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Meinen Eltern

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1 INTRODUCTION

1.1 Atrial Fibrillation

1.1.1 Definition and History

Atrial Fibrillation (AF) is the most common sustained arrhythmia and is characterized by chaotic and irregular beatings of the heart. The first to describe AF was probably a physician of the Chinese emperor who approximately lived between 1696 and 2598 BC. He reported that irregular pulse is associated with short life [1]. Also Galen (129–200 AD), an ancient Greek specialist on pulse diagnosis, described different kinds of pulse patterns relating to health status [2].

Through centuries there were many different physicians reporting pulse irregularities but it was not until the 17th century when William Harvey (1578-1657) discovered the greater circulation and successively it was suspected that the origin for these chaotic pulsations lies in the heart [1]. Jean Baptiste Sénac (1693-1770) and Robert Adams (1791-1875) were the first to associate mitral valve stenosis with rebellious palpitations [3, 4]. With the discovery of the digitalis leaf by William Withering in 1785, people suffering from a weak and irregular pulse had a chance of treatment and thus experienced a decrease of their symptoms [1].

The next major diagnostic breakthrough was in 1900 when electrocardiography was invented by William Einthoven. Thus AF could be reliably revealed and recorded for the first time [5]. But the pathophysiologic mechanisms behind the arrhythmia remained uncertain until 1970 when Bert Bootsma discovered that these ventricular irregularities arise due to random atrial impulses reaching the atrioventricular node from different directions [6]. Since 1982, AF gained more attention with the

epidemiologic Framingham study by William Kannell who investigated its importance and its association with cardiac and cerebrovascular death [7].

Until today there are many unanswered questions concerning the pathogenesis and management of AF. Due to its high incidence and prevalence, often co-existing life quality impairing symptoms as well as potential severe complications, scientists all over the world are contributing to develop best possible diagnostic and treatment options for AF patients.

1.1.2 Epidemiology

In 2010 the prevalence of AF was estimated to be approximately 0.5% of the world population, which equates to nearly 33.5 million individuals [8]. However, the real prevalence is most likely much higher as AF can also remain transient, asymptomatic or even silent and is therefore often not registered [8]. Interestingly especially patients living in high-income countries seem to have an increased risk to develop AF [9], which could be due to better health care systems as well as superior diagnostic tools. It can be assumed that one out of four middle-aged persons will be developing AF [10].

Different studies suggested that AF will undergo a continuous increase during the next years [11, 12]. On the one hand rising mean population age plays a significant role in the onset of AF, on the other hand better detection methods will provide more precise registrations of asymptomatic AF [11]. In addition, the increased prevalence of other cardiovascular diseases like structural-, valvular-, hypertensive- or coronary heart disease will also lead to higher AF incidental rates [13].

Regarding mortality and morbidity, AF is associated with increased cardiovascular complications such as stroke [14], left ventricular dysfunction as well as heart failure (HF) [15], vascular dementia [16] and death [17]. About one in seven of all patients

suffering from moderate-to-high-risk AF is hospitalized within two years [18]. However, not every AF patient suffers from an impaired life quality [19].

Interestingly, there are gender specific differences in AF. Women have generally a lower rate of incidence and prevalence than men and are less likely to develop persistent AF [20, 21]. In contrast, overall mortality is similar or even higher in female AF patients [21]. Generally, women suffer from more intense symptoms, are older and have a higher rate of comorbidities like thyroid dysfunction, valvular heart disease, diabetes and hypertension, obesity, depression and renal impairment [22, 23]. Men are more likely to present additional coronary artery (CAD) disease as well as chronic obstructive pulmonary disease (COPD) [23]. Furthermore, it is important to mention that male patients seem to have a significantly higher chance of developing tachycardiomyopathy [20], which might be due to an increased beta adrenergic stimulation during rapid ventricular rates [24].

1.1.3 Classification

AF patients often show a transition of their respective AF type [25]. That means rare and brief attacks are likely to progress into more common and longer episodes. Only a small number of patients will suffer from the same type over decades [26]. There are five different AF types that need to be differentiated from each other with regards to appearance, time period and termination: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent. Exact definitions of each AF type are depicted in table 1. However, classification of AF in practice is much more complex. Especially paroxysmal and persistent AF, the two most common arrhythmias, are often not very well distinguished from each other.

AF Pattern	Definition
First diagnosed AF	AF not previously identified, regardless of the time period of the arrhythmia or symptoms associated with AF
Paroxysmal AF	Self-terminating AF, usually within 48 hours. However, in some cases AF episodes may continue for up to 7 days. In addition, AF events that are cardioverted within 7 days should also be regarded as paroxysmal.
Persistent AF	All episodes lasting more than 7 days as well as episodes terminated after 7 days or more by either drug related cardioversion or direct current cardioversion.
Long-standing persistent AF	Continuous AF lasting for more than 1 year when it is decided to adopt rhythm control strategy.
Permanent AF	Patient and physician accept AF. Therefore, rhythm control interventions are no longer pursued. The arrhythmia would be re-classified as long-standing persistent AF if a rhythm control approach were taken.

Table 1: Classification of AF pattern according to the 2016 ESC guidelines for the management of atrial fibrillation [25]

1.1.4 Pathophysiology

The pathophysiology is highly complex and not yet completely understood. There are four main mechanisms of AF origin and AF maintenance: Ca^{2+} handling abnormalities, autonomic neural control, structural remodelling and ion channel dysfunction [27]. Delayed afterdepolarizations (DADs) give rise to ectopic atrial foci either due to an enhanced Ca^{2+} equilibrium and an increased Na^{+}/Ca^{2+} exchange or because of a dysfunction in the autonomic neural control via sympathetic activation [28, 29]. Complex multiple-circuit re-entries then maintain this ectopic activity [30]. Especially structural remodelling due to atrial fibrosis has a significant impact in the development of re-entries [31]. The formation of regions of slow conduction or even complete conduction barriers lead to re-entry stabilization [28, 32]. Atrial fibrosis increases the number of intracardiac fibroblasts which changes the electrophysiological characteristics of cardiomyocytes and may result in re-entrant arrhythmias and local conduction disturbances [33]. Ion channel dysfunction can contribute to AF by either decreasing inward L-type Ca^{2+} currents or increasing plateau outward K^{+} currents. This leads to abbreviating atrial action potential duration (APD) and accelerating repolarizations, which facilitates re-entries [29, 30]. Figure 1 provides a schematic overview on the pathophysiology of AF.

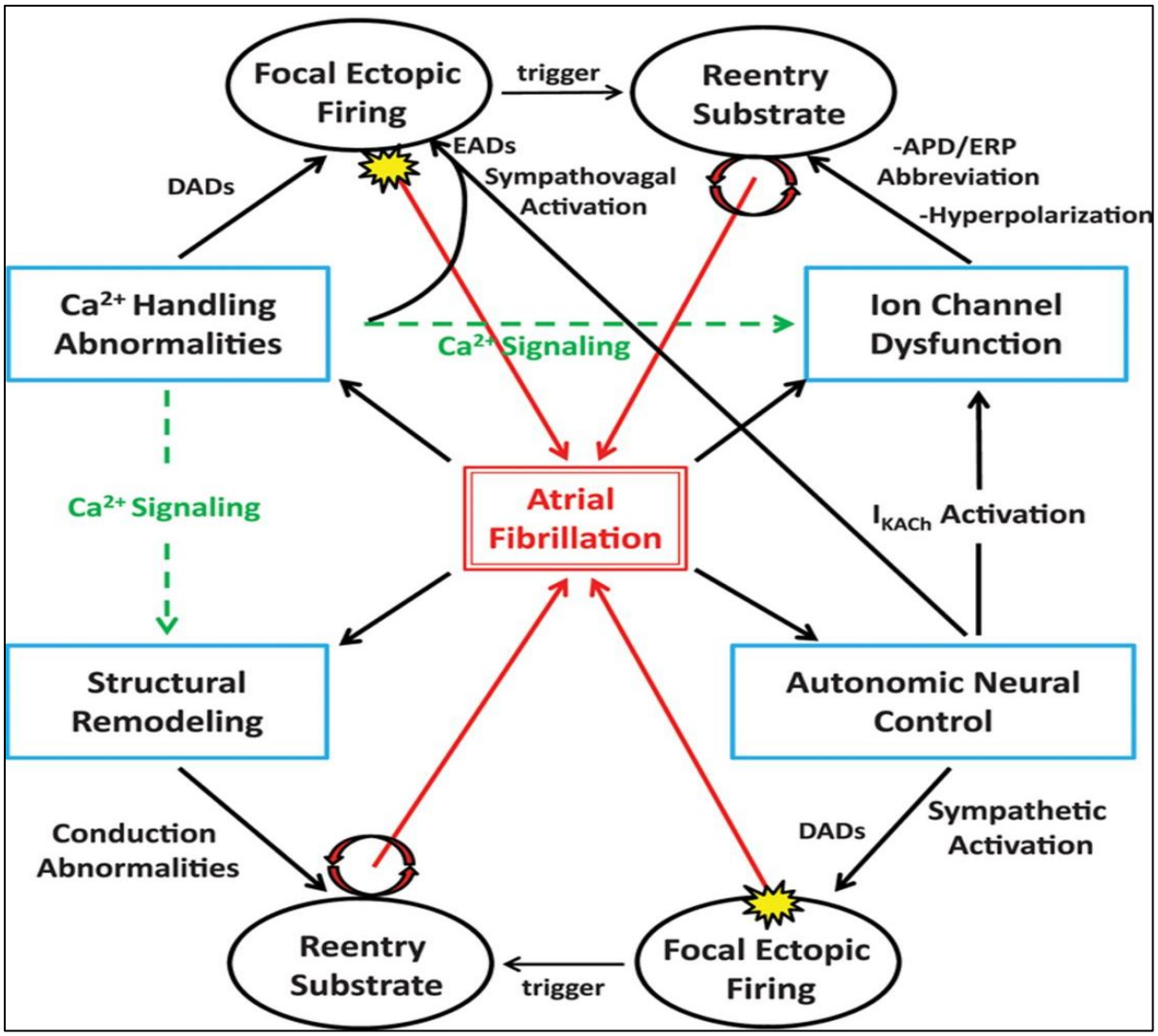

Figure 1: General overview of AF pathophysiology representing the main mechanisms of AF origin and maintenance [27]

1.1.5 Risk Factors and Causes

AF is a multifactorial disease and therefore many different conditions and comorbidities are associated with its incidence. Modifiable and non-modifiable risk factors should be identified and strict risk factor management is recommended to prevent a progression of the disease.

Male sex and older age are two highly significant risk factors. A recent trial [13] showed dramatically increasing incidental rates per advanced life decade. For example, subjects aged 60-69 have a 5-fold increased risk to develop AF than patients aged 50-

59. Moreover, male gender is associated with a 1.5-fold risk for AF occurrence after adjusting for age.

It is also widely known that AF is associated with arterial hypertension, which has a very high global prevalence and is a risk factor for many other cardiovascular diseases. The Framingham heart study [7] compared hypertensive with normotensive subjects and concluded that the risk of AF increased by 1.9-folds. Other studies [13] however showed a significantly lower risk rate increase of 1.32-folds. Hypertension can influence the risk of AF by several mechanisms. Higher pulsatile loads lead to left atrial dilation and increased tissue areas. This can favour the development of re-entries [34]. Arterial hypertension activates the renin-angiotensin-aldosterone system. Increased levels of angiotensin II can directly increase the risk of AF due to arrhythmogenic effects and promote AF indirectly via proinflammatory mechanisms and effects on the structure and function of potassium ion channels [35, 36]. Optimal blood pressure treatment should therefore play a key role in the treatment of AF.

Valvular heart disease is another common comorbidity among patients with AF. Nearly 30% of all patients with first diagnosed AF are suffering from valvular heart disease [37]. Epidemiological studies revealed that female patients had a 3.4-fold increased risk for developing AF compared to male patients with a 1.8-fold increased risk, respectively [38]. Here it needs to be considered that female AF patients are older in average and therefore more likely to present valvular heart disease. It is also known that valvular heart disease is associated with increased risks for thromboembolic and bleeding events in patients with AF [39].

HF and AF also frequently coexist. Both cardiovascular diseases share the same comorbidities such as hypertension, diabetes, coronary heart disease and valvular heart disease [17]. Both trigger also pathophysiologic left atrial changes like left atrial

enlargement and increased left atrial wall thickness [40]. HF severity highly correlates with AF prevalence. Whilst only 4% of patients with class I HF symptoms according to the New York Heart Associations (NYHA) suffered from AF [41] nearly half of the individuals with NYHA class IV symptoms presented AF [42]. Possible mechanisms identified include atrial tissue stretching due to rising atrial pressures and volumes [43] as well as degradation of the extracellular matrix and atrial fibrosis due to neurohormonal alterations, RAAS activation and Ion channel remodelling [43-45]. Overall epidemiologic studies concluded a 1.43-fold increased risk compared to patients without HF [13]. To prevent AF, it is therefore very important that HF patients receive optimal monitoring and treatment. Especially angiotensin converting enzyme (ACE) inhibitors, ß-Blockers and mineralocorticoid antagonists were shown to reduce risks of AF occurrence in these patients [46-48].

After myocardial infarction AF occurrence is a common complication with an incidental rate of 5 to 23% [49]. Other studies revealed a 1.46-fold increased risk [13]. CAD alone could not be identified as a significant risk factor for AF occurrence [50]. Nevertheless, recent studies concluded that AF patients are suffering from CAD more often than patients in sinus rhythm [51]. CAD prevalence in AF patients was estimated about 30% [52]. Moreover, it was even suggested that atherosclerosis in patients without manifest CAD represents a significant risk factor for AF [53]. Thus, asymptomatic atherosclerosis should be aggressively treated to minimize AF incidence.

Diabetes mellitus (DM) was associated with a 1.25-fold increased risk for AF occurrence [13]. Women suffering from DM seem to have higher AF incidental rates according to a recent meta-analysis [54]. Underlying mechanisms possibly contribute to structural as well as electrical remodelling via increased atrial fibrosis, ion-channel alterations and increased epicardial adipose tissue [55-57]. Optimal management of

DM including loss of weight should therefore be considered to avoid AF development. Notably, only metformin therapy showed reduced AF incidental rates compared to intensive glycaemic control [58, 59].

Obesity can also be linked to an increased risk of AF development [13]. Obviously, the risk depends on the respective body mass index (BMI). AF occurrence ranged from a 1.13-folds increased risk in overweight patients (BMI 25-30 kg/m^2) to a 1.37-folds increased risk in obese patients (BMI ≥31 kg/m^2). The transitioning of paroxysmal AF to persistent AF was also related to obesity [60]. Interestingly, a recent study reported that per 1 kg/m^2 drop in BMI, AF incidence is reduced by 7% [61]. This BMI drop can also reduce severity of AF symptoms [62]. It is no surprise that weight reduction and life style changes are important therapeutic approaches in AF prevention and support AF treatment.

Pulmonary diseases like obstructive sleep apnea (OSA) and COPD, were also associated to AF [63, 64]. OSA was related with a 2.18-folds increased risk. OSA can influence left atrial size and therefore promote incidental AF via two main mechanisms: Once it is independently related to diastolic dysfunctions and thus is directly linked to an increased left atrial size [65]. Secondly, OSA can increase left atrial size by the so-called Mueller manoeuvres which result in an increased cardiac wall stress [66, 67]. In addition, autonomic imbalances associated with OSA may contribute to the development of AF [68]. The link of COPD to AF occurrence is dependent on the forced expiratory volume in one second (FEV1) [64]. Individuals below 60% FEV1 had a 2.53-folds increased risk for AF development, whereas patients between 60-80% FEV1 were only associated with a 1.28-fold risk. Possible underlying mechanisms include hypoxia related sympathetic activation and vascular endothelial growth factor expression, hypercapnia mediated right atrial dilation and transmural pressure

increase as well as oxidative stress and inflammation linked structural remodelling [69-73]. Thus, screening and treatment of both respiratory diseases is highly important to reduce risk factors for incidental AF.

Chronic kidney disease (CKD) is an independent risk factor for AF, but it also promotes other conditions like inflammation, hypertension or left ventricular hypertrophy which are again associated with AF [74]. One out of five CKD patients suffers from additional AF [75]. Each stage of CKD has different risk rates regarding AF incidence: CKD stages one or two are associated with a 2.67-fold increased risk, CKD stage three has a 1.68-fold increased risk and CKD stages four and five have a 3.52-fold increased risk [76]. Besides pathophysiologic mechanisms related to above mentioned comorbidities, CKD causes alterations of the RAAS system as well as sympathetic activation [77-79]. Therefore, CKD screening and treatment should play an important role in patients at AF risk.

It is known for a long time that hyperthyroidism and AF are closely related [80]. However, it is of interest that decreased levels of thyroid hormones can decrease AF occurrence. Thus, the relationship between thyroidal dysfunction and AF can be classified as linear. Hypothyroidism was linked negatively to AF with a 0.67-folds decreased risk compared to individuals in euthyroidism. Subclinical hyperthyroidism was associated with a 1.31-folds increased risk. However, patients with overt hyperthyroidism had a 1.42-folds increased risk [80]. Other studies estimate the risk to be even higher [81]. Underlying mechanisms include the increasing of the ß-adrenergic tonus as well as a direct effect on pulmonary vein cardiomyocytes [82]. Patients suffering from hyperthyroidism should therefore be screened and treated rigorously to minimize AF development.

Tobacco and alcohol abuse have both been associated to incidental AF. Smoking was linked to a 2.05-folds increased risk of AF development. Even former smokers had still a 1.32-folds increased risk [83]. A possible explanation for this may be the nicotine mediated increased sympathetic neural stimulation causing a higher heart rate and blood pressure as well as the carbon monoxide related decrease of exercise tolerance [84, 85]. Alcohol consumption depended on quantity. Especially excessively drinking patients with more than 21 drinks per week had a 1.39-folds increased risk for AF development [86]. Pathophysiologic mechanisms comprise a hyperadrenergic state, impairment of vagal tone and direct effect of myocardial structures [87-89]. To decrease incidental AF smoking and heavy alcohol consumption must be limited.

1.1.6 Clinical Consequences

AF related clinical effects can vary greatly, ranging from highly restricting symptoms to completely asymptomatic dysrhythmias. Previous studies stated that asymptomatic AF was present in up to 30% of all AF patients [90]. It is important to differentiate whether symptoms occur directly as a consequence of AF or are related to the presence of other common cardiovascular comorbidities.

