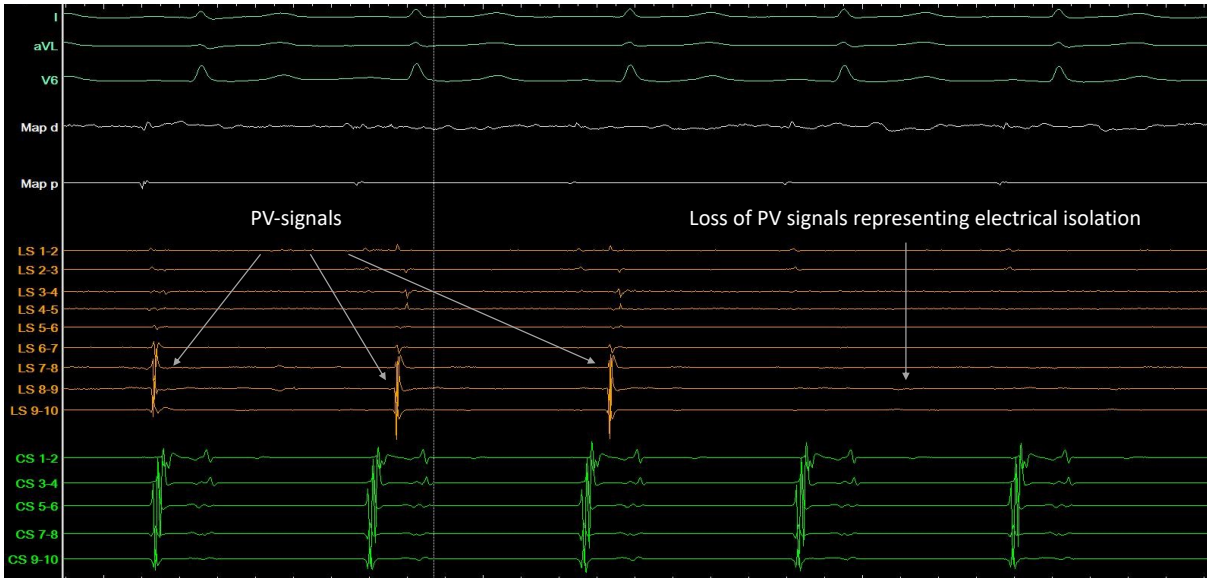


**Figure 13** Intracardiac electrograms (LS=Lasso mapping catheter, CS=coronary sinus catheter) showing the moment of electrical isolation of the pulmonary veins during RF ablation as recorded by the mapping catheter. PV= pulmonary vein

Quality of lesions was measured according to local impedance drop, in some cases contact force was also measured. The procedure was finished after all veins were checked for electrical isolation.

### 2.3.4 Index procedures - Cryoballoon pulmonary vein isolation

For cryoballoon ablation, the cryoballoon (Medtronic Inc., Minneapolis, MN, USA) and the according cryoconsole were used to perform PVI. Cryoballoon PVI was initiated by 2 punctures of the femoral vein and insertion of 2 sheaths in usual Seldinger technique. Next, intubation of the CS and transseptal puncture for left atrial access were performed under fluoroscopic guidance as shown in **Figure 14** below. Angiography of the left atrium was performed to assess left atrial and pulmonary vein anatomy. Next the cryoballoon sheath (FlexCath®; Medtronic, Inc., Minneapolis, MN, USA) was inserted into the LA via the transseptal wire, followed by the cryoballoon system (fourth-generation Arctic Front Advance®; Medtronic, Inc., Minneapolis, MN, USA) with the according mapping catheter (Achieve™, Medtronic, Inc., Minneapolis, MN, USA). Starting in the left superior pulmonary vein (LSPV) the cryoballoon was inflated and applied to the vein using fluoroscopy and dye injection to check for adequate occlusion (**Figure 14**). The standard protocol included a freezing time of 180-240 seconds (operator-dependent). Time taken for isolation (TTI), temperature required for isolation and minimal freezing temperature were recorded. A similar approach was taken for the left inferior pulmonary vein (LIPV). The pulmonary veins were isolated under control of oesophageal temperature (via an oesophageal probe) to avoid atrio-oesophageal lesions and/or fistula. The minimal oesophageal temperature was always recorded. The standard protocol was stopping ablation in case the oesophageal temperature reached 20 degrees Celsius. The right pulmonary veins were equally isolated using the same protocol; however, phrenic nerve pacing and palpation were performed to prevent phrenic nerve palsy. All pulmonary veins were finally checked for isolation at the end of the procedure.

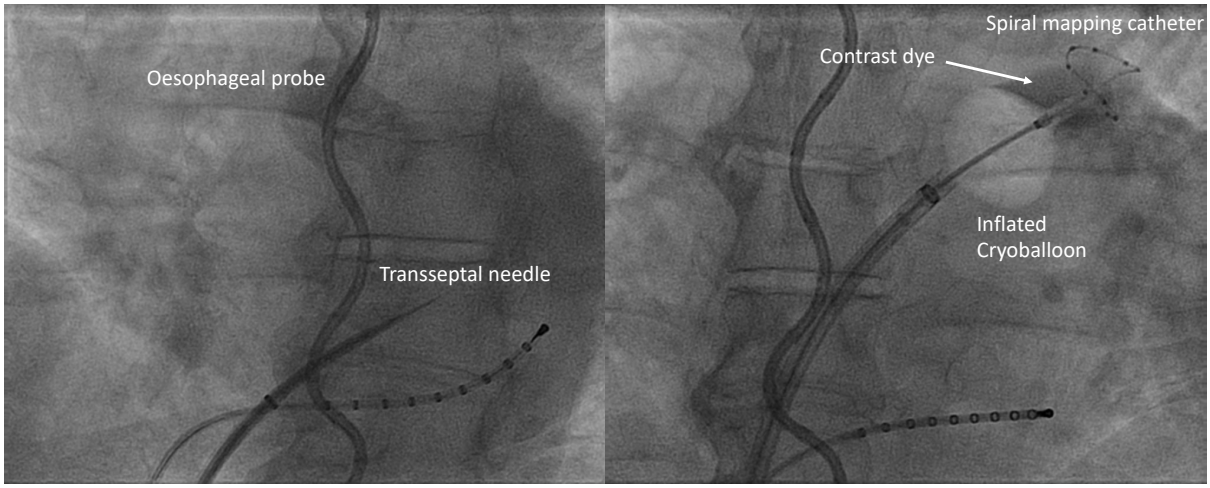


**Figure 14** Fluoroscopy of CB ablation with adequate occlusion of the left superior pulmonary vein (entrapped contrast dye shown) by the inflated CB