Most commonly AF associated symptoms include palpitations, dyspnoea, chest pain, fatigue and syncope. The presence of clinical symptoms strongly depends on the AF pattern. Surprisingly, patients with paroxysmal AF are more symptomatic than patients with persistent or permanent AF [91]. Identification of the underlying cause of symptoms is often difficult due to the high prevalence of comorbidities in AF patients such as valvular heart disease or HF which share the same symptoms, which are elaborated in more detail below.

Whilst sensory and neural mechanisms of palpitations are still unknown [92], chest pain in AF patients can be related to an impaired myocardial perfusion as well as an

increased coronary vascular resistance [93, 94]. Decreased exercise performance may be the direct consequence of dyspnoea or may result from a compromised cardiac output due to an impaired diastolic filling during AF [95]. Reduced functional capacity and dyspnoea are most likely the consequence of AF induced left ventricular dysfunction or tachycardiomyopathy. Loss of atrio-ventricular synchrony and fast ventricular heart rate are generally believed to be the two main reasons to negatively influence the ventricular function and hemodynamic status [96, 97]. Dizziness and syncope may be explained by sympathetic-vagal imbalance or sinus node dysfunction during the conversion to sinus rhythm [98, 99]. To describe the individual symptom burden of AF patients and to assess symptom-orientated treatment options the European Heart Rhythm Association (EHRA) scale was developed. It is illustrated in table 2.

Assessing quality of life (QoL) in AF patients using checklists is also an important method to evaluate the effect of AF treatment. Questionnaires include a variety of different parameters such as health perception, mental health, social functioning and many more. Overall, untreated AF patients had significantly poorer QoL when compared to healthy individuals [100]. Thus, when treated QoL could be greatly improved to approximate the population norm.

EHRA Score	Symptoms	Description
1	None	No AF related symptoms
2a	Mild	AF related symptoms that do not affect daily activity
2b	Moderate	AF related symptoms that do not affect daily activity but does disturb the patient
3	Severe	AF related symptoms that affect the daily activity
4	Disabling	AF related symptoms that completely disrupts the patients

Table 2: Modified EHRA symptom scale based on the 2016 ESC guidelines for the management of atrial fibrillation [25]

Without treatment, AF can lead to a variety of severe health conditions and complications.

AF is directly associated with increased thromboembolic events and fulfils all criteria of Virchow's triad: blood stasis, endothelial dysfunction and clotting activation. This implies most importantly a 3- to 5-fold enhanced stroke rate, representing approximately 20% of all strokes [38, 101, 102]. These AF associated strokes have a greater rate of reoccurrence and a higher overall mortality and morbidity when compared to non AF linked strokes [103, 104]. Besides the brain also other locations can be affected by thromboembolism like kidneys, spleen, intestine and extremities [105]. Therefore, it is crucial to identify patients who benefit from anticoagulation to prevent thromboembolisms. Based on important stroke risk factors many different assessment schemes to prevent thromboembolism were created. The CHA_2DS_2-VASc score, established in 2010, is the most recent score for calculating the individual risk

rate [106]. The deciphered score is shown in table 3. It shows all important major risk factors counting as 2 points as well as clinically relevant non-major risk factors counting as 1 point respectively. Stroke rate per year increases per additional risk factor [107]. Table 4 illustrates all stroke rates in relation to the CHA_2DS_2-VASc score.

Rapidly decreasing cognitive function is another complication of AF. It was shown that AF patients have an up 3.2-fold increased risk to develop cognitive impairment; and a 2.2-fold increased risk for dementia [108, 109]. Possible mechanisms include microembolizations, inflammation and cerebral hypoperfusion [110, 111].

HF can be a possible risk factor for AF, but AF can also induce HF via a decrease in the cardiac output as well as tachycardia related myocardial dysfunction [112]. However, above mentioned HF linked pathophysiological changes aggravate AF again. This leads to a vicious cycle.

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease	1
Age 65–74	1
Female sex category	1

Table 3: CHA_2DS_2-VASc score based on the 2010 guidelines for the management of atrial fibrillation [113]

CHA_2DS_2-VASc score	Patients N= 90,490	Thromboembolism rate %/year
0	5,343	0.3%
1	6,770	1.0%
2	11,240	3.3%
3	17,689	5.3%
4	19,091	7.8%
5	14,488	11.7%
6	9,577	15.9%
7	4,465	18.4%
8	1,559	17.9%
9	268	20.3%

Table 4: Estimated Thromboembolism rate per year for every possible CHA_2DS_2-VASc score [107]

1.1.7 Diagnosis

In the primary diagnostic algorithm, the evaluation of the individual cardiac stability is of importance. If the patient is considered unstable due to hypotension, HF or cardiogenic shock, immediate emergency cardioversion is indicated. In clinically stable patients however potential triggers, risk factors and comorbidities should be identified [114].

At first a precise medical history and a general physical examination should be conducted. Hereby, focus is on the severity of associated symptoms, the onset and duration of the arrhythmia and aggravating as well as alleviating factors. Moreover, the history of comorbidities, new medications and potential drug abusage must be considered. Physical examination should include the measurement of blood pressure

and heart rate as well as evaluation of cardiac murmurs and presence of HF related symptoms [115].

Chest X-ray should be performed to evaluate possible pneumonia, vascular congestion or COPD. A complete blood count can provide information of comorbid conditions like anemia, infection, diabetes, electrolyte anomalies, and kidney disease or thyroid dysfunction. Heart enzymes like troponin, creatine kinase and brain natriuretic peptide should be evaluated if acute myocardial ischemia or decompensated heart failure is suspected. Echocardiography must be used to gain knowledge of individual functional capacity. Important transthoracic measurements include heart size, heart shape, valve structure and function, chamber sizes and pressures, systolic and diastolic function, presence of pericardial effusion and wall motion abnormalities. Furthermore, transesophageal echocardiography must be used to detect possible left atrial and left atrial appendage (LAA) thrombus formation if rhythm control is the treatment strategy [114, 115].

Although irregular pulse rate alone is already highly sensitive and specific for AF diagnosis [116], 12-lead electrocardiography is the most important technique to directly diagnose AF as well as to identify other arrhythmias like atrial flutter or atrial tachycardia [114]. AF related electrocardiographic findings consist out of irregular RR-intervals, non- identifiable p-waves and variable atrial cycle lengths usually below 200ms, if detectable. Episodes should last at least 30s or longer to be classified AF [106]. As AF is a sporadic arrhythmia, especially in the paroxysmal type, it cannot be ruled out entirely by a non-pathologic test result. Further strategies to confirm suspected AF include 24-hours Holter-monitoring or even 7 to 30 days external event monitoring or implantable loop recorders. Additional tests like stress

echocardiography, myocardial scintigraphy and cardiac computed tomography or magnet resonance imaging should be used to exclude myocardial ischemia [115].

As mentioned previously the risk of AF increases with age. Thus, especially in an older population AF is common and often not diagnosed [117]. Therefore, it seems useful to implement preventive single lead electrocardiographic screenings. It was shown that in older populations with a mean age of 65 years pulse palpation and electrocardiography revealed a 2.3% prevalence of silent AF [118]. Current guidelines recommend opportunistic screening for AF by pulse taking or electrocardiographic rhythm strop in patients >65 years of age (class I, level B) [25].

1.1.8 Management and Treatment of Atrial Fibrillation

1.1.8.1 Cardiovascular Risk Reduction

Overall, there are two goals in the treatment of atrial fibrillation: improving prognosis and providing symptomatic relief (figure 2) [25].

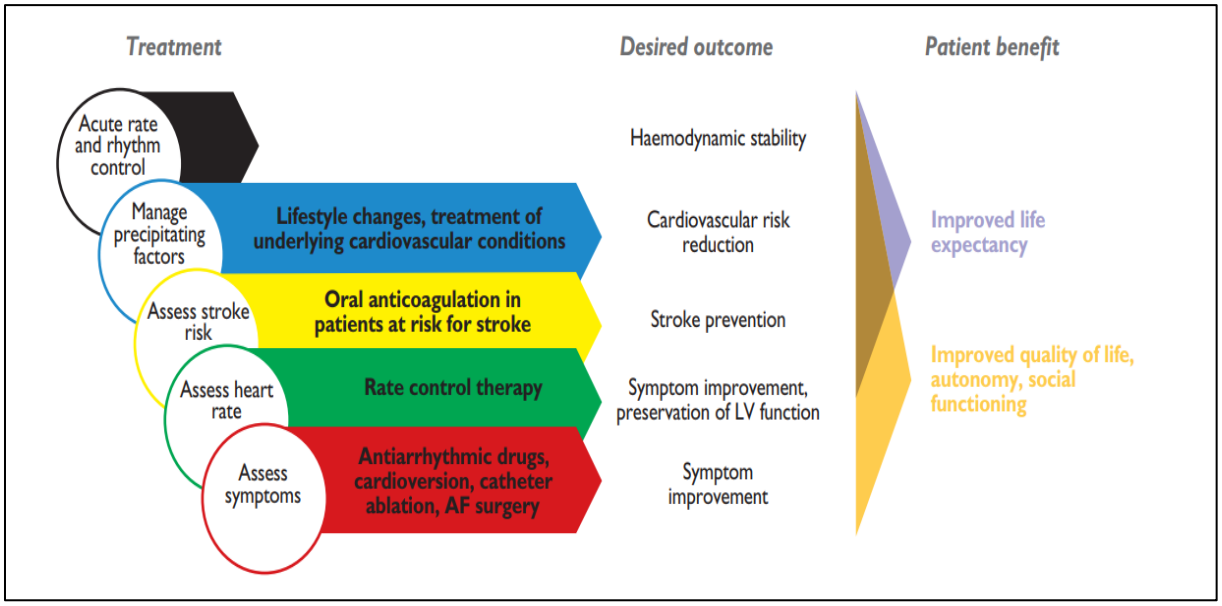

Figure 2: Overview of therapeutic approaches and their effect on the patient [118]

AF treatment begins with the reduction of AF linked lifestyle factors and optimal regulation of comorbidities. Patients are highly advised to stop consuming alcohol,

tobacco and other AF inducing stimulants like caffeine [86, 119, 120]. As arterial hypertension is the dominant risk factor for AF, regular blood pressure control is essential. OSA should be diagnosed and treated as it represents another well-known risk factor [121]. Furthermore, intensive diabetes monitoring should be an integral part of lifestyle intervention. To ensure best possible treatment physical activity as well as strict dietary modifications should be considered. Obesity should be avoided by all means possible [122]. Besides a healthy diet it is also very important to have a healthy mind-set. It was shown that days with emotional stress, anger, anxiety and impatience leads to worse AF symptoms than compared to happy days [123].

1.1.8.2 Prevention of Stroke and Thromboembolism

Strokes represent a major complication in AF patients as it represents all criteria of Virchow's triad. Thus, precise evaluation of the stroke risk with the use of the *CHA_2DS_2-VASc* score is standard to identify which patients actually need OAC therapy [113]. Even if patients are completely asymptomatic OAC is crucial for all male patients with a score of one or more and all female patients with a score of two or more according to current guidelines [25]. Oral anticoagulation (OAC) therapy is considered a highly potent protective treatment option [124, 125]. Nevertheless, decreased blood coagulability is associated with an increased bleeding risk, for which reason this therapeutic approach is often insufficient or not used at all due to impaired compliance or the fear of bleeding. To assess the individual bleeding risk for each patient several scores have been developed; most commonly used the HAS-BLED score [126]. Each letter stands for one major risk factor and counts for one point: H = arterial hypertension, A= abnormal renal or liver function, S= stroke, B = bleeding history or predisposition, L = labile international standardized ratio (INR), E = elderly > 65 years

and D = drugs and alcohol. These scores should generally not withhold OAC therapy but help with identification and modification [25].

Regarding OAC there are two main different drug classes: Vitamin K antagonists (VKA) and non-vitamin K antagonists (NOACs). The latter can be subdivided into direct Xa-Inhibitors (Rivaroxaban, Apixaban, Edoxaban) and direct thrombin inhibitors (Dabigatran). In these days, usage o VKA for stroke prevention is declining compared to NOACs due to risk of bleeding, narrow therapeutic interval and the necessity for frequent monitoring and dose adjustments with VKA treatment [127]. However, in case of optimal adjustments of the International Normalized Ratio (INR) e.g. by self-testing and -management, VKA provide effective stroke prevention in AF patients [128]. NOACs provide similar protection but most importantly a better risk-benefit profile than VKA with significant reductions in intracranial hemorrhages, stroke, and mortality [125]. Nevertheless, VKA are recommended in patients with severe CKD (creatinine clearance < 25-30mL/min), valvular heart disease defined as mitral valve stenosis, mechanical heart valves [129]. In case of OAC contraindication there are two more methods preventing stroke in patients with AF: LAA occlusion and surgical LAA exclusion. These procedures may be considered as the LAA is the most important source of cardiac thrombus formation in patients suffering from AF [130]. It was shown that interventional LAA occlusion was a similar good protector as OAC [131]. Nevertheless, this procedure is associated with serious procedural complications e.g. pericardial tamponade [132]. Surgical LAA exclusion has been performed since decades but is a highly invasive technique and should only be considered when undergoing open heart surgery for other indications [133].

1.1.8.3 Rate Control Therapy

In symptomatic AF patients rate control therapy plays an essential role in the treatment as it helps to decrease the burden of AF associated symptoms as well as prevent the development of tachycardiomyopathy [134].

In case of acute new onset atrial AF, ß-blockers or the calcium channel blockers diltiazem or verapamil should be used as a standard to improve symptoms and hemodynamics [135, 136]. In patients with HF however physicians need to consider rather digitalis and ß-blockers or even the combination of both as verapamil has a negative inotropic effect in these patients [137, 138]. Moreover, amiodarone can be used for individuals with a hemodynamic instable heart function [139].

Concerning long term rate control the optimal target heart rate is still under discussion. It was shown that there were no differences between a lenient (heart rate target < 110 bpm) and a strict (heart rate target <80 bpm at rest and <110 bpm during moderate exercise) heart rate control [140]. Current guidelines consider initially a lenient approach and in more symptomatic patients a stricter one [25]. Monotherapy with ß-blockers, calcium channel blockers or heart glycosides is usually the first line treatment to reduce AF related symptoms. However, in younger patients with sufficient left ventricular function, calcium channel blockers might have an advantage because of a better exercise tolerance [141]. In turn, ß-blockers alone or in combination with cardiac glycosides like digoxin should exclusively be used in patients with a left ventricular function < 40% and be preferred in patients with CAD or post myocardial infarction [142, 143]. Moreover, in case of difficult heart rate management or persisting symptoms combination therapies with digoxin can be considered.

Atrioventricular (AV) node ablation and implantation of a ventricular pacemaker device represents the ultimate procedure to establish a sufficient heart rate and decrease

symptoms in AF patients. It should only be considered as a last resort [144], as after AV-ablation patients are dependent on the pacemaker for the rest of their lives. The pacemaker is usually implanted a few weeks before AV node ablation and set to a heart rate of 70-80 bpm. Overall the procedure has a low complication rate and a low long term mortality [145]. It can even help HF patients to increase their left ventricular function [146].

1.1.8.4 Rhythm Control Therapy

In symptomatic patients and failing rate control therapy or when the patient is considered to have major long-term benefit, another method of AF management applied: the rhythm control therapy. Rhythm control approaches need to be separated into acute and long-term treatment:

During an acute and severe AF onset with hemodynamic stability a pharmacological or electrical cardioversion might be indicated. Most potent class Ic antiarrhythmic drugs are flecainide and propafenone, which can induce sinus rhythm in up to 50% [147]. Nevertheless, the usage is limited to patients without structural heart disease. For all other patients, amiodarone is the recommended agent [25]. However, during an acute and severe AF onset with hemodynamic instability electrical cardioversion is the method of choice to ensure sinus rhythm [148, 149]. To reduce the associated risk of stroke immediate anticoagulation is mandatory [150]. Electrical cardioversion can also be used in patients with sub-acute AF. Hereby it is essential to initiate pre-procedural anticoagulation and rule out possible thrombus formation via transesophageal echocardiography [151].

Long term heart rhythm treatment is indicated in case of a chronic severe symptom burden. It was shown that pharmacological antiarrhythmic therapy can maintain sinus rhythm double the time as compared to patients without a therapy [152]. Nevertheless

it was also associated with an increased risk for hospitalizations due to drug induced pro-arrhythmias as well as extra-cardiac adverse effects [153]. Therefore, ECG monitoring is essential and it is recommended that antiarrhythmic treatments should only be used for a reasonable fixed time period [154]. Mostly used antiarrhythmic drugs include amiodarone, dronedarone, flecainide and propafenone. In patients with heart failure amiodarone is considered to be the best choice [155]. However, it needs close monitoring due to its associations with severe side effects such as phototoxic reactions, thyroidal dysfunction, lung fibrosis or reduced vision [156]. Sotalol as a class III antiarrhythmic drug might be an option for patients with ischemic heart disease [157], normal kidney function, normal QT interval, and contraindication for amiodaron. Dronedarone can be an alternative for amiodarone in patients with CAD or significant valvular disease [158, 159]. As mentioned above flecainide and propafenone can only be used in absence of structural heart disease.

In case of failing rate control or if pharmacological rhythm control is ineffective or contraindicated, catheter ablation is an interventional treatment option to establish stable sinus rhythm. In those patients with symptomatic paroxysmal AF, catheter ablation might be indicated as a first-line strategy without prior antiarrhythmic drug treatment [160].

1.2 Catheter Ablation

1.2.1 General Information

Since the introduction of catheter ablation (CA) in 1994 [161], it was studied and improved continuously over the years and became an important therapeutic approach for symptomatic AF patients despite optimal pharmacological therapy. It was shown that in these patients CA can provide a better outcome compared to antiarrhythmic therapy [162, 163]. Nevertheless, being a highly complex procedure with possible severe complications, CA should be conducted by highly experienced operators. Moreover, physicians need to take into account the stage of the atrial disease, cardiovascular comorbidities and the patient's preference. While CA can be very effective in patients with paroxysmal AF and minimal heart disease, outcomes in individuals with persistent or long-standing persistent AF are usually less promising [164]. Therefore, extensive or repeat ablation procedures may be required.