### 2.3.5 Index procedures - Pulsed field ablation (PFA)

After achievement of venous access (2 to 3 sheaths) and placement of a diagnostic decapolar catheter in the CS, single transseptal access was gained to the left atrium (LA). Angiography of the left atrium was carried out. Next, three-dimensional mapping of the LA (Ensite X™, Abbott, North Chicago, Illinois, USA; Rhythmia™ or Boston Scientific Corp., Marlborough, MA, USA) was performed as by discretion of the electropohysiologist. After insertion of the steerable sheath (FARADRIVE™, Boston Scientific) into the left atrium via a guidewire previously placed in the left superior pulmonary vein (LSPV), the pentaspline PFA catheter (FARAWAVE™, Boston Scientific) was now positioned into the left atrium. Atropine (0.5-1mg) was administered intravenously routinely before ablation start to antagonise vagal reactions. To carry out ablation, the generator delivered biphasic waveforms with 5 trains (total 2.5 seconds) per application. The standard protocol involved 8 applications per pulmonary vein (PV) (2x2 flower and 2x2 basket configurations). An example of PFA as shown in fluoroscopy and the intracardiac signals are illustrated in **Figure 15**.

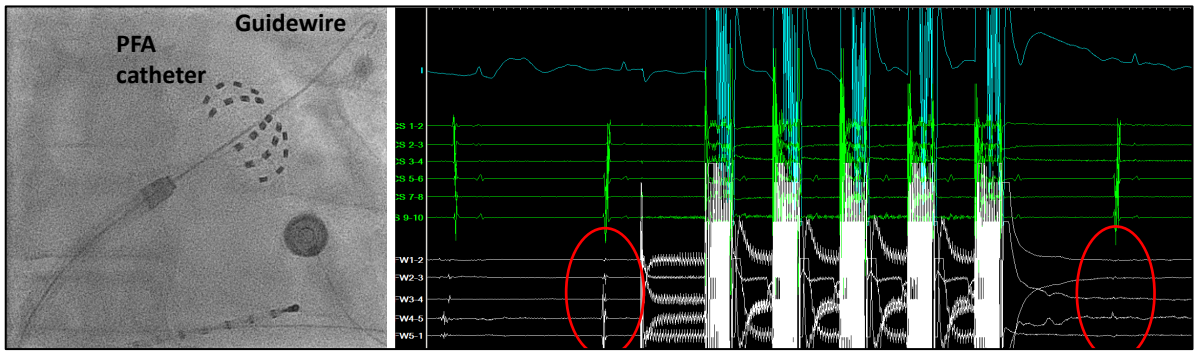


**Figure 15** Fluoroscopic view of PFA as being applied to the LSPV (left image) and the according isolation as recorded by the intracardiac electrograms (right image, red circles showing PV-signal prior to and after PFA-application)

### 2.3.6 Repeat procedures

***Repeat procedures for atrial fibrillation***

In patients presenting with AF recurrence after previous AF ablation, repeat ablation was carried out using radiofrequency or in rare cases PFA as an energy source. 3D-Mapping in either sinus rhythm or AF was performed in all these patients to further examine and characterise the substrate of the left atrium, as shown in **Figure 16**. All pulmonary veins were checked for electrical connectivity and gaps were isolated if applicable. If low-voltage areas were identified, more extensive ablation was carried out in some cases (linear lesions or

ablation of CFAEs), which was operator dependent. In the case of PV-reconnection, the endpoint was isolated PVs.

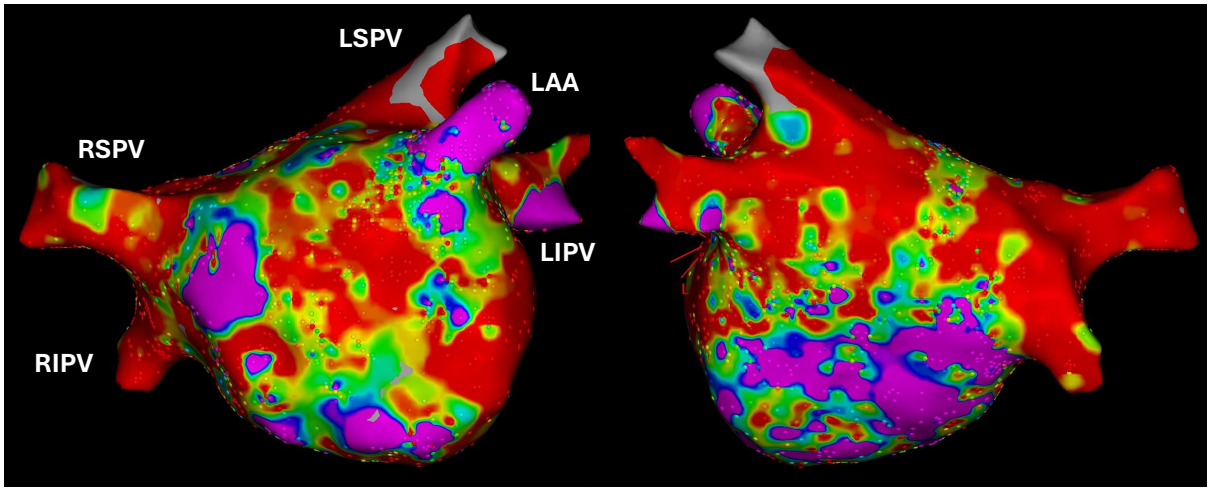


**Figure 16** Voltage mapping using Carto3 showing the left atrium with extensive anterior scar/low-voltage (red mass) in anterior-posterior (AP) projection (left image) and a posterior-anterior (PA, right image) view also showing scarring of the posterior wall and roof (purple mass indicated healthy tissue, red mass indicating severe fibrosis). LSPV=left superior pulmonary vein LIPV= left inferior pulmonary vein RSPV= right superior pulmonary vein RIPV= right inferior pulmonary vein LAA= left atrial appendage

### *Atrial tachycardia (AT) ablation*

In patients with documented AT or ongoing AT, ablation was performed using radiofrequency ablation. If presenting with an AT, local activation time (LAT) mapping was performed to identify the critical isthmus. In some instances, entrainment mapping was performed to confirm the critical isthmus. Subsequently, ablation of the critical isthmus was performed to terminate the tachycardia. In the case of macroreentrant AT, linear lesions were performed depending on the site of the critical isthmus. In the case of microreentrant AT, focal ablation was performed to terminate the arrhythmia. In both instances, re-induction was performed to induce the same/and or different ATs, which were subsequently treated. The endpoint of AT procedures was non-inducibility. If patients presented in sinus rhythm, tachycardia was induced using burststimulation manoeuvres (usually stimulation via the CS catheter) and subsequently mapped using LAT mapping and ablated.