It could be shown that especially left atrial muscle sleeves extending to the pulmonary veins (PV) are the most common trigger of AF (80% of patients) [165]. Thus, the cornerstone of AF ablation is the electrical isolation of all pulmonary veins (PVI). Although most patients benefit from PVI about one third has an AF recurrence [166]. The main pathophysiological mechanism of AF recurrence after the ablation procedure is the reconnection of previously isolated PV [167]. However, in 20% also non-PV triggers (e.g. from the right atrium, the coronary sinus) were identified in additional ablation procedures [168]. To improve the success rate of CA procedure in patients with persistent AF, some experts suggest modifying also the substrate that may maintain fibrillation additional to PVI [169]. Most commonly used techniques for substrate modification are the creation of empirical linear left and right atrial lesions, linear lesions at the mitral isthmus or even multiple lesions forming a box between all

pulmonary veins at the posterior wall of the left atrium (LA) [170]. Recently, it was shown that also the LAA may originate extra-PV triggers and may influence the risk of AF recurrence after CA procedure [171, 172]. Therefore, some experts have proposed empirical electrical isolation of the LAA [173], which remains controversial due to several unresolved issues, e.g., the reconnection rate, the preferred technique to isolate the LAA, and the risk of thrombus formation in the LAA, which is without mechanical contraction when electrically isolated [173-176].

1.2.2 Complications

Being an invasive technique there are several complications associated with catheter ablation. It could be shown in a meta-analysis comprising 83,236 patients that major complication rate is approximately 3% [177]. Vascular complications were experienced most commonly at 1.4% followed by cardiac tamponade at 1%, pericardial effusion at 0.7%, stroke and transient ischaemic attack at 0.6% as well as pulmonary vein stenosis at 0.5%. Less frequent complications included diaphragmatic paralysis at 0.3%, pneumothorax at 0.2%, haemothorax at 0.2% and sepsis at 0.1%. The overall incidence of procedure-linked deaths was 0.06%. Moreover, there was a 0.4% incidence of phrenic nerve injury and a 0.1% risk of atrioesophageal fistula.

1.2.3 Techniques for Pulmonary Vein Isolation: Radiofrequency vs. Cryoballoon Ablation

Circumferential PVI is more dominantly performed by the radiofrequency method, which is well established and uses a point-by-point technique. In 2007, a newer cryoballoon-based approach was introduced as a single-shot technique for en bloc isolation of each PV. Despite similar results on AF recurrence after the ablation procedure in paroxysmal AF [166] there are some important differences between those two techniques that need to be mentioned. It was shown that radiofrequency ablation

(RFA) is associated with an increased risk for thromboembolic events compared to cryoballoon ablation (CBA) as CBA leads to a preserved tissue ultrastructure [178]. Singular radiofrequency lesions could create oedema and small gaps that might not be detected during the procedure. CBA can provide a completely closed circular isolated area with a high durability [179]. Due to the ability to detect intra-procedural PV-potential recordings in cryoballoon ablation, the procedural parameter “time-to-PV-isolation” (TTI) has been established as the unique predictor for durable isolation [180]. Moreover, a recent cohort trial comparing CBA and RFA did not find differences for the primary endpoint. However, rehospitalization rates due to repeat ablations and adverse events during follow-up were observed significantly less frequently after CBA than after RFA. [181]. In the FIRE & ICE Trial, PV reconnection rates in patients undergoing a repeat ablation were lower in the CBA group as compared to the RFA group [182].

Nonetheless, CBA associated disadvantages include more radiation exposure as the balloon catheter requires optimal positioning, limited options of extra PV ablations and no additional substrate characterization and modification due to the absence of an electroanatomical mapping system [183, 184]. Moreover, CBA is also restricted in overall variability compared to RFA as balloon sizes are limited to 28 or 23 mm. While CBA does also require bigger sheaths with 15 French compared to RFA with 8.5 French it only demands a single transseptal puncture (TSP) and no double TSP as in RFA.

New techniques like the laser balloon, RF balloon and electroporation are not yet commonly applied.

1.2.4 Biophysics of Cryo-Lesion Formation

The formation of cryoballoon induced lesions is generated by hypothermia at the adjacent tissue and consists of three main stages: the freeze/thaw phase, the haemorrhagic/inflammatory phase and the replacement fibrosis phase [213].

Overall, progressive hypothermia leads to several adverse impacts regarding the cardiomyocytes and ultimately to their dysfunction. Those effects include a slowed down metabolism, impaired ion pump transport capabilities and a more acidic intracellular pH value. Extracellular ice crystal formation starts when tissue temperature levels drop below -15°C. After cooling below -40°C ice crystals manifest also in the intracellular space. This results into a dysregulated osmotic equilibrium and eventually to an irreversible damage of mitochondria, cellular proteins and lipoproteins of the plasma membranes. Ice crystal formation induces microcirculatory failure, interstitial oedema, cessation of the blood flow and ultimately ischemia. After the ablation the freezing stage is followed by the thawing phase. Tissue returns to body temperature levels causing ice crystals to morph into larger masses and thus amplify the cellular damage.

The period of haemorrhage and inflammation is characterized by damaged microvascular endothelial cells and persistent oedema, which leads to ischemic necrosis.

Ultimately, mature lesions are formed due to apoptosis and replacement fibrosis of cells adjacent to the damaged tissue.

1.3 Imaging in Atrial Fibrillation and Predictors of Recurrence

1.3.1 Imaging in Interventional Electrophysiology

There are multiple imaging modalities for pre-, intra- or postprocedural evaluation of individual anatomical landmarks in patients undergoing CA like transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), fluoroscopy, rotational angiography of the left atrium, intracardiac echocardiography (ICE), computed tomography angiography (CCTA) and MRI. TTE and TEE are most frequently performed as in all patients, thrombus formation must be ruled out prior to the left atrial ablation procedure. In addition, TTE is also used to assess underlying cardiac pathologies that are linked to AF such as mitral valve disease, left ventricular dysfunction, and hypertensive heart disease [185]. Moreover, LA dimensions can be measured by echocardiography which can give information about the substrate of AF. LA size is an independent predictor of AF recurrence after CA [186]. During ablation procedure, ICE might be used to guide trans-septal puncture as variations of septal anatomy can lead to an increased complication risk [187]. Postprocedural CCTA is the method of choice in case of severe ablation related complications such as PV stenosis or atrio-esophageal fistula.

As the success rate of PVI is often impaired due to highly complex and variable left atrial anatomy, pre-procedural CCTA can be used to ensure an optimal understanding of individual left atrial anatomy and allows an individualized therapeutic approach [188]. Despite also reducing fluoroscopy time [189, 190], CCTA showed to be the best method for the assessment of pulmonary vein as well as left atrial structures and had a similar high diagnostic value in depicting accessory veins compared to ICE [191, 192]. Furthermore, CCTA can be used for thrombi exclusion. However, TEE should still be considered the gold standard as it yields in comparison no radiation dose. This

outweighs its less effective diagnostic value and interobserver variability compared to CCTA [193].

In order to improve continuous transmural lesions, to reduce radiation exposure and to avoid complications, electroanatomical mapping (EAM) systems have been developed [194]. These systems are based on electroanatomical visualizations using mapping catheters and three-dimensional reconstruction without the use of fluoroscopy. Via map points electrical information is recorded and then either displayed as electrical activation, as post-pacing intervals or as unipolar/bipolar electrograms [195]. Image integration of previously acquired CCTA data can help to improve the placement of anatomically guided ablation lesions and does therefore provide an advantage for complex, anatomically based procedures [190, 196, 197].

1.3.2 Predictors of Atrial Fibrillation Recurrence and the role of the Left Atrial Appendage

Although CA represents a curative treatment option for AF patients, there is constant research to further improve long-term effectiveness. This seems to depend on the AF type but also on other patient-specific related factors. For example, in persistent AF patients, recurrence rates up to 50% were described [198]. Therefore, identification of special patient characteristics predicting AF recurrence would greatly increase the success rate of CA overall.

Within the last decade multiple risk factors have been revealed. According to a recent study comprising 3.703 patients of the German Ablation Registry [199], most important baseline characteristics include the female gender, the persistent type of atrial fibrillation and comorbidities like renal insufficiency and valvular heart disease. Moreover, heart failure with NYHA class II was more likely to occur in patients with AF recurrence. Other studies also described an association between obstructive sleep

apnea [200], an impaired left ventricular function [201], age [202] and the duration of AF episodes [203, 204].

Despite the baseline characteristics there are also many other parameters identified that are linked to an increased risk of AF recurrence. Most importantly, patients with larger left atrial volumes were associated with a significantly higher rate of recurrence [205, 206]. Also, the left atrial diameter measurable via echocardiography could be linked to more frequently occurring AF after ablation [207]. Moreover, it was shown that a prolonged P wave duration could serve as a predictor for AF recurrence [208]. Other studies also suggested AF recurrence being associated with the presence of inflammatory markers such as white blood cell count and high-sensitivity C-reactive protein [209] or larger left atrial appendage volumes [210].

1.3.3 Impact of Left Atrial Appendage Morphology

In the last decade the LAA gained a lot of attention. As mentioned before, the LAA is the most important location for the formation of intracardiac thrombus. It was also identified as a possible region for extra-PV triggers of AF. In 2010, four different LAA morphologies were defined: chicken-wing, windsock, cactus, and cauliflower [211]. Interestingly, it was shown that patients with chicken-wing morphology were associated with a decreased risk for thromboembolic events [212]. However, whether a certain LAA morphology could also be a risk factor for AF itself is yet unknown.

2 OBJECTIVES

Catheter ablation is an established treatment option of symptomatic drug-refractory AF patients. Nevertheless, success rates vary strongly and are dependent on the method used. Therefore, identification of predictors for AF recurrence is highly important to improve the outcome and even develop new therapeutic approaches.

The primary goal was to evaluate whether LAA morphology and detailed measurements of a variety of LAA parameters determined by pre-procedural CCTA and post-processed in a standard 3D mapping system can predict atrial arrhythmia recurrence after initial cryoballoon PVI in symptomatic AF patients. Therefore, the rate of recurrence was statistically compared between the four different LAA morphologies (windsock, chicken-wing, cactus, and cauliflower) previously defined by Wang et al. [211] with Kimura's quantitative qualifiers [213] and detailed measurements of the LA and LAA.

Persistent AF is generally associated with a higher recurrence rate after CBA as compared to paroxysmal AF patients. As there is currently limited information available on risk factors predicting CA outcome regarding this specific type of AF a subgroup was formed and evaluated.

Thirdly, classification of LAA morphology is often rather subjective and susceptible to errors. Therefore, another aim of this study is to objectify LAA morphological definitions.

3 METHODS

3.1 Study Population and Trial Design

Heart Center Munich Bogenhausen is a Municipal Hospital with maximum-care and a teaching hospital of the Technical University Munich (TUM). Since cryoballoon ablation became available in 2007/2008, consecutive patients with an indication for PVI as the endpoint of AF ablation were treated by means of CBA. From 2007 to 2020, over 3.200 CBA procedures were performed at the local institution. In 2012, the second-generation CB was released. Compared to its predecessor it shows a higher efficacy due to an increase of the refrigerant flow and a more uniform cooling zone covering the distal hemisphere [214, 215]. All patients scheduled for an AF ablation using the cryoballoon system (Arctic Front™, Arctic Front Advance™, Arctic Front Advance ST™, Arctic Front Advance Pro™, all Medtronic Inc., MN, USA) were consecutively enrolled into the local prospective observational quality assurance registry.

AF ablation was not conducted in patients with following exclusion criteria: permanent atrial fibrillation, left atrial diameter >60mm, severe valvular disease, intracardiac thrombi, and patients on triple therapy (OAC + ASS + Clopidogrel). No patient was excluded because of a variation in LA, PV, or LAA anatomy or LA volume, as determined by CCTA.

All patients undergoing second-generation CBA (Arctic Front Advance™, Medtronic Inc., MN, USA) in the initial ablation procedure were included into this analysis with a blinded retrospective evaluation. Only patients were considered who underwent recent pre-procedural CCTA imaging with sufficient quality to assess the LAA. Clinical indications for CCTA were a) exclusion of CAD and b) determination of LA and PV

anatomy prior to the CBA. To qualify for retrospective evaluation every patient included had to have a follow-up time greater than one year.

All patients were precisely informed about the procedure itself, possible complications as well as prospects of success. Informed consent was obtained from all patients. The non-interventional registry study was announced to the regional ethics review board and complies with the Declaration of Helsinki. Statistical methods used were also validated by the Statistical Institute for Medical Information Processing, Biometry and Epidemiology of the Ludwig-Maximilians-University Munich.

For the substudy in persistent AF, two cohorts were formed: Cohort one consisted of all patients, independent of their underlying type of AF. Cohort two only included patients with persistent AF.

3.2 Ablation Procedure

3.2.1 Pre-procedural Investigations

Patients were admitted to the hospital a day before the ablation procedure. Besides the assessment of the patient's history and the conduction of a detailed physical examination the patients also received a blood withdrawal for evaluation of blood count, coagulation parameters, C-reactive protein as well as all important biomarkers like thyroid hormones, creatine kinase, creatine kinase-MB and troponin. Electrocardiograms were recorded and analyzed. All patients underwent transthoracic as well as transesophageal echocardiography to exclude possible LA thrombus formation and to gain information of the heart function. Important analyzed parameters included the flow velocity of the LAA, the left atrial diameter and the ejection fraction of the left ventricle. Echocardiographic measurements evaluated the function of the mitral and aortic valves, the presence of thrombotic aortic deposits and possible underlying anatomical variants like left common PV ostium, accessory right pulmonary veins or the presence of a patent foramen ovale.

On the day of the ablation procedure patients had to be sober. In individuals receiving thromboembolic treatment with Vitamin K antagonists, INR was adjusted to levels between 2.0 and 3.0. In case of values below 2.0, low-molecular-weight heparins were used for bridging. In patients receiving NOACS, the anti-thrombotic agents were discontinued the day before the examination and restarted immediately after the ablation procedure. Patients with CAD on triple therapy were scheduled for AF ablation after de-escalation to dual therapy (OAC + ASS or Clopidogrel).

3.2.2 Pre-procedural Cardiac Computed Tomography Angiography

The individual left atrial anatomy was determined using a 64-slice computed tomography scanner (Brilliance 64, Philips Medical Systems, Cleveland, Ohio, USA) with retrospective ECG gating and 3D reconstruction. The local institutional scanning protocol was previously described [216] and includes following important technical parameters: a peak tube voltage set at 120 kV, an effective tube current of 600 mAs, a slice collimation of 64 × 0.625 mm and a gantry rotation time of 0.4 s with a pitch of 0.2. Contrast enhancement was performed by injection of 80 mL contrast agent (Imeron 400 MCT, Iomeprol 81.65 g/100 mL, Bracco, Konstanz, Germany) at a flow rate of 5 mL/s, followed by a 50-mL saline flush. Images were then reconstructed at increments of 0.45 mm at 0.9 mm slice thickness.

3.2.3 Cryoballoon Ablation System

The ablation procedure was performed using the second-generation cryoballoon system consisting of four major components: the cryo-console (CryoConsole™, Medtronic Inc., USA), a steerable sheath (FlexCath Advance™, Medtronic Inc., USA), and the cryoballoon catheter (28 mm Arctic Front Advance™, Medtronic Inc., USA) and a circular mapping catheter (Achieve™ or Achieve Advance™, Medtronic Inc., USA).

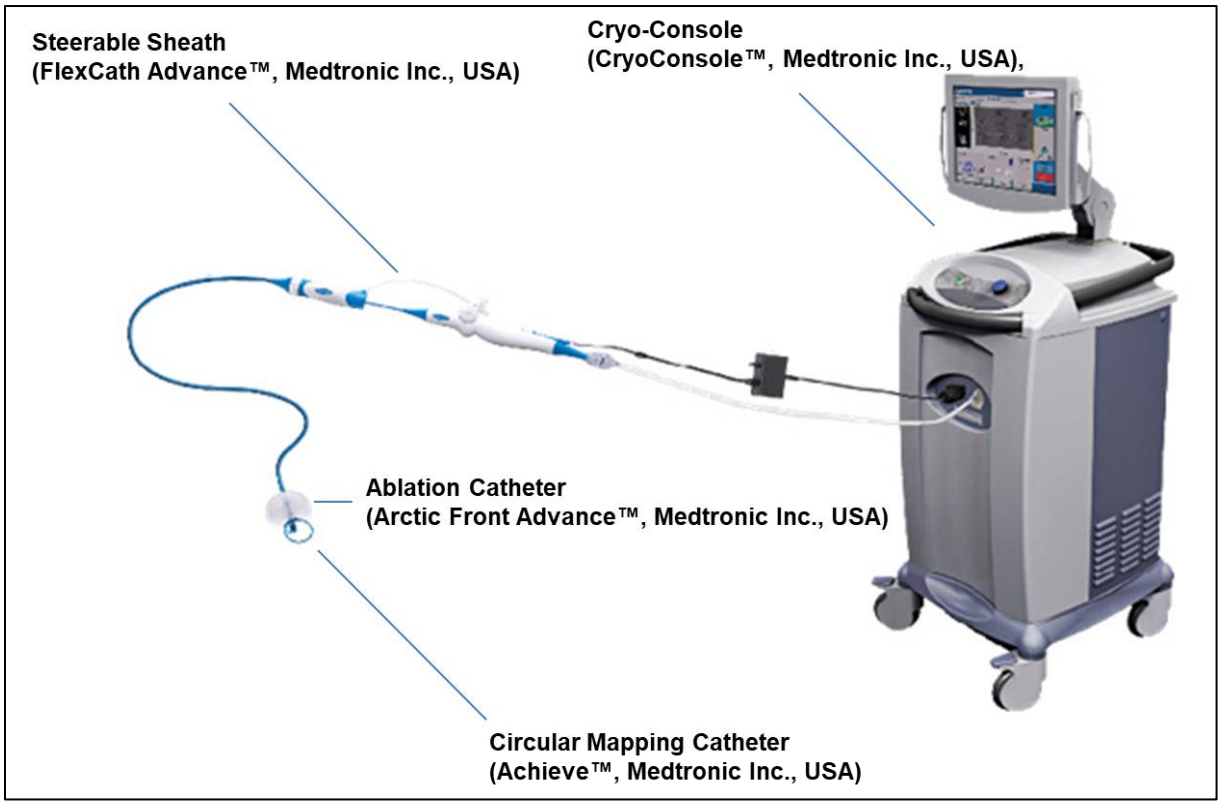

Figure 3: Cryoballoon ablation system and its components (Courtesy: Medtronic Inc, USA)

The cryo-console, which is connected to the ablation catheter via a coaxial umbilical, contains a pressure cylinder with the cryorefrigerant (N_2O). It can be controlled via a touchscreen display. During the ablation procedure the pressurized refrigerant is transferred to the cryoballoon, vaporizes at the tip of the catheter and induces a temperature drop to a maximum of -80°C. The balloon temperature is measured in a proximal position of the balloon and is a surrogate parameter of the efficacy of the application. Post-procedurally a vacuum mediated lumen delivers the cryorefrigerant back to the console for disposal. The acquired ablation data is obtained in a case report ablation form.

The transseptal puncture was guided by ICE and performed using an 8.5 french guiding sheath (e.g. Swartz™ Braided Transseptal Guiding Introducers LAMP™ Series, St. Jude Medical, Saint Paul, MN, USA) and a transseptal needle (BRK™, St.

Jude Medical, Saint Paul, MN, USA). After trans-septal puncture a stiff guide wire is placed in the left superior pulmonary vein, and the steerable cryosheath (15 French, Flexcath Advance™) is positioned in the LA in an over the wire technique. The flexible sheath is used for the precise positioning of the cryoballoon. The sheath is 135 degrees deflectable. It contains a hemostasis valve for introduction, exchange and withdrawal of wires and catheters as well as preventing air ingress and minimizing blood loss.

The balloon is available in two sizes for accommodation to individual anatomy: 23mm and 28mm. In the present study all evaluated patients were treated initially with the 28mm catheter. The 23mm was allowed in small PV (<21mm) if acute PVI was not obtained with the big balloon. Both consist of following important components:

1. The guide wire lumen, which enables contrast injection to confirm optimal placement of the cryoballoon for pulmonary vein occlusion.
2. The outer balloon, which is under a constant vacuum to help maintain the refrigerant in case of inner balloon destruction.
3. The inner balloon, which is inflated by refrigerant and facilitates the freezing process.
4. The deflectable pull wires, which help to navigate the catheter.
5. The Thermocouple, to control the vaporized refrigerant temperature and to measure the balloon temperature for the operating physician.
6. The injection tube, through which the refrigerant is delivered to the inner balloon, the distal hemisphere and the uniform cooling zone

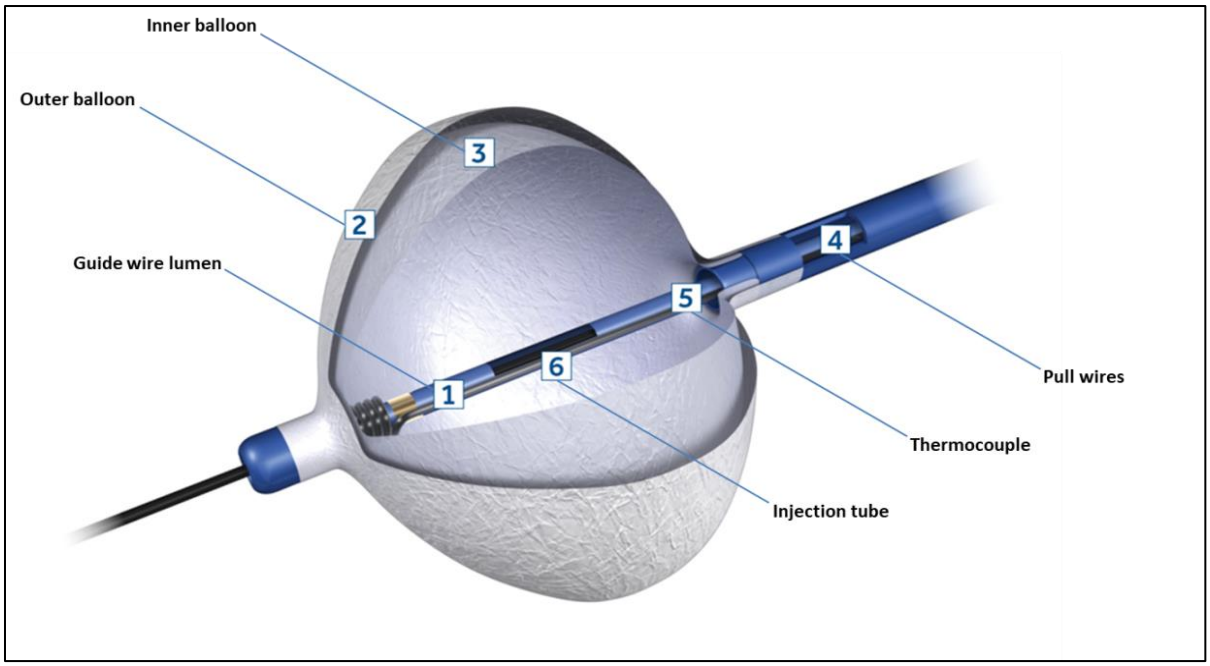

Figure 4: Detailed Overview of a cryoballoon catheter (Courtesy: Medtronic Inc, USA)

The spiral mapping catheter is an intracardiac diagnostic catheter, which can be navigated with the sheath to gain access to the pulmonary vein and to give stability for balloon positioning and optimal occlusion of the PV. The most distal part consists out of a circular loop containing eight electrodes. On the one hand it provides mapping for electrical conduction to evaluate pulmonary vein activity, entrance and exit conduction from LA to PV and vice versa, and to determine PV isolation. On the other hand, it can also be used for intracardiac stimulations. The mapping catheter enables real-time PV potential recordings and the determination of the time to isolation, a unique biophysical surrogate parameter for estimating the efficacy of the cryoballoon application. A low value (e.g. ≤45 seconds; data on file) is usually associated with a higher chance for a durable PV isolation [180].

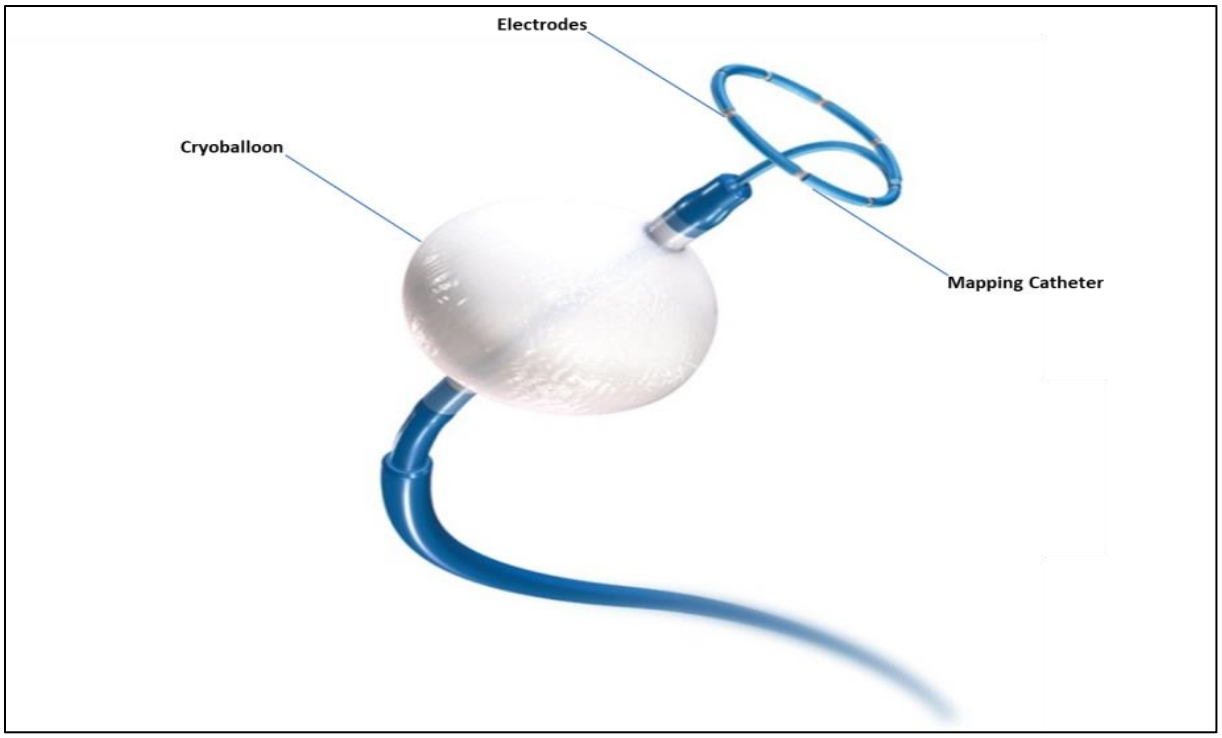

Figure 5: Mapping Catheter (Courtesy: Medtronic Inc, USA)

3.2.4 Cryoballoon Ablation Protocol

All cryoballoon ablation procedures were performed standardized in an electrophysiological laboratory under sterile conditions. PV angiography was conducted in -30° degree left anterior oblique (LAO) and -30° degrees right anterior oblique (RAO) projections with a picture rate of 7.5 per second for the left and right PV's respectively. The patient was monitored throughout the entire procedure via 12-lead ECG electrocardiographic recordings as well as intermittent measurements of the blood pressure and continuous oxygen saturation measurement. Midazolam was used as an anxiolytic drug at arrival of the patient. After thorough disinfection of the skin at both groin areas, local anesthetics (Mecain 2%) was applied subcutaneously and three venous femoral sheaths were placed (12F, 11F and 7F). ICE catheter was placed in RA. Decapolar catheter (WEBSTER Decapolar Catheter™, Biosense Webster, Diamond Bar, CA, USA) was placed in the coronary sinus. Analgo-sedation was

obtained by continuous intravenous administration of propofol and intermittent morphine application.

To avoid esophageal damage, an endoluminal esophageal temperature probe (SensiTherm™, St. Jude Medical, Saint Paul, MN, USA or Circa™ probe or CIRCA Scientific, Englewood, CO, USA) was used in all patients. The cut-off was ≤+15 °C. Phrenic nerve (PN) pacing with a cycle length of 1200ms and manual diaphragm examination was performed to reduce the risk of PN palsy during ablation of the right PVs with the multipolar catheter from the CS. Diaphragmatic motion was also visualized by ICE imaging.

Transseptal puncture was performed using a specialized needle (BRK™, St. Jude Medical, Saint Paul, MN, USA) over an 8.5F guiding sheath and guided by intracardiac echocardiography (ICE; Vivid I, GE Healthcare EUROPE, GE Ultraschall Deutschland GmbH, Solingen, Germany). ICE was also used to assure optimal balloon positioning, vessel occlusion, and to visualize diaphragmatic motion during ablation of the right-sided PVs if palpation of the diaphragm was difficult. To prevent thrombus formation in the left atrium weight adapted intravenous heparin was administered after venous sheath placement (2.500 IE) and right after transseptal puncture (5.000-7.500 IE). Aimed activated clotting time (ACT) was between 300 and 400 s during the entire procedure. ACT measurements were taken at least every 30 min while in the LA. Over a 15 French steerable sheath (Flexcath Advance™, Medtronic Inc., Minneapolis, MN, USA) the 28-mm cryoballoon catheter (CBG2: Arctic Front Advance, Medtronic Inc., Minneapolis, MN, USA) was introduced to the left atrium and successively navigated into each of the pulmonary vein ostiae. The ablation procedure follows a clockwise sequence: left superior pulmonary vein (LSPV), left inferior pulmonary vein (LIPV), right inferior pulmonary vein (RIPV) and right superior pulmonary vein (RSPV). An 8-

pole micro-circular mapping catheter (20-mm Achieve™ or Achieve Advance™ Mapping Catheter, Medtronic Inc.) was used for CB positioning and the assessment of real-time PV potentials. To ensure best possible pulmonary vein occlusion angiography was performed via the injection of a contrast agent into the pulmonary vein over the guide wire lumen of the ablation catheter. In addition to the intraprocedural ICE imaging and PV angiography, a 3D reconstruction of the LA via CT was available to guide the operator and identify PV variants.

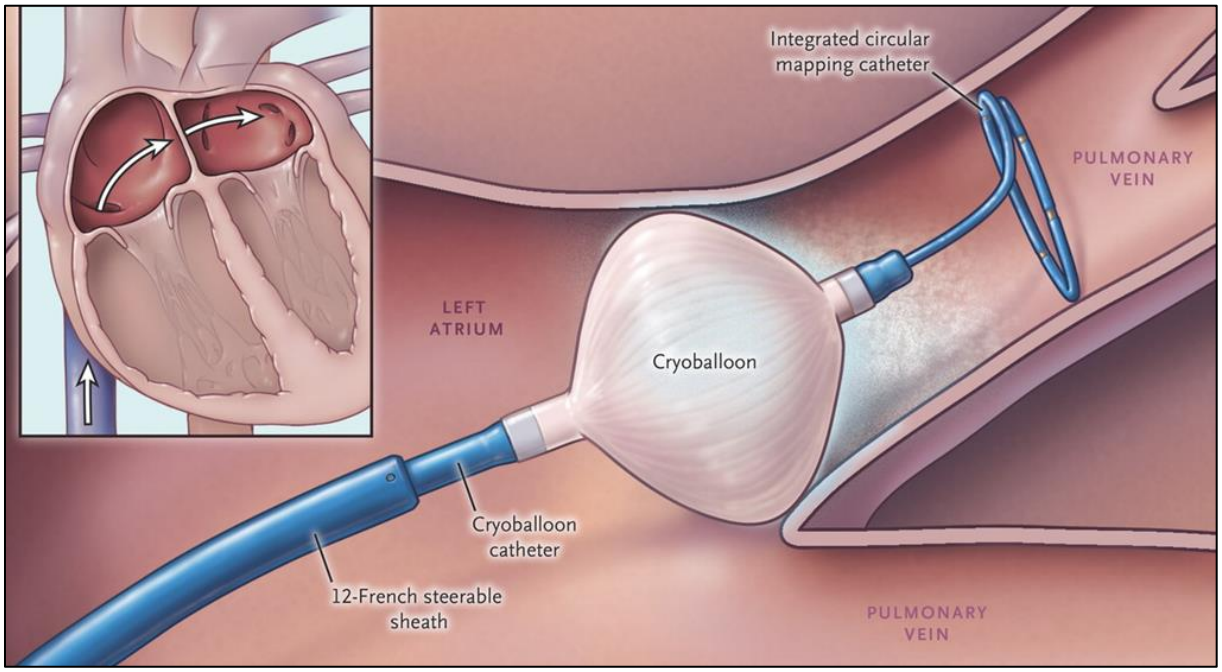

Figure 6: Schematic illustration of the cryoballoon ablation procedure including the left atrial access route [166]

The refrigerant supply was started and PVI was performed with at least one freeze-thaw-freeze cycle per vein. The standard application time was between 180 and 240 s. If PV potentials could be identified during the freeze cycle, the time to PV isolation (TTI) was determined. An additional application was conducted in those veins with TTI >45 s or if no time to isolation was detected. For safety measures, the balloon temperature limit for right sided PV was ≤-55 °C. The esophageal temperature limit was ≤+15 °C. In case of a decrease or loss of diaphragmatic motion during ablation of

the right PVs the application was stopped immediately. Double-stop technique for active balloon deflation was applied. In addition, PV potentials were mapped before and after each freeze cycle and again 15 min at the end of the last freeze. After achieving a successful isolation an additional freeze application was only performed if TTI was ≥45s or no TTI was available to ensure durable PVI. If PVI was not achieved with the 28-mm CB, the 23-mm CB size (Arctic Front Advance™, Medtronic Inc., USA) was allowed exclusively for small PV ≤21 mm.

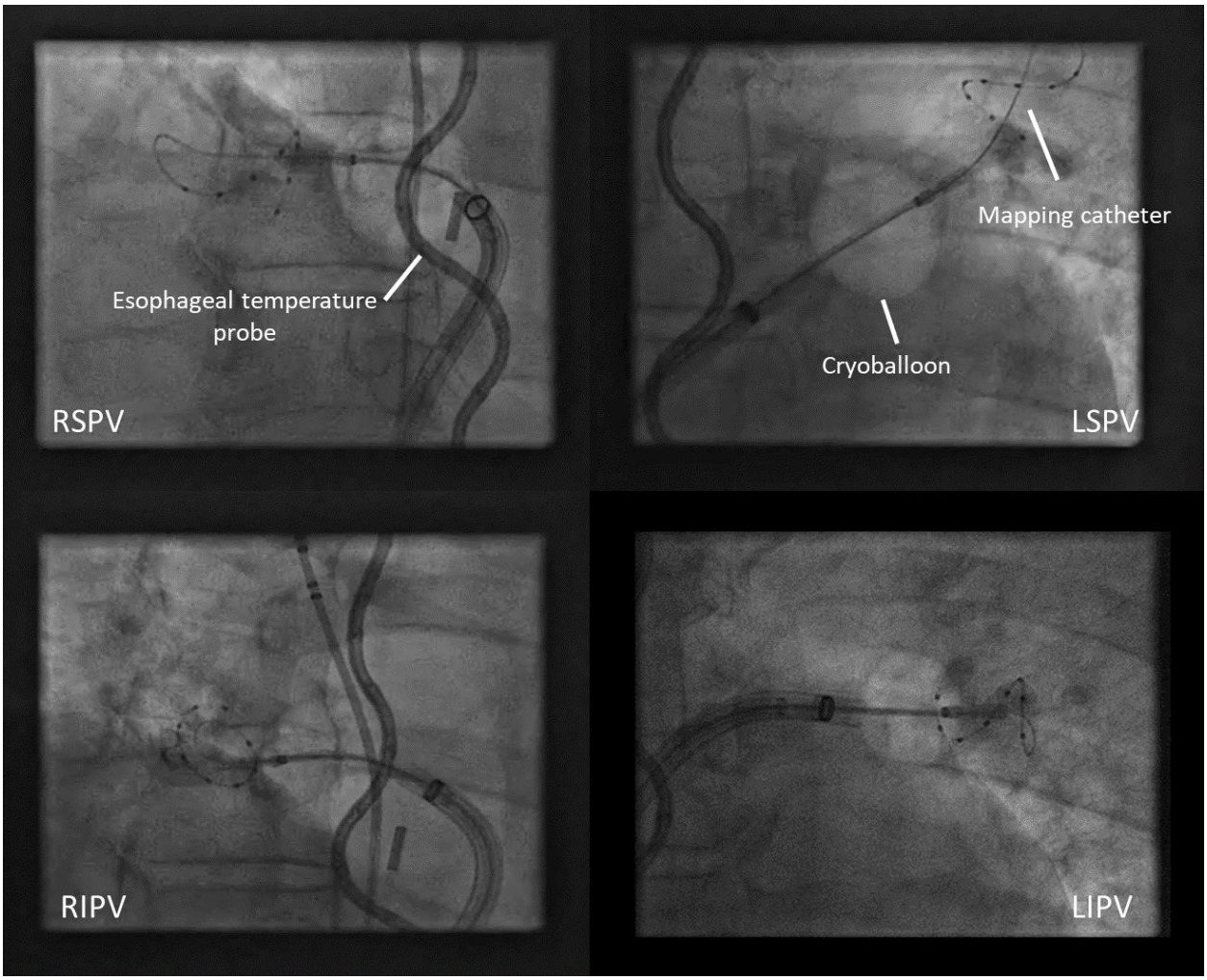

Figure 7: Fluoroscopic depiction of the cryoballoon ablation. The cryoballoon is positioned in each pulmonary vein ostium. LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary

At the end of the procedure but prior to sheath removal from the groin, protamine was given intravenously to antagonize the effect of the heparin and thus to reduce the bleeding risk. Administered dosage depended on the previously given heparin. An ACT <250 s was targeted. Manual compression until the onset of hemostasis and a pressure bandage for twelve hours were applied. No later than one hour after sheath removal, either continuous unfractionated heparin was applied with a target partial thromboplastin time of 50-70 s or NOACs were restarted immediately. Finally, oral anticoagulation was reinitiated on the day after the procedure and continued for at least 3 months and then according to the CHA_2DS_2-VASc Score.