## 2.4 Postprocedural routine

All patients received echocardiography immediately after the procedure before removal of sheaths and again one hour later to rule out pericardial effusion or pericardial tamponade. Manual compression of the groin was always performed, in addition suture techniques were applied to aid compression. All patients were monitored for a minimum of 24 hours after the procedure under heart rhythm monitoring. A 12-lead ECG to assess cardiac rhythm and echocardiography to rule out pericardial effusion were performed routinely prior to discharge. In addition, all patients received a control of the puncture site in the groin with suture removal if applicable. In the case of PFA, upper gastrointestinal endoscopy was performed to rule out lesions to the oesophagus before discharge. Irrespective of the energy source, all patients were given a proton pump inhibitor (Pantoprazole 40 mg) for 6 weeks after ablation. Patients, who were on AADs, were recommended to continue AAD for 6-12 weeks after ablation as decided by the operator in consensus with the patients.

## 2.5 Definition of complications

Complications of catheter ablation in this study were defined according to the current AF guidelines. These have classified AF complications into life-threatening, severe and moderate/minor.

- Life-threatening:
    - Death
    - oesophageal perforation/fistula
    - periprocedural thromboembolic event
    - cardiac tamponade

- Severe Complications:
    - Pulmonary vein stenosis
    - persistent phrenic nerve palsy
    - vascular complications
    - conversion to sternotomy
    - pneumothorax

- Moderate/minor complications (not specified)

- Complications of unknown significance

- asymptomatic cerebral embolism

## 2.6 Data collection

The institutional review board and ethics committee approved the study. Data was retrospectively collected using an anonymised excel table starting in November 2023 using the institutional, digitalized patient data base. The data collected involved baseline patient characteristics (age, sex, past medical history, medication at presentation, frailty index), arrhythmia information (arrhythmia at presentation, previous cardioversion, AAD, previous CA), imaging information (transthoracic and transoesophageal echocardiography including LVE, valvular disease, left atrial size and information regarding the LAA), procedural information (arrhythmia treated, energy source used, procedure performed, acute procedural success, acute complications, procedure length, fluoroscopy times) and postprocedural details (complications, recurrences, discharge).

## 2.7 Study outcomes

The primary outcomes of this study were:

1. Acute and chronic efficacy of catheter ablation, defined as acute procedural success (acute efficacy) and arrhythmia-free survival after a predefined 90-day blanking period during follow-up (chronic efficacy)
    a. Acute success was defined of acute isolation of all PVs and bidirectional block of all lines, as well as non-inducibility in AT cases.
    b. Chronic success was defined as freedom from any atrial arrhythmia, including AF, atrial flutter and/or AT > 30 seconds, past 90 days after ablation.

2. Safety, which encompassed procedural/periprocedural complications of catheter ablation

## 2.8 Follow – up (FU)

Patients received a recommendation at discharge to present to their ambulatory cardiologists at 3, 6 and 12 months after the procedure to receive 12-lead ECG and/or Holter-Monitoring to assess rhythm control. In the case of patients with pacemakers and/or implanted defibrillators,

recommendations were given to assess rhythm using those devices. A proportion of patients regularly visit the outpatient clinic at our institution, where 12-lead ECG, Holter-Monitoring and if applicable, cardiac devices were assessed. All patients were followed up with additional telephone interviews and follow-up information was requested from ambulatory cardiologists if patients presented there for follow-up. In addition, smartwatch documentation and reports from other hospitals/clinics were used if applicable.

## 2.9 Statistical Analysis

As this was a retrospective and observational study no specified comparative statistical test were carried out. Continuous data was shown as mean ± standard deviation. Statistical analyses, such as Kaplan-Meier curves were performed with the GraphPad Prism 9.0 software (GraphPad Software Inc., San Diego, CA, USA). This was the case for calculating arrhythmia-free survival as a measure of chronic success of CA. Due to the blanking period, as explained earlier, the starting time for the time-to-recurrence analysis was at 3 months (90 days).

# 3 Results

### 3.1 Baseline characteristics

A total of 175 patients were included in this study. The mean age was 82.1 ± 1.9 years. The mean Barthel frailty score was 97 ± 7.2, highlighting that most patients were able to carry out activities of daily living independently. Paroxysmal AF was documented in N=54/175 (30.9%) of patients, indicating persistent forms of AF to be more prevalent in this cohort. Mean $CHA_2$-$DS_2$-VASc-Score was 4.2 ± 1.3, indicating a high level of comorbidities of this patient cohort. This is reflected further by N= 27/175 (15.4%) of patients with previous stroke or TIA, N= 54/175 (30.9%) coronary artery disease, N=136/175 (73.5%) arterial hypertension, N=30/175 (17.1%) type II diabetes and N=32/175 (18.3%) congestive heart failure. The incidence of patients with already permanent pacemakers in place was N=15/175 (8.6%). The mean left ventricular ejection fraction was 57.4 ± 6.3 % and mean left atrial diameter was 44.4 ± 9 mm. Looking at baseline medication, N=41/175 (23.4%) of patients were on antiarrhythmic drugs, N=154/175 (88%) on betablockers and N=175/175 (100%) on OAC. Baseline characteristics are summarised in **Table 9.**

| **Characteristic** | N= 175 |
|---|---|
| Age – yr | 82.1 ± 1.9 |
| Male sex – no (%) | 89 (50.9) |
| Barthel frailty index | 97 ± 7.2 |
| Paroxysmal AF – no (%) | 54 (30.9) |
| $CHA_2$-$DS_2$-VASc-Score | 4.2 ± 1.3 |
| Left atrial diameter – mm | 44.4 ± 9 |
| Left ventricular ejection fraction (LVEF) - % | 57.4 ± 6.3 |
| EHRA score | 2.4 ± 1 |
| Previous TIA/stroke – no (%) | 27 (15.4) |
| Coronary artery disease – no (%) | 54 (30.9) |
| Arterial hypertension – no (%) | 136 (73.5) |
| Type 2 diabetes – no (%) | 30 (17.1) |
| Congestive heart failure – no (%) | 32 (18.3) |
| Chronic kidney disease – no (%) | 46 (26.3) |
| Pacemaker – no (%) | 15 (8.6) |
| Antiarrhythmic drug – no (%) | 41 (23.4) |
| Betablocker – no (%) | 154 (88) |
| Oral Anticoagulation – no (%) | 175 (100) |