Following the intervention, all patients were monitored with continuous electrocardiography (ECG) for at least 24-48 hours. Moreover, additional blood tests were conducted to provide detailed information about possible adverse events and myocardial damage. Besides frequent inspections of the femoral puncture sites, pericardial effusion was excluded via TTE in all patients. In case of symptoms, additional ECG and Holter studies were continued up to 7 days. Holter recordings after 1, 3, 6, and at least 12 months were organized to screen for symptomatic or asymptomatic atrial arrhythmias. Follow-up was also ensured in cooperation with the referring physicians, with detailed questionnaires, and individual telephone calls. If there was any suspicion of recurrence, the referring physician was contacted to validate the diagnosis. Only recurrences outside of the 90-day blanking period were categorized as failures.

3.3 Data Acquisition and Management

3.3.1 Baseline Parameters

Before every cryoballoon procedure all important patient related data were prospectively obtained from the medical records. Follow-up data was entered manually. Besides patients' age, gender, height and weight table 4 depicts and explains other important baseline parameters.

Baseline parameters	Definition
Age	Years of age at baseline
Sex category	Male, female, divers
Body Mass Index (BMI)	Weight in kilograms / (height in m)^2
Persistent AF	Definition according to table 1
Mitral regurgitation ≥°II*	RVol < 30-44 ml/beat, RF < 30 %, EROA < 0.2-0.29 cm^2
Valve disease ≥°II*	Dysfunction of the mitral-, aortic- or tricuspid valve
LA diameter*	Maximal antero-posterior diameter at ventricular end systole
Ejection fraction*	Left ventricular volumetric fraction ejected per beat in %
Hypertension	Underlying arterial hypertension diagnosed according to age and current guidelines
Hypertensive heart disease	Presence of heart failure, ischaemic heart disease or left ventricular hypertrophy induced by arterial hypertension
Cardiomyopathy	Genetic or acquired heart muscle disease

Prior myocardial infarction	Previously experienced myocardial infarction
Ischaemic heart disease	Underlying coronary artery disease
Structural heart disease	Underlying non-coronary heart disease
Overweight	BMI: 25 – 29.9
Obesity °I	BMI: 30 – 34.9
Obesity °II/III	BMI ≥ 35
Left common ostium[#]	Presence of combined superior and inferior left pulmonary before anastomosing in the left atrium
Accessory pulmonary veins[#]	Presence of additional pulmonary veins

*Table 5: Explanations of baseline parameters; Rvol, regurgitant volume; RF, regurgitant fraction; EROA, effective regurgitant orifice area; *measured via transthoracic echocardiography, [#]measured via computed tomography angiography*

3.3.2 Procedural Data

Important data acquired during the entire cryoballoon ablation procedure are depicted in table 6.

Procedural parameter	Definition
Procedural time	The overall time from sheath insertion to sheath removal
LA time	Time with any catheter placed in the left atrium
Fluoroscopy time	Overall time of continuous x-ray application
Dose area product	Absorbed radiation multiplied by the irritated area

Table 6: Definitions of procedural parameters

3.3.3 Cardiac Computed Tomography Measurement Data

After sorting out every CCTA image with insufficient quality, all remaining images were retrospectively analysed, segmented, and measured with regards to the previously defined parameters using the electrophysiological workstation Ensite Precision™ (Abbott Medical GmbH, Eschborn, Germany). The investigator was blinded for the primary endpoint. Multiplan volume-rendered post-processing was used to create a 3D model. After anatomical segmentation into PV, LA, and LAA, all 2D and 3D measurements were realized.

LA related parameters included the LA volume, computed directly after segmentation excluding the LAA and PVs, the septum orifice distance and the distance of the mitral valve annulus to the LA roof. Further data comprised LA depth, the width of the LAA ridge and multiple measurements regarding each of the PVs. Those consisted out of all PV ostial diameters, perimeters and areas. On the posterior face of the LA parameters included the roof top and roof bottom lines the posterior wall box height and the trapezoid area of the posterior LA wall.

LAA related parameters consisted of the LAA volume, also calculated after anatomical segmentation, the maximal width, height and depth of the LAA as well as the ostial diameters, the ostial perimeter and ostial area of the LAA. Further evaluated measurements comprised the distance of the first bend, the angle of the first bend, the maximal LAA length and the number of LAA lobes. As a new measurement approach a fictive cuboid was introduced by the author, in the following also named “bounding box” using the maximal width, height and depth of the LAA. At last its maximal diagonal, respective angle α and sinus of the angle were computed.

All measurements are illustrated in figures 8, 9, 10, and 11.

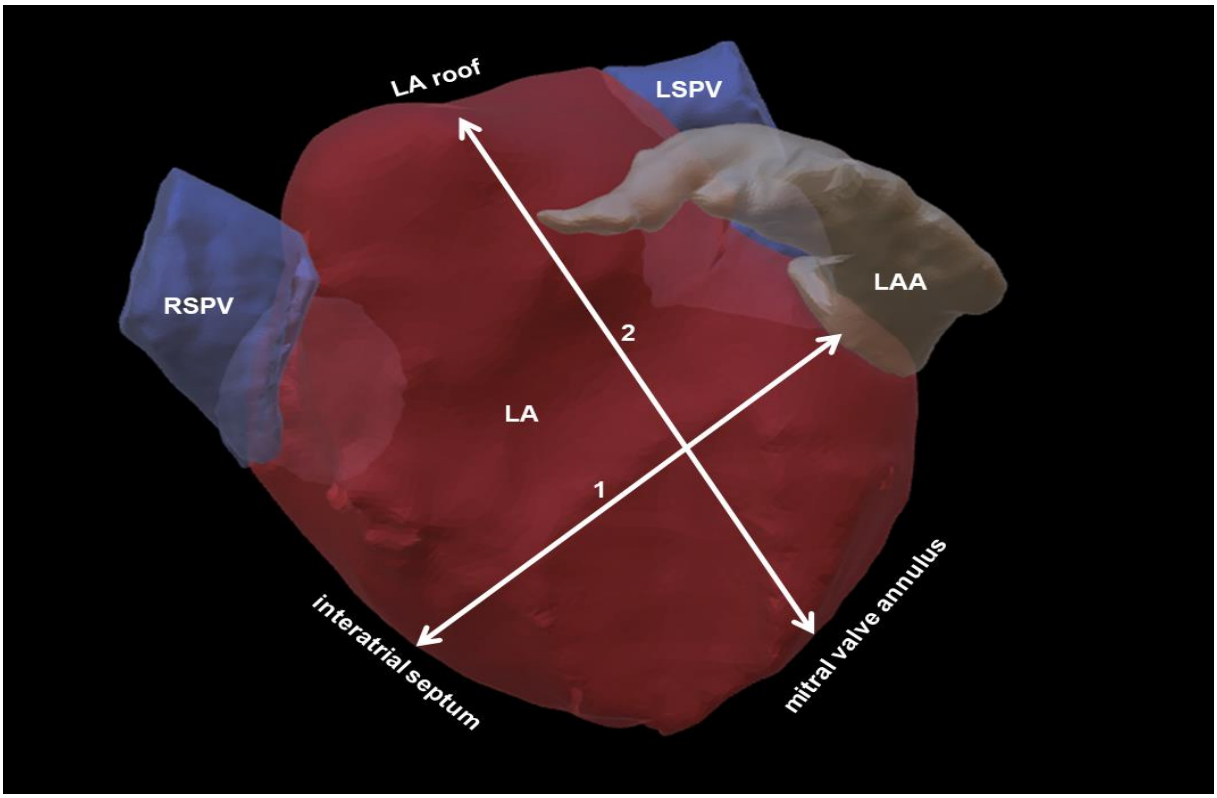

Figure 8: Left atrial measurements in anterior view. LA: left atrium; LAA left atrial appendage; LSPV: left superior pulmonary vein; RSPV: right superior pulmonary vein; 1: septum-orifice distance; 2: distance from the mitral valve annulus to the LA roof.

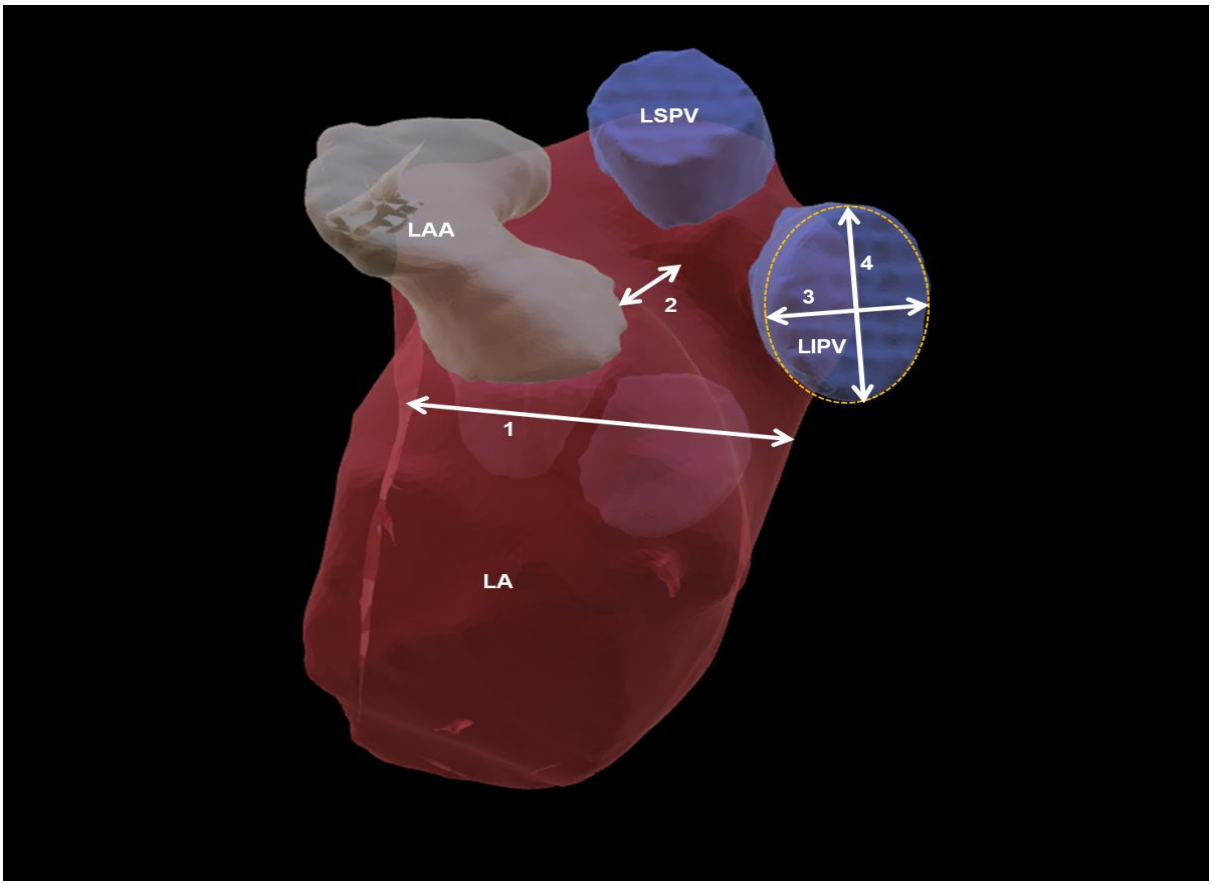

Figure 9: Left atrial measurements in left lateral view. LA: left atrium; LAA: left atrial appendage; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; 1: LA depth; 2: width of the LAA ridge; 3: maximal diameter of the left inferior pulmonary vein; 4: minimal diameter of the left inferior pulmonary vein.

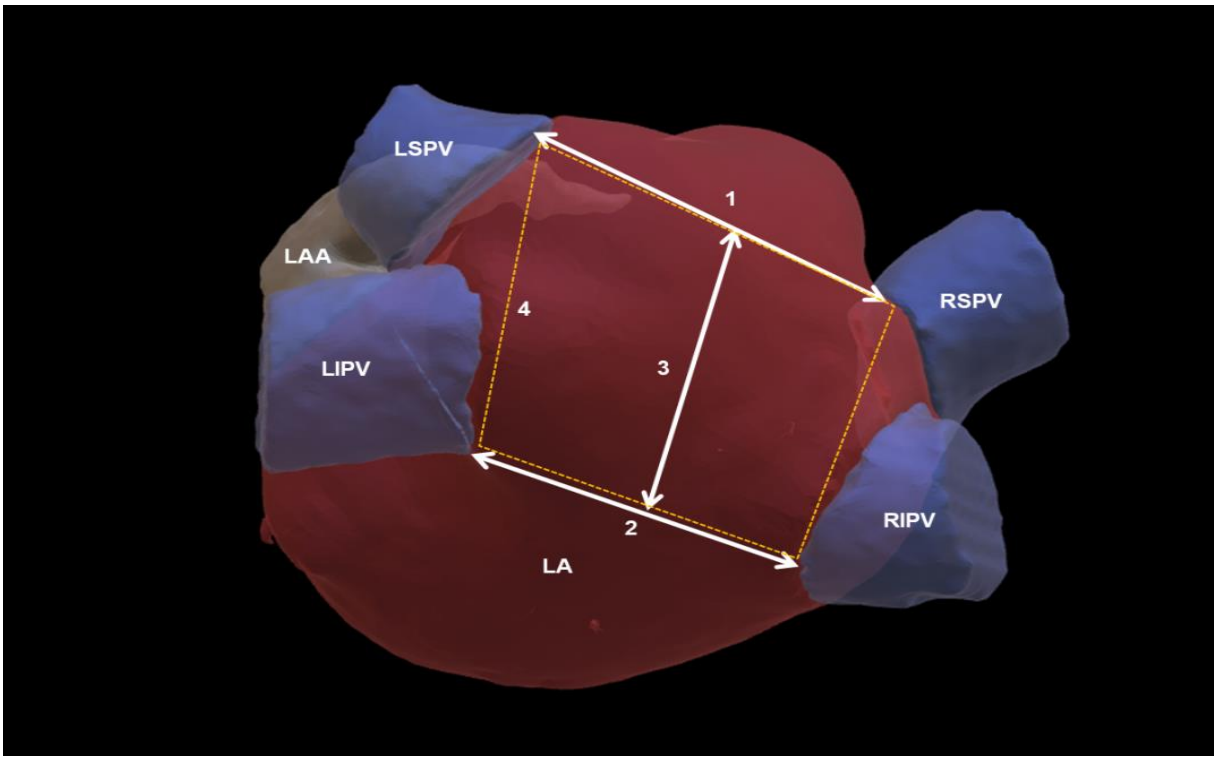

Figure 10: Left atrial measurements in posterior view. LA: left atrium; LAA: left atrial appendage; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; 1: roof top line; 2: roof bottom line; 3: posterior wall box height; 4: trapezoid area of the posterior left atrial wall.

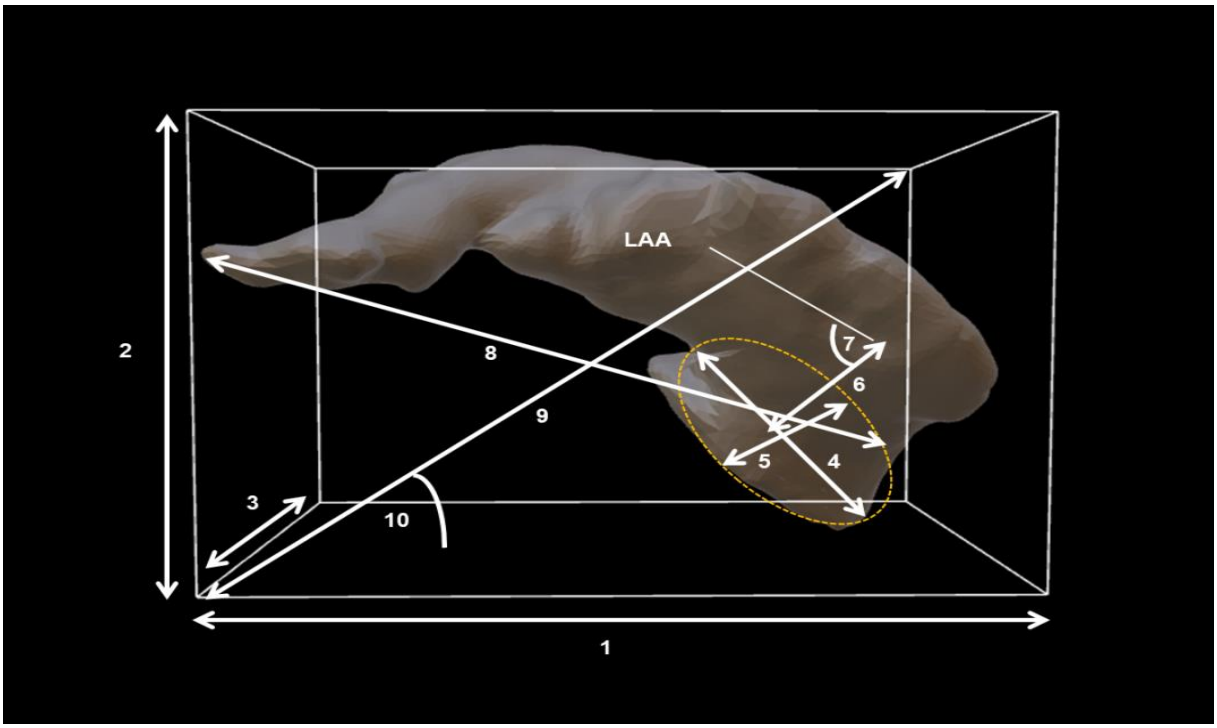

Figure 11: Left atrial appendage measurements in anterior view. LAA: left atrial appendage; 1: maximal LAA width; 2: maximal LAA height; 3: maximal LAA depth; 4: maximal ostial diameter of the LAA; 5: minimal ostial diameter of the LAA; 6: distance to the first bend; 7: angle of the first bend; 8: maximal LAA length; 9: LAA bounding box diagonal; 10: LAA bounding box angle α.

3.4 Morphological Classification of the Left Atrial Appendage

Based on the criteria established by Wang et al. [211] and Kimura et al. [213], the LAA was classified into one of four morphological types: windsock, chicken-wing, cactus, and cauliflower. After initial classification, there was a reassessment of all images in a team of four for objectification. Furthermore, inter-rater reliability was calculated. Figure 12 depicts the exact definition of the LAA with selected examples.

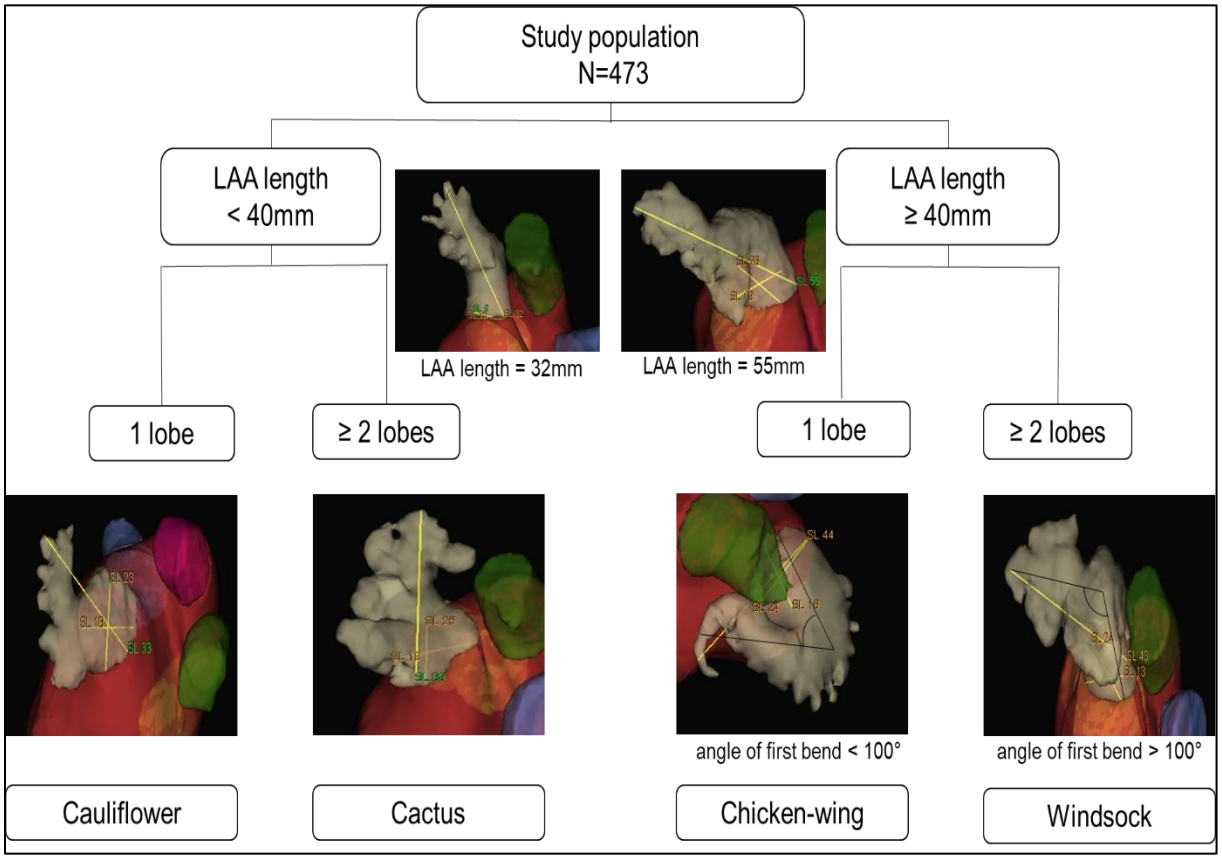

Figure 12: Classification of left atrial appendage morphology. According to the measured LAA length and number of lobes, LAA morphology was classified into one of four types: windsock, chicken-wing, cactus, and cauliflower.

3.5 Statistical Analysis

The statistical data analysis as well as the illustration of the results was performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). In the descriptive results all categorical data were illustrated as numbers and percentages and all continuous variables were expressed as means with standard deviations (SD) or as medians with quartiles in accordance to the Shapiro-Wilk test for normal distribution.

Identification of differences between two independent continuous variables was analysed either by the student T-test when normally distributed or via the Mann-Whitney U-Test when non-normally distributed. When comparing more than two independent parameters either the single factor variance analysis (ANOVA) was used when normally distributed or the Kruskal-Wallis test in case of non-normal distribution.

Univariate Cox Regression as well as Kaplan Meier plots with log-rank tests were applied to reveal relationships between all parameters and the recurrence of AF after CBA. Pearson's and Spearman's correlation coefficients were calculated to evaluate general correlations between all variables and to avoid problems concerning multicollinearity in multivariate models. A multivariate Cox Regression model was then used in a stepwise approach and main features with the highest univariate significance were included to determine independent risk factors. Parameters which highly correlated with these main features were eliminated. The resulting p-values, hazard-ratios and 95-% confidence intervals are listed below.

Subsequently, specific cut-off values were calculated by a receiver operating characteristic analysis (ROC) and depicted as Kaplan-Meier-plots.

Statistical significance was defined as $p \leq 0.05$.

4 RESULTS

4.1 Study Population

From May 2012 to September 2016, a total of 1,103 patients underwent initial AF ablation symptomatic paroxysmal or persistent AF. All patients underwent second generation CBA. In 725 (65.7%) patients CCTA was available, and 473 (42.9%) had sufficient image quality for LAA measurements. Only 196 (41.4%) patients had symptomatic persistent AF. Figure 13 represents a flow chart explaining the selection criteria.

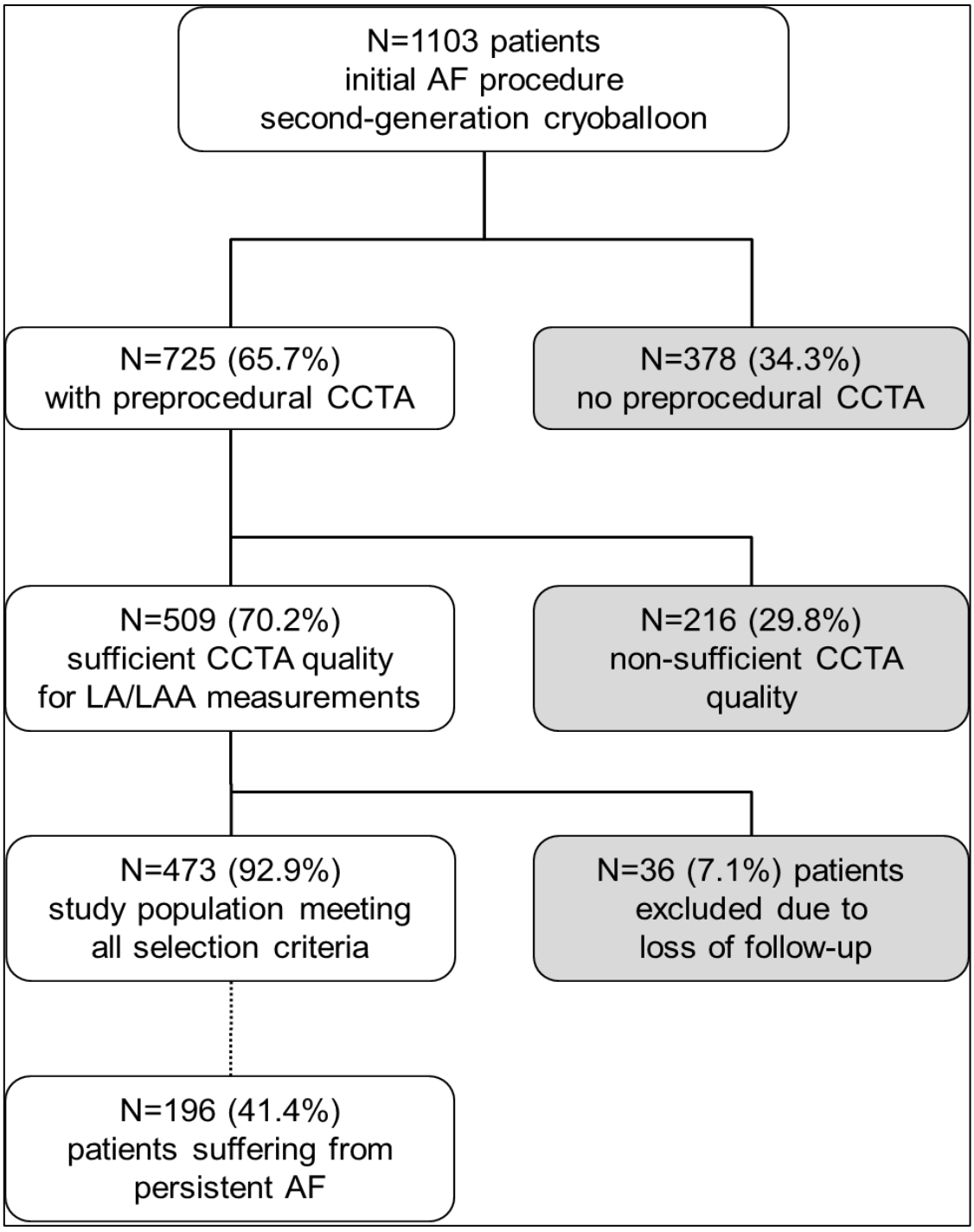

Figure 13: Study population – selection criteria. This flow chart explains the selection process of the study population. The top box shows the number of all patients included at the beginning. Each branching demonstrates one step of selection. The dotted line shows the additional cohort of all patients with symptomatic persistent AF.

The mean age of patients who underwent PVI was 66.2±9.5 years, with 189 (40%) females. The most common comorbidities included arterial hypertension (66.2%), hypertensive heart disease (21.8%) and structural heart disease (35.9%). Ischemic heart disease was only present in 13.3%, and 1.7% of the study population had suffered from a prior myocardial infarction. Cardiomyopathy was described in 16 (3.4%) patients. Baseline characteristics measured by echocardiography included the left atrial diameter with a median of 43mm [40; 47] and the left ventricular ejection fraction with a mean of 56.9±6.1%. Twenty-five (5.3%) patients presented a relevant valve disease ≥°II. Out of these, mitral valve regurgitation≥°II was the most common within 18 (3.8%) patients.

Frequently identified anatomical variations of pulmonary veins included a left common ostium in 101 (21.4%) patients and accessory pulmonary veins in 83 (17.5%) patients. All baseline characteristics of the study population are listed in Table 7.

Baseline Characteristics	n=473
Age, years	66.3±9.5
Females (%)	189 (40.0)
Height, cm	175±0.1
Weight, kg	80 (70.8; 90)
BMI, kg/m²	26.0 (23.5; 28.6)
Persistent AF	196 (41.4)
Mitral regurgitation ≥°II	18 (3.8)
Aortic stenosis ≥°II	3 (0.6)
Any Valve disease ≥°II	25 (5.3)
LA diameter mm	43 [40; 47]

Ejection fraction **(%)**	56.9±6.1
Hypertension	313 (66.2)
Hypertensive heart disease	103 (21.8)
Cardiomyopathy	16 (3.4)
Prior myocardial infarction	8 (1.7)
Ischemic heart disease	63 (13.3)
Structural heart disease	170 (35.9)
Overweight (BMI: 25 – 29.9)	206 (43.6)
Obesity (BMI: 30 – 34.9)	59 (12.5)
Obesity °II/III (BMI > 35)	25 (5.3)
Left common ostium[#]	101 (21.4)
Accessory veins[#]	72 (17.5)

Table 7: Baseline characteristics. [#]: assessed by the treating physician. n (%), Mean ± SD, or Median (IQR)

4.2 Procedural Results and Complications

All patients underwent cryoballoon PVI with complete isolation of all PVs. All PVs were successfully isolated with the cryoballoon. Out of all 473 patients, 300 (63.4%) patients were treated with 28mm cryoballoon, 77 (16.3%) patients were treated with 23mm cryoballoon and 96 (20.3%) patients were treated with both CB sizes. No additional RF or cryo-tip catheter ablations were performed. The median procedural time was 130 (110; 155) min with an LA time of 90 (75; 110) min. The fluoroscopy time was 22 (17; 27) min, and the median dose area product was 1,829 (1,044; 3,099) cGycm2. Procedural data are depicted in table 8.

Procedural results	
Procedural time, min	130 (110; 155)
LA time, min	90 (75; 110)
Fluoroscopy time, min	22 (17; 27)
Dose area product, $cGycm^2$	1829 (1044; 3099)

Table 8: Procedural results. LA: left atrial. Median (IQR).

Overall, in-hospital complication rate was 11.6%, with 10.8% minor and 0.8% major complications. Most common minor adverse events included phrenic nerve injury with 7.2%, puncture side hematoma with 0.8% and pericardial effusion (no drainage) with 0.8%. Phrenic nerve injury occurred after a mean ablation time of 124.1±69.6 seconds. Phrenic nerve palsy was transient in most patients and subsided before discharge. Most important major in-hospital complications comprised AV-fistula with 0.4%, transient monocular vision loss with 0.2% and symptomatic gastroparesis with 0.2%.

All complications are depicted in table 9.

In-hospital complications	n=473
Minor in-hospital complications	51 (10.8)
Phrenic nerve injury	34 (7.2)
Pericardial effusion	1 (0.2)
Pericardial effusion (no drainage)	4 (0.8)
Puncture site hematoma (conservative)	4 (0.8)
Urinary tract infection	2 (0.4)
Puncture site oozing	1 (0.2)
Groin aneurysm (conservative)	1 (0.2)
Gross haematuria	1 (0.2)
Oesophageal ulcer	1 (0.2)
Respiratory tract infection	1 (0.2)
Bronchitis	1 (0.2)
Major in-hospital complications	4 (0.8)
AV-Fistula (requiring intervention/surgery)	2 (0.4)
Transient monocular vision loss	1 (0.2)
Gastroparesis	1 (0.2)

Table 9: In-hospital complications. n (%), Mean ± SD.

4.3 Long-term Outcome Results

The overall median follow-up time for the study was 19 (15; 28) months. More than a third of the patients (166; 35.1%) experienced atrial arrhythmia recurrence. In those patients the median time until recurrence was 18 (12; 26) months. After a complete follow-up of 12 months approximately 80% of patients were free from AF including a 90-day blanking period.

Follow-Up Data	
Follow-Up time, months	19 (15; 28)
Atrial fibrillation recurrence	166 (35.1)
Time until AF recurrence, months	18 (12; 26)

Table 10: Follow-Up Data. n (%), Median (IQR).

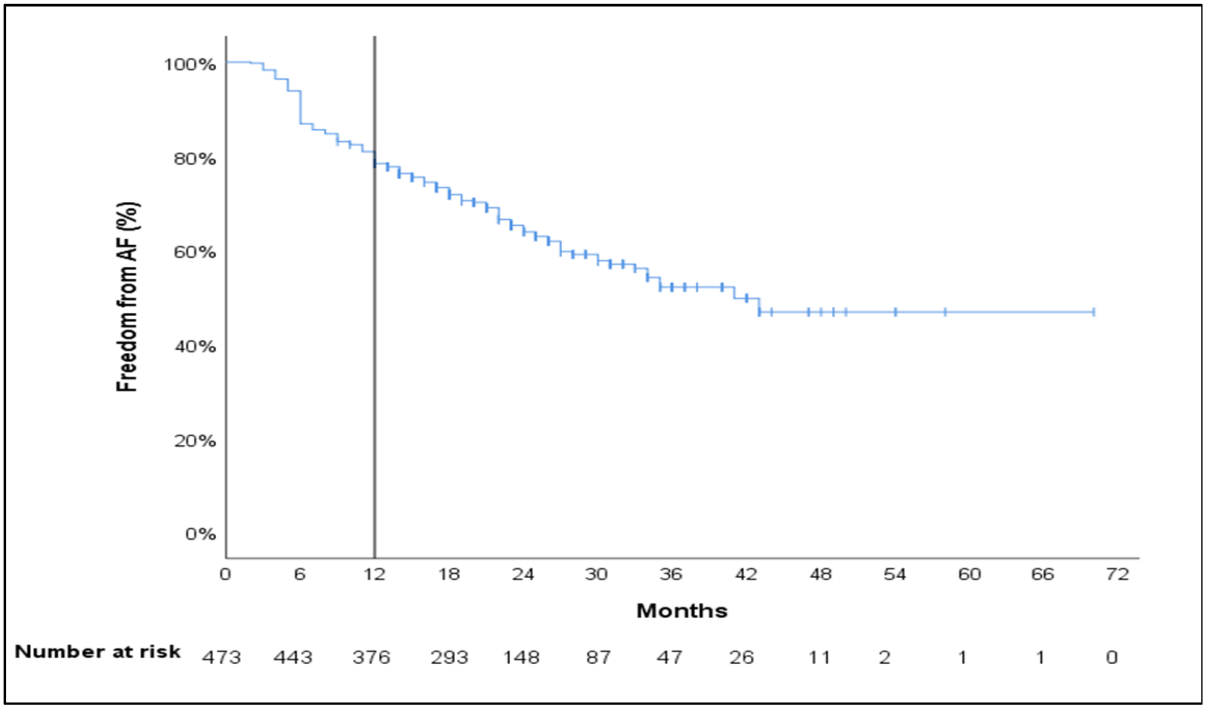

Figure 144: Kaplan-Meier-Plot regarding AF recurrence and the overall follow-up time. The black vertical line depicts the percentage of AF recurrence (approximately 80%) at 12 months follow-up.