**Table 9** Baseline characteristics

**Plus-minus value are means ± standard deviation. Note: $CHA_2$-$DS_2$-VASc score is a clinical estimation of the risk of stroke in patients with AF; scores range from 0 to 9, with higher scores indicating a greater risk of stroke = Congestive heart failure, Hypertension, age > 75 years, diabetes, previous Stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–75 years, and sex category. The EHRA score is an estimation of the symptoms attributed to AF ranging from 1 to 4, with higher scores indicating greater burden of symptoms. The Barthel frailty index is widely used in Germany and is a score encompassing eating, washing, maintaining hygiene, clothing, continence, bathroom use, mobility, and ability to walk stairs. The maximum score is 100 points, meaning no assistance is required. A score of 0-30 signals total dependence, 35-80 dependence and 85-95 partial assistance.**

### 3.2 Distribution of procedures according to exact strategy and energy source

Of the N=175 procedures in this study, N=100/175 (57.1%) were index procedures, the remaining N=75/175 (42.9%) procedures were repeat procedures. Index procedures included RF PVI N=49/175 (28%), CB PVI N=31/175 (17.7%), HPSD RF PVI N=9/175 (5.1%), RF PVI + additional ablation N=9/175 (5.1%) and PFA PVI N=2/175 (1.1%). Distribution of repeat procedures revealed re-PVI N=24/175 (13.7%), re-PVI + additional ablation N=17/175 (9.7%), linear lesions N=12/175 (6.9%), CFAE N=10/175 (5.7%), PFA re-PVI + additional ablation N=5/175 (2.9%), CFAE + linear lesions N=4/175 (2.3%) and micro re-entry atrial tachycardia N=3/175 (1.7%). Distribution of procedures are illustrated in **Figure 17**.

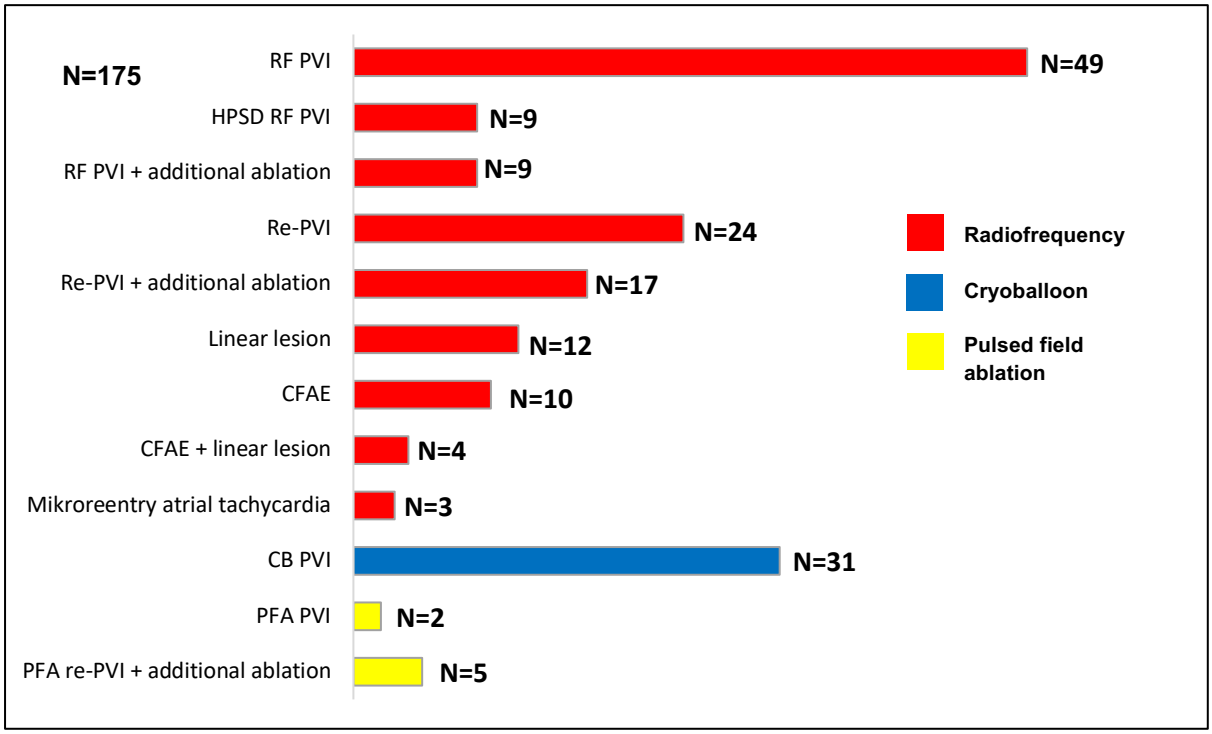


**Figure 17** Distribution of all procedures according to strategy and energy source

RF= radiofrequency PVI= pulmonary vein isolation HPSD= high power short duration CB= cryoballoon CFAE= complex fractionated atrial electrograms

### 3.3 Distribution according to ablation strategy

According to the ablation strategy irrespective of the energy source used, the distribution of procedures was as follows: Overall, N=100/175 (57.1%) patients received an index PVI +/- additional left atrial ablation. This was followed by N=46/175 (26.3%) treated with repeat PVI +/- additional ablation. Lastly, N=29/175 (16.6%) of patients underwent repeat ablation beyond the pulmonary veins. The above-mentioned distribution is illustrated in **Figure 18**.

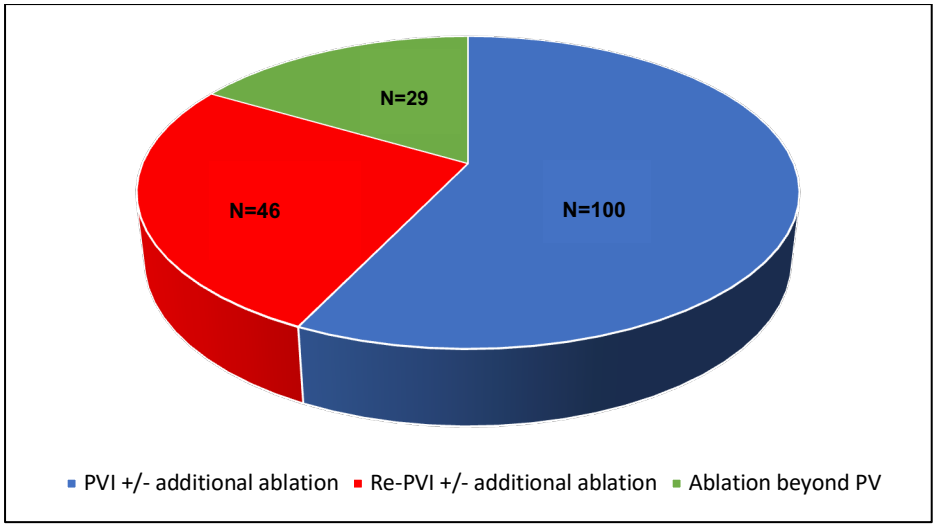


**Figure 18** Distribution of procedural according to ablation strategy

### 3.4 Procedural data

The acute procedural success in this study was achieved in N=175/175 (100%) with a mean procedure time of 107.8 ± 38.1 mins and a mean fluoroscopy time of 10.1 ± 5.1 mins. 3D-Mapping systems were used in 82.3% of cases. Mean hospitalisation after CA was 2.08 ± 1.5 days. Procedural data are summarised in the **Table 10.**

| | |
|---|---|
| Acute success – no (%) | 175 (100) |
| Procedure time – min | 107.8 ± 38.1 |
| Fluoroscopy time – min | 10.1 ± 5.1 |
| Mapping system – no (%) | 144 (82.3) |
| Nights in hospital after ablation | 2.08 ± 1.5 |

**Table 10** Procedural data

Plus-minus value are means ± standard deviation. Min = Minutes

### 3.5 Chronic efficacy of CA

After a mean follow-up of 466 ± 179 days in N=145/175 (82.3%) of patients, the Kaplan-Meier estimate for freedom from any atrial arrhythmia recurrence after one-year was at 69.1% (excluding the 90-day blanking period, **Figure 19**), equating to an arrhythmia-recurrence rate of 31.9. Rhythm at recurrence was AF in N=49/55 (89.1%) and AT in N=6/55 (10.9%) of

patients. A total of N=31/145 (21.4%) of patients were still on AADs at the time of follow-up. Of the patients suffering from recurrence, N=19/55 (34.5%) underwent repeat catheter ablation and N=17/55 (30.9%) cardioversion. A strategy change to rate control was decided in N=13/55 (23.6%) of patients including one case of pacemaker-implantation with subsequent AV-node ablation.

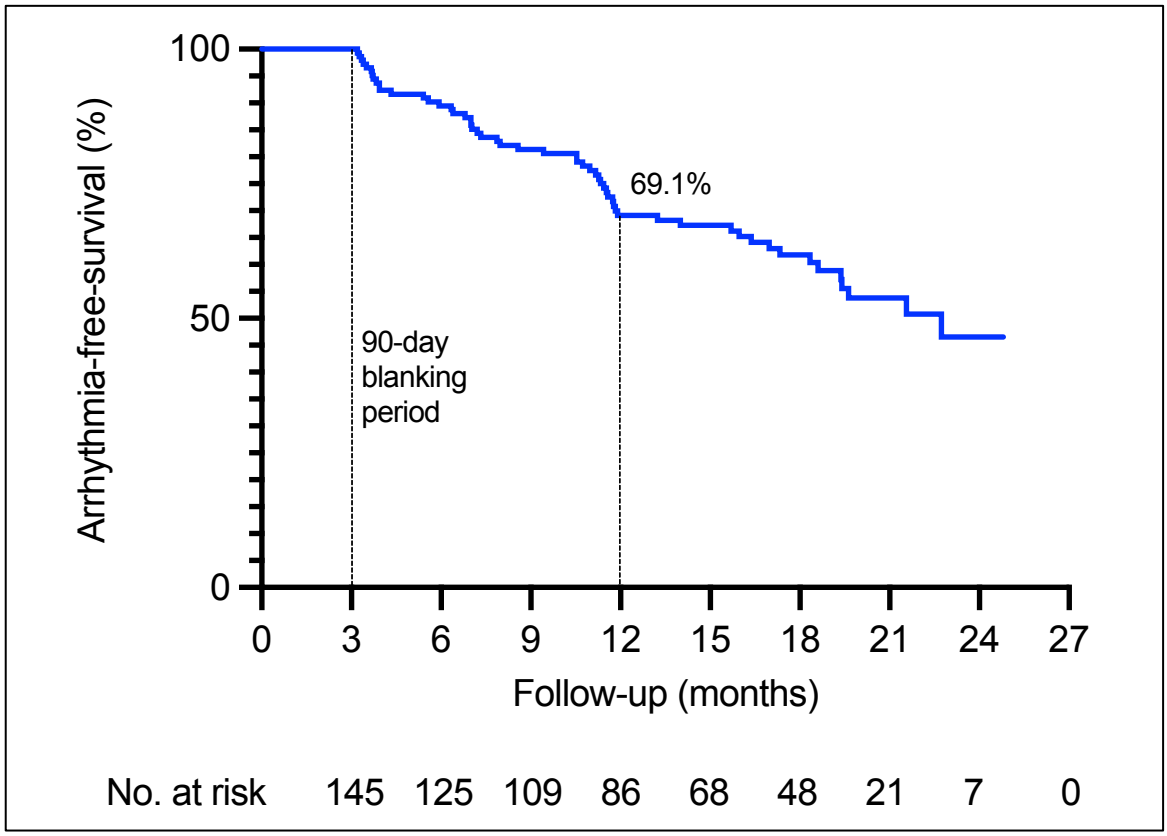


**Figure 19** Kaplan-Meier curve for overall chronic efficacy

### 3.6 Complications

Complications in this study were observed in N=12/175 (6.9%). Complications were divided into procedural, meaning as a direct consequence of CA, and periprocedural, which were not a direct consequence of CA.

Procedural complications were recorded in N=3/175 (1.7%) of patients and involved groin site complications in N=2/175 (1.1%), which were both pseudoaneurysms with subsequent thrombin-injection. Cardiac tamponade requiring pericardiocentesis occurred in N=1/175 (0.6%). Alongside pericardiocentesis, mass transfusion and transfusion of clotting products

was necessary in this case. There were no deaths from any cause, stroke, atrio-oesophageal fistula, phrenic nerve palsy or pulmonary vein stenosis in this study.

Periprocedural complications were observed more commonly than procedural complications at N=9/175 (5.1%) and included bradycardia with permanent pacemaker requirement, pneumonia and urinary tract infection, UTI, all in N=3/175 (1.7%). All cases of pneumonia and UTI were treated successfully using antibiotics. Bradycardia with subsequent pacemaker implantation was always a result of sick-sinus-syndrome in patients with persistent AF and never as a consequence of ablating close to the sinus and/or atrioventricular node. Complications are summarised in **Table 11.**

| **Complications** | N= 175 |
|---|---|
| **Procedural complications** | |
| Death from any cause | 0 (0) |
| Stroke or TIA | 0 (0) |
| Groin Site complication | 2 (1.1) |
| Phrenic nerve injury | 0 (0) |
| Cardiac tamponade | 1 (0.6) |
| Atrio-oesophageal fistula | 0 (0) |
| Pulmonary vein stenosis | 0 (0) |
| **Periprocedural complications** | |
| Bradycardia with permanent pacemaker requirement | 3 (1.7) |
| Pulmonary infection | 3 (1.7) |
| Urinary tract infection | 3 1.7) |