4.4 Results of Cardiac Computed Tomography Measurements

Important measurement data included: the LA and LAA volume with a median size of 115.1 (97.2; 135.2) mL and 8.7 mL (6.5; 11.6), the septum orifice distance with a median value of 58 (54; 61) mm, the trapezoid area of the posterior left atrial wall with a median value of 12.1 (10.3; 14.2) cm^2, the roof top and roof bottom lines with median distances of 35 (31; 41) mm and 42 (37; 46) mm, the distance from the mitral valve annulus to the left atrial roof with a median value of 69 (65; 74) mm, the depth of the LA with a mean distance of 38.5±5.9 mm and multiple ostial left atrial appendage parameters.

LA CCTA Measurements	
LA volume, mL	115.1 (97.2; 135.2)
Septum orifice distance, mm	58 (54; 61)
Distance from the MVA to the LA roof, mm	69 (65; 74)
LA depth, mm	38.5±5.9
Width of the LAA ridge, mm	4 (3; 5)
PV Measurements	
LSPV maximal ostial diameter, mm	21 (19; 23)
LSPV minimal ostial diameter, mm	14 (12; 16)
LSPV ostial perimeter, mm	56 (52; 61.6)
LSPV ostial area, cm^2	2.3 (1.9; 2.9)
LIPV maximal ostial diameter, mm	17 (16; 19)
LIPV minimal ostial diameter, mm	13 (11; 15)
LIPV ostial perimeter, mm	48.5 (43.4; 53.6)
LIPV ostial area, cm^2	1.8 (1.4; 2.3)

RIPV maximal ostial diameter, mm	18 (16; 20)
RIPV minimal ostial diameter, mm	15 (13; 17)
RIPV ostial perimeter, mm	52.3 (47.1; 59)
RIPV ostial area, cm^2	2.1 (1.7; 2.7)
RSPV maximal ostial diameter, mm	21 (19; 24)
RSPV minimal ostial diameter, mm	17 (14; 19)
RSPV ostial perimeter, mm	60.2 (53.8; 66.5)
RSPV ostial area, cm^2	2.8 (2.2; 3.4)
LCO maximal ostial diameter, mm	30.5±4.3
LCO minimal ostial diameter, mm	17.7±4.2
LCO ostial perimeter, mm	75.9 (69.1; 88)
LCO ostial area, cm^2	3.9 (3.3; 5.4)
RMPV maximal ostial diameter, mm	9.5 (6; 12.3)
RMPV minimal ostial diameter, mm	5.5 (4; 7.8)
RMPV ostial perimeter, mm	30 (23.3; 41)
RMPV ostial area, cm^2	70.3 (43; 124.3)
Roof top line, mm	35 (31; 41)
Roof bottom line, mm	42 (37; 46)
Posterior wall box height, mm	32 (29; 35)
Trapezoid area of the posterior LA wall, cm^2	12.05 (10.32; 14.23)

Table 11: LA CCTA Measurement Data. LA: left atrium; MVA: mitral valve annulus; LAA: left atrial appendage; PV: pulmonary veins; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; LCO: left common ostium; RMPV: right middle pulmonary vein. Mean ± SD, or Median (IQR).

CCTA LAA Measurements	
LAA volume, mL	8.7 (6.5; 11.6)
LAA maximal width, mm	37.4±6.7
LAA maximal height, mm	26.8 (22.8; 30.9)
LAA maximal depth, mm	39.9±8.7
LAA maximal ostial diameter, mm	25 (22; 28)
LAA minimal ostial diameter, mm	18 (15; 20)
LAA ostial perimeter, mm	67.9±12.2
LAA ostial area, cm^2	3.4 (2.7; 4.3)
Distance of the first bend, mm	12 (10.3; 14)
Angle of the first bend, degree	98 (95; 115)
Maximal LAA length, mm	44.4±7.8
Number of LAA lobes	2 (1; 2)
Bounding Box volume, mL	38.4 (28.6; 52.5)
Bounding Box diagonal, mm	61.6±9.2
Bounding Box diagonal angle α, degree	23.9 (21.4; 27.1)
Bounding Box sinus of α	0.42 (0.37; 0.47)

Table 12: LAA Measurement Data. LAA: left atrial appendage. Mean ± SD, or Median (IQR).

4.5 Left Atrial Appendage Morphology Findings and Modification of Classification Criteria

Among all patients, windsock morphology was the most common type with 51.6%, followed by chicken-wing with 20.7%, cauliflower with 15.2% and cactus with 12.5%. These results were validated by a reassessment session with four reviewers. According to Landis and Koch the calculated inter-rater reliability (kappa) showed a substantial agreement (Cohen`s Kappa = 0.69; $p<0.001$).

To evaluate volumetric differences between the four different morphological types we compared the LAA and LA volumes for each type against all other types. Chicken-wing morphology had the largest volumes overall, with an LAA volume of 9.9 (7.9; 12.8) mL and an LA volume of 122.8 (103.6; 149.1) mL. It was followed by windsock morphology with an LAA volume of 9.7 (7.7; 13.1) mL and an LA volume of 117.9 (101.6; 132.2) mL. Cactus and cauliflower morphologies were considerably smaller, with LAA volumes of 5.4 (4.6; 7.5) mL and 5.6 (4.4; 7.6) mL and LA volumes of 102.4 (84.7; 118.1) mL and 103.7 (88.5; 122.6) mL. Tests on differences between the four types regarding LAA and LA volume showed high statistical significance ($p<0.001$). Figure 15 illustrates LAA and LA volumetric differences of each morphological LAA type.

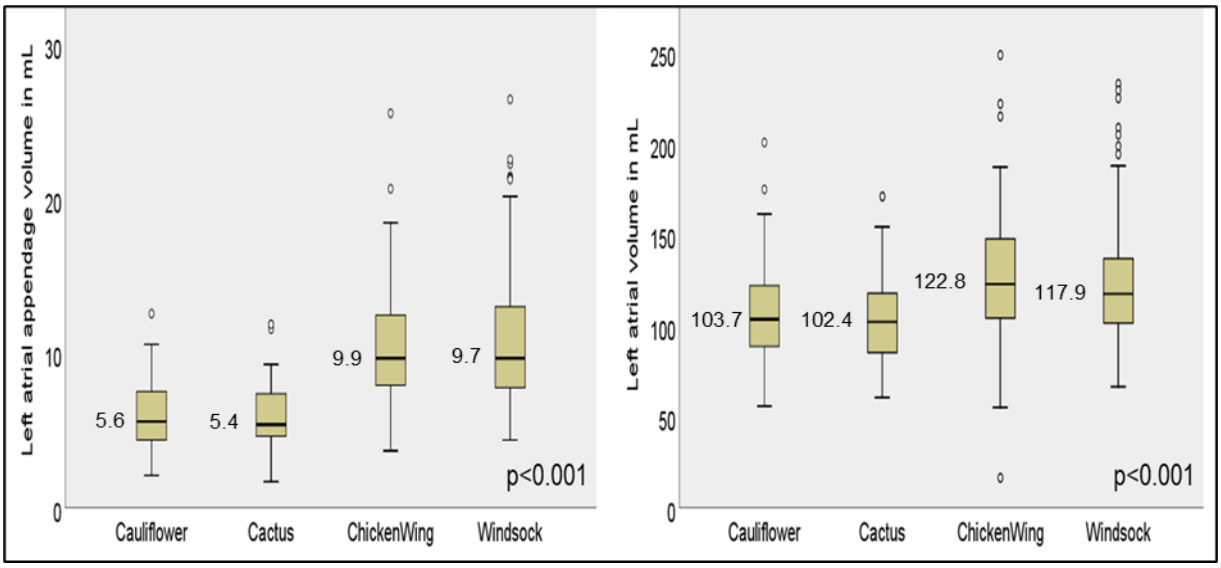

Figure 155: Box-Plots to show volumetric differences of each LAA type. Each box illustrates the range of either LA or LAA volume regarding the respective LAA type. The median volume is depicted as the small number beside each box. There exists a statistically significant difference in volumetric measures between the four LAA types. As each measurement is distributed non-normally the Kruskal-Wallis test was used.

As the study also aimed for improvement of the current classification system, a new bounding box approach was applied. Its parameters were identified as possible candidates for objectification. Especially differentiation between cactus and cauliflower type is difficult, which is why the study focused primarily to improve distinction between those types. Nevertheless, it also aimed to objectify classification of windsock and chicken wing type. Most significant parameters to differentiate between cactus and cauliflower morphology included: the maximal LAA depth and the angle α as well as the respective sinus of the bounding box. Mean maximal LAA depth for cauliflower was 30.42±5.0 mm and 33.4±4.3mm for cactus ($p<0.001$). Mean sinus of the bounding box was 0.48±0.08 for cauliflower and 0.44±0.07 for cactus ($p<0.05$). Figure 16 depicts the most important differences.

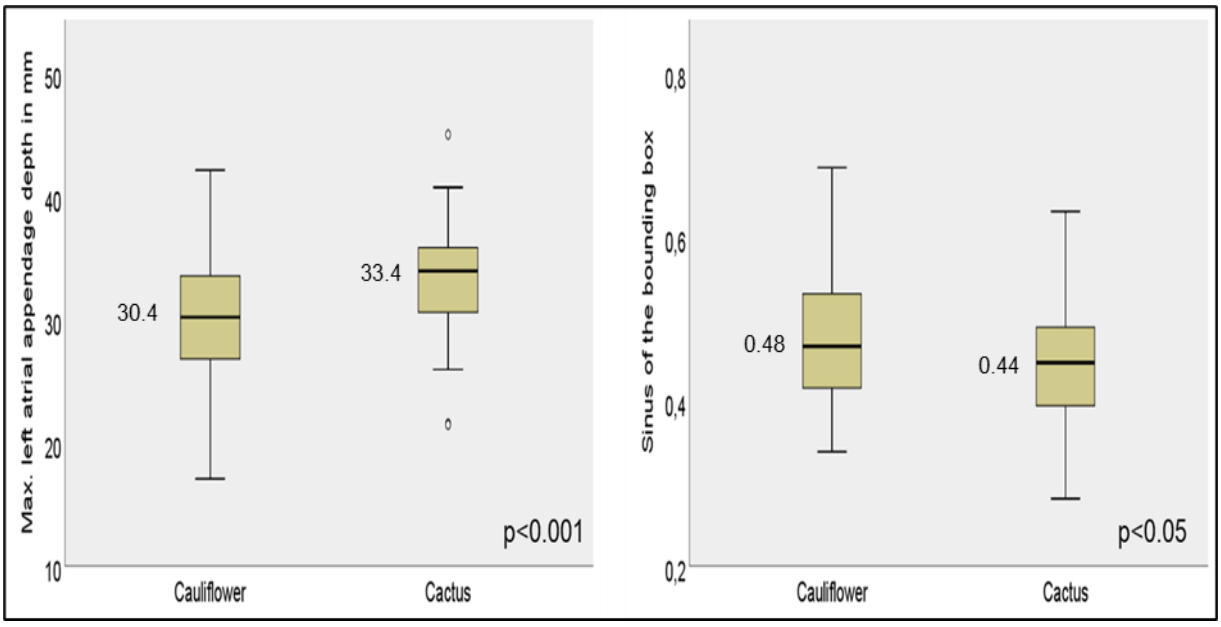

Figure 166: Box-Plots regarding differences between cactus and cauliflower LAA-type. This figure demonstrates two statistical relevant differences: the maximal left atrial appendage depth as well as the sinus of the bounding box. As both measurements are distributed normally the small numbers beside each box illustrate the respective mean and were analysed with the student t-test.

Major parameters to compare windsock and chicken wing also consisted of the maximal LAA depth and the angle α as well as the respective sinus of the bounding box. Mean maximal LAA depth was 44.3±7.1 mm for windsock and 40.1±8.6 mm for chicken-wing ($p<0.001$). Mean sinus of the bounding box was 0.40±0.06 for windsock and 0.44±0.08 for chicken wing ($p<0.001$). All important differences are illustrated in figure 17.

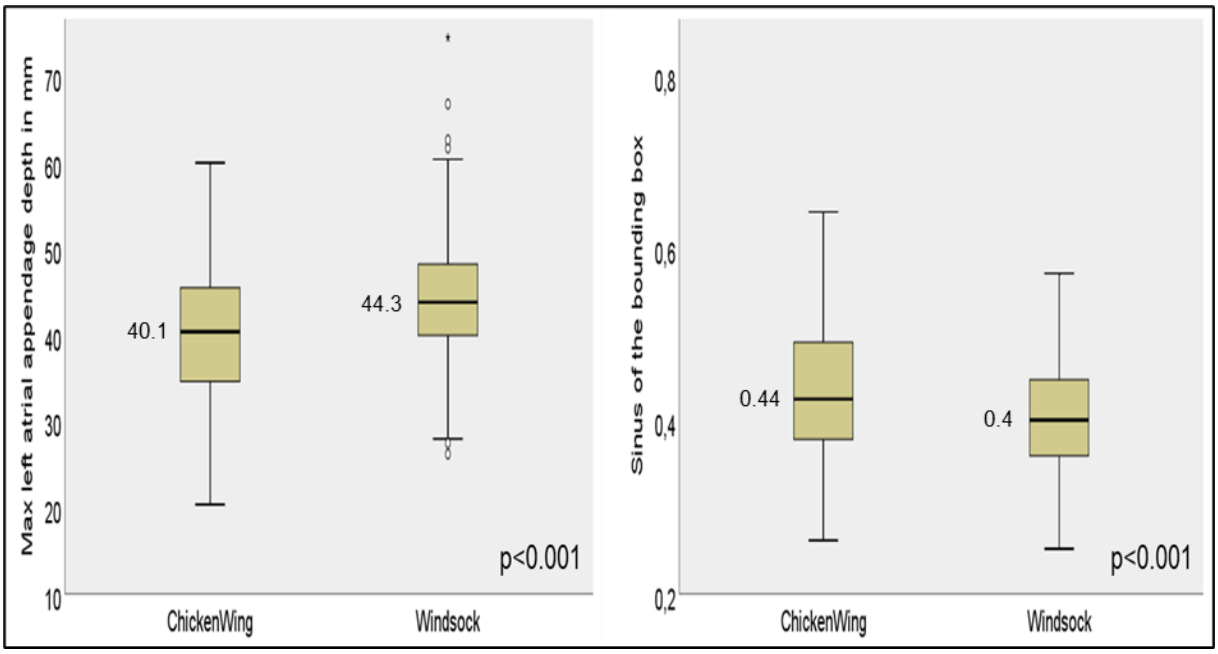

Figure 177: Box-Plots demonstrate differences between chicken-wing and windsock LAA-type. This figure illustrated that the same two measures that help to differentiate between cactus and cauliflower LAA type can also help to differentiate between chicken-wing and cactus LAA type: the maximal left atrial appendage depth and the sinus of the bounding box. Both measurements were evaluated with the student t-test as they are normally distributed. The numbers next to each box represent the respective mean.

4.6 Univariate Analysis and Predictors of Atrial Fibrillation Recurrence

Univariate predictor analysis for baseline characteristics, procedural results, complications, CCTA data and LAA morphological types was performed using a Cox-regression model. The time component was defined as the freedom of atrial fibrillation.

4.6.1 Baseline Parameters as Predictors

Regarding baseline parameters most important factors predicting AF recurrence included: the left atrial diameter, mitral regurgitation ≥°II, presence of persistent AF, overall valve disease ≥°II, weight, height and the presence of structural heart disease. The results (p-value, hazard ratio and 95%-confidence interval) of the univariate Cox Regression analysis of baseline characteristics regarding AF recurrence are illustrated in table 13 in more detail.

Baseline Characteristics	HR	95%-CI	p-value
Age, years	1.02	1.000 - 1.034	0.05
Females (%)	1.31	0.966 - 1.784	0.08
Height, cm	0.13	0.024 - 0.737	0.021
Weight, kg	0,98	0.975 - 0.998	0.017
BMI, kg/m²	0.98	0.944 - 1.016	0.265
Persistent AF	1.54	1.140 - 2.090	0.006
Mitral regurgitation ≥°II	2.50	1.311 - 4.752	0.005
Valve disease ≥°II	2.18	1.231 - 3.849	0.007
LA diameter, mm	1.04	1.015 - 1.060	0.002
Ejection fraction (%)	0.98	0.959 - 1.002	0.07
Hypertension	1.12	0.803 - 1.551	0.51

Hypertensive heart disease	1.34	0.946 - 1.900	0.10
Cardiomyopathy	0.47	0.151 - 1.482	0.20
Prior myocardial infarction	1.02	0.323 - 3.188	0.98
Ischemic heart disease	1.14	0.734 - 1.772	0.56
Structural heart disease	1.38	1.012 - 1.878	0.04
Overweight (BMI: 25 – 29.9)	0.81	0.578 - 1.147	0.24
Obesity (BMI: 30 – 34.9)	0.75	0.472 - 1.199	0.23
Obesity °II/III (BMI > 35)	1.18	0.601 - 2.327	0.63
Left common ostium	1.04	0.722 - 1.501	0.83
Accessory veins	1.44	0.995 - 2.068	0.05

Table 13: Results of Cox regression analysis regarding baseline characteristics. This table shows the previously descriptively depicted baseline characteristics and their respective hazard ratios, confidence intervals as well as p-values with regards to the time until AF recurrence as well as the rate of recurrence after cryoballoon ablation. It could be shown that especially the persistent AF type, mitral regurgitation ≥°II and the LA diameter measured with transthoracic echocardiography had a high significant impact on the recurrence of atrial fibrillation after CBA.

4.6.2 Procedure Times, Complications and Outcome

There were no predictors revealed by the analysis of the procedural results. Exact values are depicted in table 14 below.

Procedural results	HR	95%-CI	p-value
Procedural time, min	1.00	0.997 - 1.003	0.82
LA time, min	1.00	0.993 - 1.004	0.66
Fluoroscopy time, min	1.00	0.986 - 1.021	0.69
Dose area product, cGycm^2	1.00	1.000 - 1.000	0.98

Table 14: Results of Cox regression analysis regarding procedural results. Procedural data could not be identified as relevant predictors with regards to AF recurrence after cryoballoon ablation.