**Table 11** Procedural and periprocedural complications

**TIA = transient ischaemic attack**

# 4 Discussion

Major findings of this study are:

- CA for AF in octogenarians' results in very high procedural success in a large volume-centre (100% acute efficacy)
- Chronic efficacy of CA in this cohort with largely persistent forms of AF is acceptable (69.1% at one year)
- A high proportion of patients (>20%) are still on AADs to maintain sinus rhythm during FU
- CA in this cohort shows a good safety profile, as procedural complications were very low (1.7%)
- Periprocedural complications, such as pneumonia, UTI and bradycardia with subsequent pacemaker implantation are observed more commonly in octogenarians (5.1%)

## 4.1 Previous studies

In the past, the AFFRIM-Trial compared a rate control strategy with rhythm control (cardioversion and AADs) in the elderly population (≥ 65 years). In this trial, hospitalisation rate and mortality were both higher in the rhythm control group in patients aged ≥65 years, thereby favouring rate control (Wyse *et al.*, 2002) . Recent comparisons of rhythm control and rate control, especially in the octogenarian population, are scarce so it remains unknown whether one strategy is superior to the other. Blandino et al. compared catheter ablation with AADs in ≥75-year-old patients with persistent AF, demonstrating significantly improved rhythm control in the ablation arm (58% vs. 43%, p=0.003) (Blandino *et al.*, 2013). Furthermore, a study comparing PVI in paroxysmal AF between elderly and non-elderly patients by Lioni et al. was able to demonstrate no significant difference with regards to efficacy after a follow up of 34 +/- 15 months, however the mean age of the elderly population was 68.9 ± 3.0, which is far from the octogenarian population investigated in this study (Lioni *et al.*, 2014). Similar results to younger cohorts were shown by Metzner et al., who showed for patients with a mean age of 78 years receiving PVI and in some cases ablation of CFAE an arrhythmia-free survival of 76% in paroxysmal AF and 41% in persistent AF after 37 months +/- 20 months (Metzner *et al.*, 2016) . It has to be noted, however, that only 10 patients suffered from long-persistent AF, the population of which was much higher in this study. When looking at octogenarians only, data is very limited. Bunch et al. performed a prospective cohort study, comparing octogenarians to non-octogenarians with mostly paroxysmal AF. It has to be stated, that the

octogenarian group consisted of n=35 patients only. After 12 months follow up, arrhythmia-free survival was 78% with no difference in complications between the groups (Bunch *et al.*, 2010), suggesting similar efficacy and safety. Compared to this study, the sample size was much smaller with little patients suffering from persistent AF, therefore this data cannot be extrapolated for persistent forms of AF. Tan et al. carried out a cohort trial, which compared 3 groups (60-69 years, 70-79 years, and octogenarians). This sample size was slightly larger than Bunch et al.'s with n=49 in the octogenarian group. Arrhythmia free survival in octogenarians was 70%, which was not significantly different than the other groups (Tan *et al.*, 2010), again suggesting similar outcomes.

Regarding procedural safety, Srivatsa et al. investigated risk predictors for stroke and mortality after AF ablation. Here, age ≥80 years and heart failure were identified, however, details about the actual octogenarian patient population was lacking (Srivatsa *et al.*, 2014). This data is supported by studies showing longer hospitalisation in patients aged ≥80 years and a higher incidence of pulmonary infection (Bunch *et al.*, 2010). It has to noted, that the studies mentioned were older and recent data with the endpoint of safety are scarce. In summary, previous smaller studies of octogenarians have shown similar efficacy and safety, mostly for patients with paroxysmal AF. There was a signal hinting at higher complication rates in some studies, details about these octogenarian populations are however very limited.

### 4.2 Patient population

This study investigated octogenarians with a very good frailty score, meaning that most patients were able to carry out activities of daily living independently. Nevertheless, the mean $CHA_2DS_2$-VASc score mirrored the high burden of comorbidities in this patient collective. The mean age of 82.1 years was significantly higher than in previously published data with an additional larger sample size of 175 patients. In addition, a high proportion of patients suffered from persistent forms of AF already, which correlates with progressive atrial substrate, which was mirrored by echocardiography as moderately dilated atria on average. The left ventricular ejection fraction was preserved on average, meaning that this data cannot be extrapolated to heart failure patients in any way.

### 4.3 Efficacy CA in octogenarians

This study showed an acute procedural success of 100%, meaning that the procedural endpoint for the ablation was met in every patient. Acute procedural success, however, is not surprising given that PVI and AF ablation have become routine clinical practice, especially in

large-volume centres. Arrhythmia-free survival over the follow up period was at 69.1%. Previous studies documented within AF guidelines have reported success rates for paroxysmal AF of 70% and 50% in persistent AF, very similar to the outcome of this study, which included both paroxysmal and persistent AF patients (Kirchhof et al., 2016). Recurrences were most commonly treated with ablation in both AF and AT recurrence, highlighting more progressive atrial cardiomyopathy and the need for more extensive ablation to finally maintain sinus rhythm. Additionally, a significant number of patients (>20%) were on AADs at FU to maintain sinus rhythm, possibly hinting at the necessity of multiple rhythm control measures, especially in octogenarians with persistent/long-standing persistent AF. However, AADs should be used with caution, especially in combination with betablockers due to the possibility and risk of bradycardia in this patient population. In summary, arrhythmia-free survival matches previous data with a significant proportion of patients still being on AADs, especially in persistent forms of AF.

### 4.4 Complications

With regards to life-threatening and severe complications, one cardiac tamponade (0.6%) and 2 groin complications (1.2%) falls within the range reported by the guidelines (Steinbeck *et al.*, 2018; Hindricks *et al.*, 2020). The most common complications seen were of a periprocedural nature, such as infections requiring antibiotic treatment (pneumonia and UTI) and bradycardia with the requirement of permanent pacemaker implantation. It can be discussed whether bradycardia and pacemaker implantation should be defined as a complication or as demasking of a concomitant disease (sick-sinus syndrome) after successful achievement of rhythm control by catheter ablation. Nevertheless, it was documented as a complication in this study and there should be awareness for its frequency, especially in the context of medication adding to bradycardia such as beta-blockers and AADs. In previous landmark trials investigating non-octogenarian patients, stroke incidence was reported in less than 1% with cardiac tamponade in around 0.5-1% which roughly also matches the results in this study (no stroke/TIA, 1 tamponade) although direct comparisons cannot be drawn as the patient populations and timing of trials were different (Kuck *et al.*, 2016; Packer *et al.*, 2019). In general, very low life-threatening and severe complications matching larger ablation studies, which included non-octogenarian populations can be reported in this study. It is important to highlight, that while procedural complications were low, periprocedural complications such as bradycardia or infections were seen more commonly. In clinical practice, measures (early mobilisation, modified sedation protocols, single-shot/short procedures) should be undertaken to minimise periprocedural risk.

### 4.5 Limitations

This study focussed on octogenarians only and assessed procedural success, complications, and longer-term outcome of only one patient population. Results were compared and discussed relative to previously published data. A control group of non-octogenarians and a direct randomised comparison would be useful to assess the outcome relative to a younger cohort. A limitation with regards to the FU carried out was the lack of continuous monitoring of heart rhythm with e.g., an implantable loop recorder (ILR) to detect asymptomatic arrhythmia recurrence. In this study, FU was based on patients becoming symptomatic and presenting for treatment again or visiting their cardiologist for routine FU. Therefore, there is uncertainty with regards to asymptomatic recurrences. In addition, these patients weren't frail on average and showed a high level of functional independence, thereby possible showing a selection bias. This data therefore cannot be extrapolated to frail patients with very low Barthel scores.

### 4.6 Conclusion and outlook

In general, catheter ablation can be considered for rhythm control in octogenarians, given that efficacy and safety in this study match available data for non-octogenarians. Ablation in this population more commonly involves persistent AF and therefore a relatively large number of these patients may require additional/multiple ablations, in some cases beyond PVI to achieve sinus rhythm. Antiarrhythmic therapy may be additionally required; however, it is important to keep in mind that bradycardia with subsequent pacemaker-implantation in this population is not uncommon. Risk factors for arrhythmia recurrence should be assessed individually and in the case of unlikely rhythm control, rate control, including a pace and ablate strategy, can be considered. This may apply especially in cases where AF recurrence is seen despite pulmonary veins being already isolated, as recurrence after these procedures (ablation beyond pulmonary veins) where relatively high in this study. Screening of patients before ablation and identifying patients at risk for the most common complications, namely infection and bradycardia, may help reduce complication rate and hospitalisation. As of now, it is unknown whether these patients have a prognostic benefit from rhythm control. Additionally, comparisons to non-octogenarian patients would show whether ablation is as effective and safe as in octogenarians. With regards to persistent AF requiring multiple ablation procedures, randomised comparisons of additional ablation vs. a pace and ablate strategy could help identify patients that would benefit from pace and ablate rather than multiple ablations, especially beyond PVI. Finally, new energy sources such as PFA may help shorten procedure times and help reduce complication rates in the future. Overall, more data, especially

randomised trials, should be generated for octogenarians in the future to help predict complications and improve outcomes.

## Summary (English)

Background: Catheter ablation for atrial fibrillation (AF) in octogenarians poses a challenge due to comorbidities, frailty, and suspected higher complication rates. Data regarding the outcome of catheter ablation in this population is scarce.

Methods: We retrospectively analysed octogenarians with symptomatic AF undergoing catheter ablation in a single centre, including first and re-ablation procedures. Study endpoints were acute success, complications, and arrhythmia-free survival.

Results: A total of 175 patients (mean age 82.1 ± 1.9 years, paroxysmal AF n=54/175, persistent AF n=121/175, mean $CHA_2DS_2$-VASc-Score 4.2 ± 1.3) were included. Acute success was achieved in n=175/175 (100%) of patients. The overall complication rate was 6.9% (most commonly bradycardia with pacemaker implantation n=3/175 (1.7%), pulmonary infection n=3/175 (1.7%) and urinary tract infection n=3/175 (1.7%), followed by groin site complications n=2/175 (1.1%) and cardiac tamponade n=1/175 (0.6%)}. After a mean follow-up of 466 ± 179 days, arrhythmia free survival was seen in 69.1% after one year.

Conclusion: Catheter ablation for AF in octogenarians yields acceptable rhythm control and low complication rates. The most common complications in this cohort are bradycardia with subsequent pacemaker implantation and infections.

## Zusammenfassung (Deutsch)

Einleitung: Die Katheterablation von Vorhofflimmern (VHF) bei ≥80-jährigen Patient:innen stellt aufgrund von Vorerkrankungen und vermutlich höheren Komplikationsraten eine große Herausforderung dar. Die Datenlage hinsichtlich des Therapieerfolges der Katheterablation bei diesem Patientenkollektiv ist unzureichend.

Methoden: Es erfolgte eine retrospektive Analyse ≥80-jähriger Patient:innen mit symptomatischem VHF, welche einer Katheterablation, inklusive Index – und Re-ablationen zugeführt wurden. Endpunkte der Studie waren prozeduraler Erfolg, Komplikationen und Freiheit von atrialen Arrhythmien.

Ergebnisse: Insgesamt wurden 175 Patienten (Alter 82.1 ± 1.9 Jahre, paroxysmales VHF n=54/175, persistierendes VHF n=121/175, $CHA_2DS_2$-VASc-Score 4.2 ± 1.3) analysiert. Ein akuter prozeduraler Erfolg wurde bei n=175/175 (100%) der Patient:innen beobachtet. Die Rate an Komplikationen betrug 6.9% (am häufigsten Bradykardien mit nachfolgender Schrittmacher-Implantation n=3/175 (1.7%), pulmonale Infekte n=3/175 (1.7%) und Harnwegsinfekte n=3/175 (1.7%), gefolgt von Leistenkomplikationen n=2/175 (1.1%) und Herzbeuteltamponaden n=1/175 (0.6%)}. Nach einer durchschnittlichen Nachbeobachtungszeit von 466 ± 179 Tagen, wurde eine Freiheit von atrialen Arrhythmien nach einem Jahr bei 69.1% der Patient:innen dokumentiert.

Schlussfolgerung: Die Katheterablation von VHF bei ≥80-jährigen Patient:innen resultierte in einer akzeptablen Freiheit atrialer Arrhythmien und niedrigen Komplikationsraten. Die häufigsten Komplikationen in dieser Kohorte waren Bradykardien mit nachfolgender Schrittmacher-Implantation und Infektionen.

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## 7. Abbreviations

| | |
|---|---|
| AAD | antiarrhythmic drugs |
| ACT | activated clotting time |
| AF | atrial fibrillation |
| AFFIRM | A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation |

| | |
|---|---|
| AMICA | Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure |
| AT | atrial tachycardia |
| AV | atrioventricular |
| CAD | coronary artery disease |
| CABANA | Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure |
| CAST trial | Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo — The Cardiac Arrhythmia Suppression Trial |
| CASTLE-AF | Catheter Ablation for Atrial Fibrillation with Heart Failure |
| CB | cryoballoon |
| CFAE | complex fractionated atrial electrograms |
| CHASE AF | Pulmonary Vein Isolation Versus Defragmentation |
| CRP | c-reactive protein |
| CRT | cardiac resynchronisation therapy |
| CT | computer tomography |
| CTI | cavotricuspid isthmus |
| CKD | chronic kidney disease |
| COPD | chronic obstructive pulmonary disease |
| CPAP | continuous positive airway pressure |
| CS | coronary sinus |
| DOAC | direct oral anticoagulant |
| EAST | early treatment of atrial fibrillation for stroke prevention trial |
| ECG | electrocardiogram |
| EHRA | European Heart Rhythm Association |

| | |
|---|---|
| ERASE-AF | Low-Voltage Myocardium-Guided Ablation Trial of Persistent Atrial Fibrillation |
| ESC | European Society of Cardiology |
| FU | follow-up |
| HPSD | high-power-short-duration |
| IMPULSE | A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation |
| INR | international normalised ratio |
| LA | left atrium |
| LAA | left atrial appendage |
| LAT | local activation time |
| LAO | left anterior oblique |
| LEGACY | Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study |
| LFT | liver function test |
| LIPV | left inferior pulmonary vein |
| LSPV | left superior pulmonary vein |
| LV | left ventricle |
| MANIFEST | Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation |
| MRI | magnetic resonance imaging |
| PCI | percutaneous coronary intervention |
| PEFCAT | A Safety and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation |
| PFA | pulsed field ablation |

| | |
|---|---|
| PRAGUE-17 | Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients With Atrial Fibrillation |
| PREVAIL-AF | Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy |
| PROTECT-AF | Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation |
| PV | pulmonary vein |
| PVI | pulmonary vein isolation |
| OAC | oral anticoagulation |
| OSA | obstructive sleep apnoea |
| RACE II | Lenient versus Strict Rate Control in Patients with Atrial Fibrillation |
| RENAL- AF | Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation |
| RF | radiofrequency |
| RIPV | right inferior pulmonary vein |
| RSPV | right superior pulmonary vein |
| RCT | randomized controlled trial |
| SR | sinus rhythm |
| TIA | transient ischaemic attack |
| TOE | transoesophageal echocardiography |
| TSH | thyroid stimulating hormone |
| TTI | time taken for isolation |
| UFH | unfractionated heparin |
| UTI | urinary tract infection |
| VKA | vitamin K antagonist |

| | |
|---|---|
| VT | ventricular tachycardia |

## 8. Figures

**Figure 9** Cardiac Mapping (Carto3) showing the LA with isolated PVs and additional anterior line (left image) and additional roof line (right image)

**Figure 10** 12-lead ECG (25mm/s) with inferior leads II and III showing typical atrial flutter with negative p-waves and the characteristic “saw-tooth” appearance as highlighted by the orange arrows

**Figure 11** Transthoracic echocardiography showing a large pericardial effusion in a four-chamber view (left image) and in a parasternal view (right image). LV= left ventricle RV= right ventricle

**Figure 12** Fluoroscopic image showing RF ablation of the left pulmonary veins with the ablation catheter and mapping catheter placed in the left atrium (left image) and the according 3D map with the lesions performed as shown by the red dots

**Figure 13** Intracardiac electrograms (LS=Lasso mapping catheter, CS=coronary sinus catheter) showing the moment of electrical isolation of the pulmonary veins during RF ablation as recorded by the mapping catheter. PV= pulmonary vein

**Figure 14** Fluoroscopy of CB ablation with adequate occlusion of the left superior pulmonary vein (entrapped contrast dye shown) by the inflated CB

**Figure 15** Fluoroscopic view of PFA as being applied to the LSPV (left image) and the according isolation as recorded by the intracardiac electrograms (right image, red circles showing PV-signal prior to and after PFA-application)

**Figure 16** Voltage mapping using Carto3 showing the left atrium with extensive anterior scar/low-voltage (red mass) in anterior-posterior (AP) projection (left image) and a posterior-anterior (PA, right image) view also showing scarring of the posterior wall and roof (purple mass indicated healthy tissue, red mass indicating severe fibrosis). LSPV=left superior pulmonary vein LIPV= left inferior pulmonary vein RSPV= right superior pulmonary vein RIPV= right inferior pulmonary vein LAA= left atrial appendage

**Figure 17** Distribution of all procedures according to strategy and energy source

**Figure 18** Distribution of procedural according to ablation strategy

**Figure 19** Kaplan-Meier curve for overall chronic efficacy

## 9. Tables

## 10. Erklärung des Eigenanteils

Im folgenden Abschnitt erkläre ich meinen Anteil für das Fertigstellen dieser Promotion. Die Konzeption der Arbeit erfolgte im Konsens mit den Betreuern der Promotion. In diesem Rahmen wurde das Thema, die notwendigen Daten, Analysen und Endpunkte der Arbeit festgelegt. Zunächst identifizierte ich zunächst alle Patienten, welche für die Analyse in Frage kämen (alle ≥80-jährigen Patienten, die mittels Katheterablation bei Vorhofflimmern behandelt wurden). Nach entsprechender Identifikation und Aufnahme in eine anonymisierte Excel-Tabelle, führte ich die Datenerhebung zur Erfassung aller notwendigen Parameter durch. Nach Abschluss der Datenerhebung führte ich die statistischen Analysen durch. Hier waren Rechnungen von Mittelwerten und Prozentrechnungen erforderlich, welche ich mittels Microsoft Excel durchführte und in entsprechende Grafiken umwandelte, welche in dieser Arbeit vorzufinden sind. Die Kaplan-Meier Kurve für das „Rezidivfreie“ überleben führte ich mittels „GraphPad Prism“ durch.

Es folgte eine ausgiebige Literaturrecherche zu dem Thema, welche ich durchführte und in der „Introduction“ der Monografie zusammenfasste. Anschließend verfasste ich die Methodik, wobei die periprozeduralen Standards und Abläufe aus der Klinik erläutert wurden. Zudem erklärte ich in diesem Abschnitt die Endpunkte der Studie und die Auswertung der Daten. Die Ergebnisse, welche ich zuvor ausgerechnet hatte, verfasste ich, genauso wie die nachfolgende Diskussion. Die Abbildungen in der Arbeit sind alle aus eigenem Bestand (z.b. 12-Kanal EKGs, 3D-Mapping Bilder oder fluoroskopische Aufnahmen aus Prozeduren) oder wurde von mir angefertigt und bearbeitet (Schematische Darstellungen, z.b. Erklärung des Konzepts der Pulmonalvenenisolation), um verschiedene Inhalte zu erklären und illustrieren. Somit war mein Eigenanteil zusammenfassend die Identifikation der Patienten, die Datenerhebung, statistische Analyse und das Verfassen der Monografie.

## 11. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

**Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.**

**Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.**

**Unterschrift: .....**

## 12. Danksagung

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