In-hospital complication analysis could not identify any predictors with high significance besides the presence of AV-fistula with p=0.003. It is important to mention that there were only two patients suffering from fistula as a complication. Complications that represented only one event were not calculated.

In-hospital complications	HR	95%-CI	p-value
Minor in-hospital complications	0.92	0.570 - 1.483	0.73
Phrenic nerve palsy	0.84	0.444 - 1.598	0.60
Puncture site oozing	2.57	0.359 - 18.406	0.35
Pericardial effusion	1.64	0.407 - 6.634	0.49
Puncture site hematoma	2.62	0.833 - 8.215	0.10
Urinary tract infection	0.90	0.125 - 6.402	0.91
Major in-hospital complications	0.51	0.163 - 1.603	0.26

AV Fistula	8.28	2.038 - 33.606	0.003
Time until phrenic nerve palsy, s	1.00	0.994 - 1.004	0.72

Table 15: Results of Cox regression analysis regarding in-hospital complications. Besides arteriovenous fistula no other predictor for AF recurrence was identified after cryoballoon ablation regarding in-hospital complications.

4.6.3 Cardiac Computed Tomography Angiography Data and Outcome

LA and LAA measurement data analysis showed four highly significant parameters that predicted AF recurrence, with LA volume in mL demonstrating the most statistically significant impact (HR 1.01; 95% CI [1.006-1.015]; p<0.000001). For LA volume, CCTA accuracy is also higher than that of previously described echocardiographic measurement [217] and showed a higher significance (HR 1.04; 95% CI [1.015-1.060]; p=0.001). The second most important parameter was the septum orifice distance (HR 1.053; 95% CI [1.028-1.08]; p<0.001), followed by the trapezoid area of the posterior left atrial wall (HR 1.001; 95% CI [1-1.001]; p<0.001), and the left atrial appendage volume (HR 1.051; 95% CI [1.025-1.078]; p<0.001). All LA and LAA measurements are listed in Table 16 and 17.

LA measurement data	HR	95%-CI	p-value
LA volume, mL	1.01	1.006 - 1.015	<0.000001
Septum orifice distance, mm	1.05	1.028 - 1.080	<0.0001
Distance from MVA to LA roof, mm	1.04	1.014 - 1.064	0.002
LA depth, mm	1.04	1.013 - 1.067	0.003
Width of the LAA ridge, mm	1.03	0.968 - 1.087	0.39
PV Measurements			
LSPV max ostial diam, mm	1.01	0,955 - 1.071	0.70

LSPV min ostial diam, mm	1.04	0.985 - 1.095	0.16
LSPV ostial perimeter, mm	1.01	0.988 - 1.031	0.38
LSPV ostial area, cm^2	1.01	0.999 - 1.010	0.90
LIPV max ostial diam, mm	1.06	0,999 - 1.116	0.05
LIPV min ostial diam, mm	1.06	0.999 - 1.117	0.05
LIPV ostial perimeter, mm	1.02	1.001 - 1.042	0.044
LIPV ostial area, cm^2	1.06	0.999 - 1.220	0.43
RIPV max ostial diam, mm	1.02	0.971 - 1.064	0.48
RIPV min ostial diam, mm	1.02	0.973 - 1.075	0.38
RIPV ostial perimeter, mm	1.01	0.990 - 1.022	0.48
RIPV ostial area, cm^2	1.05	0.999 - 1.230	0.59
RSPV max ostial diam, mm	1.01	0.970 - 1.056	0.58
RSPV min ostial diam, mm	1.03	0.979 - 1.075	0.29
RSPV ostial perimeter, mm	1.01	0.991 - 1.022	0.45
RSPV ostial area, cm^2	1.07	0.999 - 1.223	0.36
LCO max ostial diam, mm	1.04	0.970 - 1.118	0.26
LCO min ostial diam, mm	1.02	0.943 - 1.108	0.59
LCO ostial perimeter, mm	1.02	0.988 - 1.044	0.27
LCO ostial area, cm^2	1.10	0.999 - 1.325	0.36
RMPV maximal ostial diameter, mm	0.99	0.859 - 1.132	0.84
RMPV minimal ostial diameter, mm	0.95	0.790 - 1.140	0.58
RMPV ostial perimeter, mm	1.11	0.968 - 1.071	0.48
RMPV ostial area, cm^2	0.96	0.914 - 1.005	0.08
Roof top line, mm	1.03	1.013 - 1.050	0.001

Roof bottom line, mm	1.03	1.012 - 1.054	0.002
Posterior wall box height, mm	1.03	1.003 - 1.065	0.031
Trapezoid area of the post. LA wall, cm^2	1.08	1.040 - 1.100	<0,0001

Table 16: Results of Cox regression analysis regarding LA measurement data. LA: left atrium; MVA: mitral valve annulus; LAA: left atrial appendage; PV: pulmonary veins; max: maximal; min: minimal; LSPV: left superior PV; LIPV: left inferior PV; RSPV: right superior PV; RIPV: right inferior PV; LCO: left common ostium; RMPV: right middle pulmonary vein. This table illustrates all LA measurement parameters with regards to AF recurrence after cryoballoon ablation. It could be shown that especially LA volume as well as all its associated dimensions like LA depth or the septum orifice distance had a significant impact on the recurrence after cryoballoon ablation. All parameters were analysed with univariate Cox regression.

LAA measurement data	HR	95%-CI	p-value
LAA volume, mL	1.05	1.025 - 1.078	<0.0001
LAA maximal width, mm	1.03	1.003 - 1.049	0.029
LAA maximal height, mm	1.02	0.990 - 1.044	0.22
LAA maximal depth, mm	1.02	1.000 - 1.036	0.047
LAA maximal ostial diameter, mm	1.06	1.021 - 1.107	0.003
LAA minimal ostial diameter, mm	1.02	1.006 - 1.032	0.004
LAA ostial perimeter, mm	1.04	1.008 - 1.078	0.015
LAA ostial area, cm^2	1.20	1.100 - 1.300	0.001
Distance of the first bend, mm	1.02	0.967 - 1.060	0.61
Angle of the first bend, degree	0.99	0.988 - 1.001	0.11
Maximal LAA length, mm	1.02	1,002 - 1.041	0.03

Number of LAA lobes	0,89	0.670 - 1.171	0.40
Bounding Box volume, mL	1,01	1.003 - 1.017	0.008
Bounding Box diagonal, mm	1.02	1.005 - 1.039	0.01
Bounding Box diagonal angle α, °	0.99	0.952 - 1.023	0.48
Bounding Box sinus of α	0.47	0.059 - 3.743	0.48

Table 17: Results of Cox regression analysis regarding LAA measurement data. LAA: left atrial appendage. This table demonstrates the impact of all LAA measurement data regarding AF recurrence after cryoballoon ablation. It could be shown that LAA volume has a highly significant impact on AF recurrence.

4.6.4 Left Atrial Appendage Morphology and Outcome

Among all 166 recurrence events, chicken-wing morphology had the highest chance of recurrence with a HR of 1.13, followed by windsock with 1.09, cauliflower with 0.94 and cactus with 0.73. Nevertheless, neither of these morphological types was found to have a statistically significant impact on the AF recurrence rate (p=0.596). Results are depicted in table 18 and figure 18.

LAA morphology	HR	95%-CI	p-value
Chicken-Wing	1.13	0.781 - 1.624	0.52
Winsock	1.09	0.802 - 1.476	0.59
Cactus	0.73	0.440 - 1.201	0.21
Cauliflower	0.94	0.604 - 1.459	0.78

Table 18: Results of Cox regression analysis regarding LAA morphology. LAA morphological types could not be identified as significant parameters regarding AF recurrence after cryoballoon ablation.

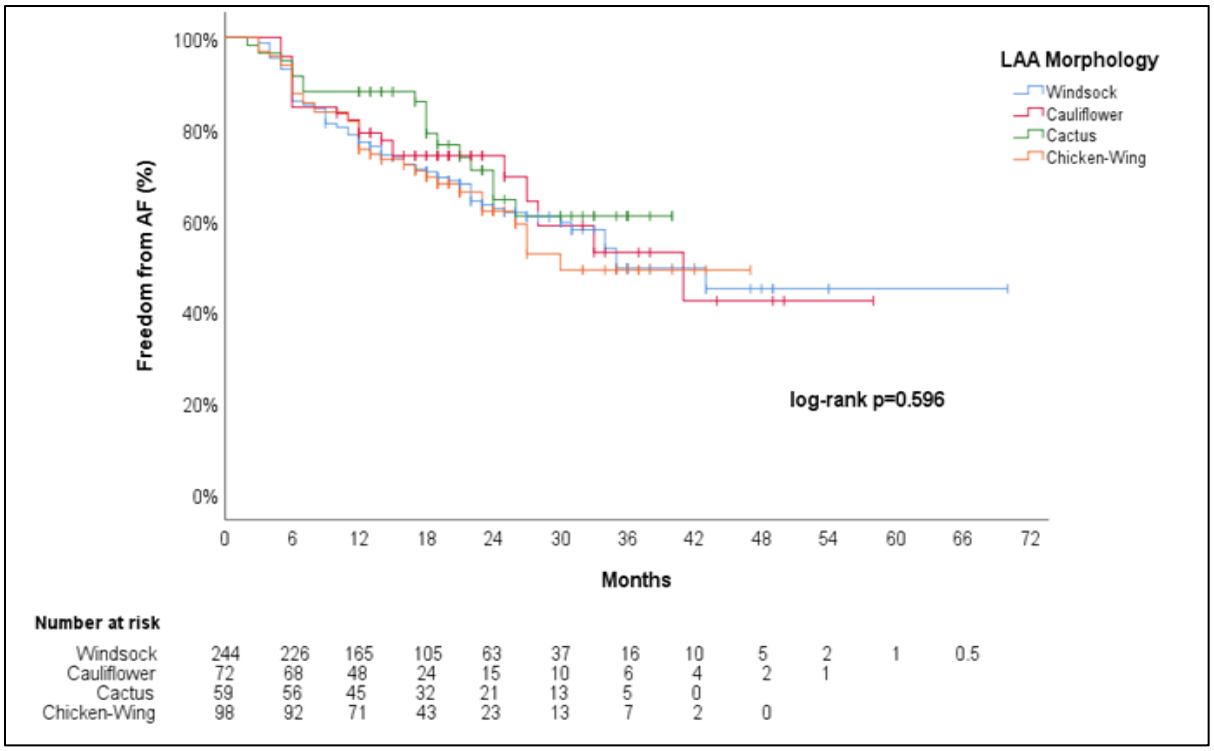

Figure 188: Kaplan-Meier-Plot for left atrial appendage morphologies and AF recurrence. AF: atrial fibrillation, LAA: left atrial appendage. LAA morphology showed no statistical impact on the recurrence rate of AF after cryoballoon ablation. The log-rank test was used to calculate the respective p-value.

4.7 Intervariable Correlations

Prior to multivariate analysis correlation analysis was performed to avoid problems of multicollinearity and to include the best possible parameters. Therefore, the statistically significant measurement data, baseline characteristics and the LAA morphological types were correlated according to Pearson and Spearman.

As the LA diameter measured in echocardiography did strongly correlate to LA volume (0.53; p<0.001) and showed to be an inferior univariate predictor for AF recurrence as compared to LA volume, it was excluded for multivariate analysis. Also, the presence of valve disease ≥°II was excluded because of its strong correlation to mitral regurgitation ≥°II (0.84; p<0.001) and its inferior prediction ability. Mitral regurgitation ≥°II showed weak correlations to LA volume (0.09; p=0.04) and stronger correlations to structural heart disease (0.27; p<0.001 and presence of persistent AF (0.12; p=0.007). The presence of persistent AF strongly correlated to LA volume (0.27; p<0.001) and mitral regurgitation ≥°II (0.12; p=0.007) and demonstrated weak correlations to the presence of structural heart disease (0.10; p=0.02). Height correlated strongly to LA volume (0.14; p=0.003) and weight (0.51; p<0.003), whereas LA volume was negatively correlated to sex (-0.73; p<0.001) and age (-0.37; p<0.001). Weight correlated to arterial hypertension (0.11; p=0.03) and hypertensive heart disease (0.13; p=0.01) and did correlate strongly to height as well as negatively to sex (-0.43; p<0.001) and age (-0.30; p<0.001). Structural heart disease showed strong correlation to LA volume (0.17; p<0.001), mitral regurgitation and age (0.18; p<0.001). It can be stated that LA volume did significantly correlate to mitral regurgitation, type of AF, sex (-0.2; 0<0.001), age (0.14; p=0.003), height and structural heart disease.

As expected, all CCTA measurement data that related logically to the LA volume, such as the septum orifice distance (0.71, p<0.001), the trapezoid area of posterior left atrial

wall (0.61; p<0.001) as well as the depth of the LA (0.72, p<0.001) showed significant positive correlations.

Interestingly a significant correlation was revealed between LA volume and LAA volume (0.52; p<0.001) and its companion parameters such as the area of the LAA ostium (0.54; p<0.001) or the bounding box volume (0.41, p<0.001). To quantify the correlation of LA volume with LAA volume, linear regression analysis demonstrated that the LAA volume increased by 0.70 mL per 10 mL increase in LA volume (p<0.001). Figure 19 illustrates this relationship.

As LA volume was statistically the best parameter for predicting AF recurrence it can be concluded that multivariate analysis should not include any other measurement parameters as they are all correlated.

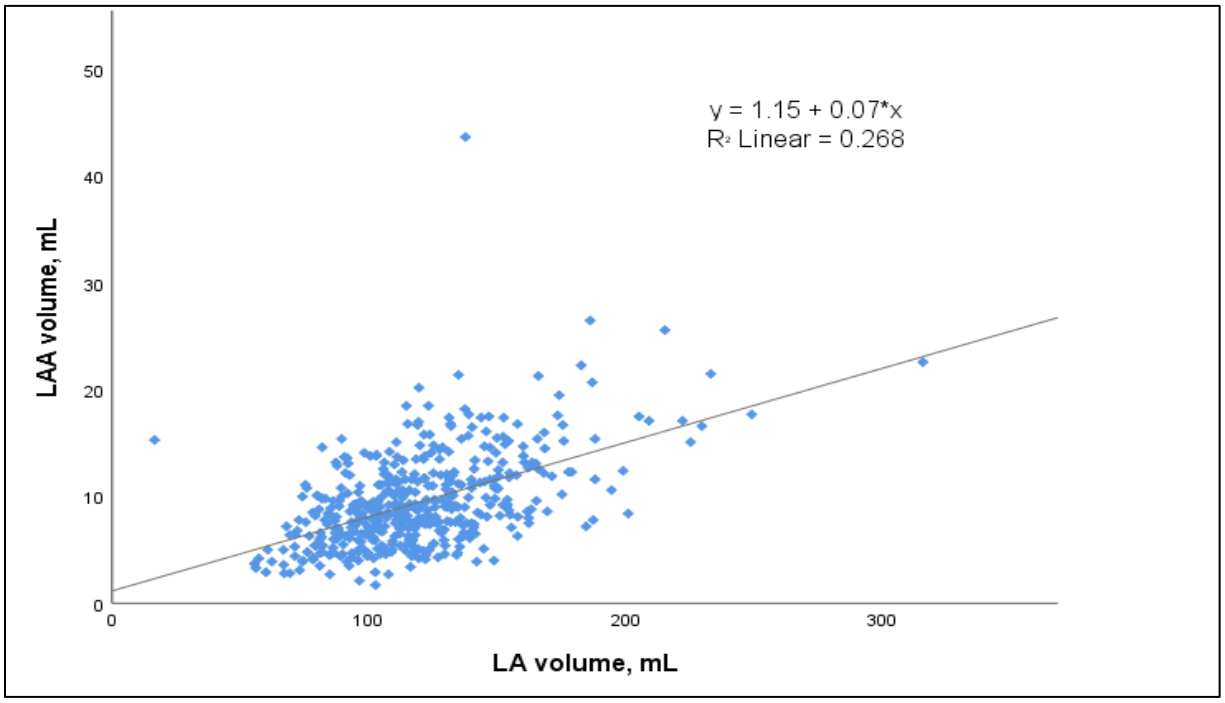

Figure 199: Linear regression analysis between LA volume and LAA volume. The figure shows a linear regression model of LAA volume and LA volume. It demonstrates that per 10 mL increase of LA volume, LAA volume increases by 0.7 mL. The significance level of the model was p<0.001.

4.8 Independent Predictors of Atrial Fibrillation Recurrence

Multivariate Cox regression analysis was performed considering all previously identified risk factors and intervariable correlations. The model revealed three main statistically independent risk factors for AF recurrence: the left atrial volume (p<0.001), the presence of mitral regurgitation ≥°II (p=0.013) and female sex (p=0.002). Mean age of female patients was 69.7±7.8 years, which was higher than that of the males at 63.94±9.8 years. The exact values are illustrated in Table 19.

Multivariate Analysis	HR	95%-CI	p-value
Female Sex	1.65	1.196 - 2.271	0.002
Age, years			
Weight, kg			
Height, cm			
Persistent AF			
Mitral regurgitation ≥°II	2.27	1.189 - 4.330	0.013
Structural heart disease			
LA volume, mL	1.012	1.008 - 1.016	<0.001

Table 19: Multivariate Cox Regression model showing all independent risk factors for AF recurrence. LA: left atrial. Univariate analysis of baseline characteristics and measurement data according freedom of AF after cryoballoon ablation provided multiple highly significant parameters. To prevent multicollinearity in the multivariate analysis, CCTA measurements were reduced to LA volume as it represents the most significant univariate parameter and showed highly significant correlation to all other measurement parameters. After stepwise multivariate regression with bidirectional elimination three parameters could be identified as independent risk factors: female

sex, mitral regurgitation ≥ °II and LA Volume. The significance model of the multivariate Cox regression model was p<0.000001.

To objectify the impact of LA volume on AF recurrence after CBA, a cut-off value was determined by ROC analysis. It could be shown that especially LA volumes ≥122.7 mL (sensitivity 0.53, specificity 0.69, area under the curve 0.63) were associated with AF recurrence (p<0.001). To illustrate the impact of the cut-off value a Kaplan-Meier-Plot was created and depicted in figure 20.

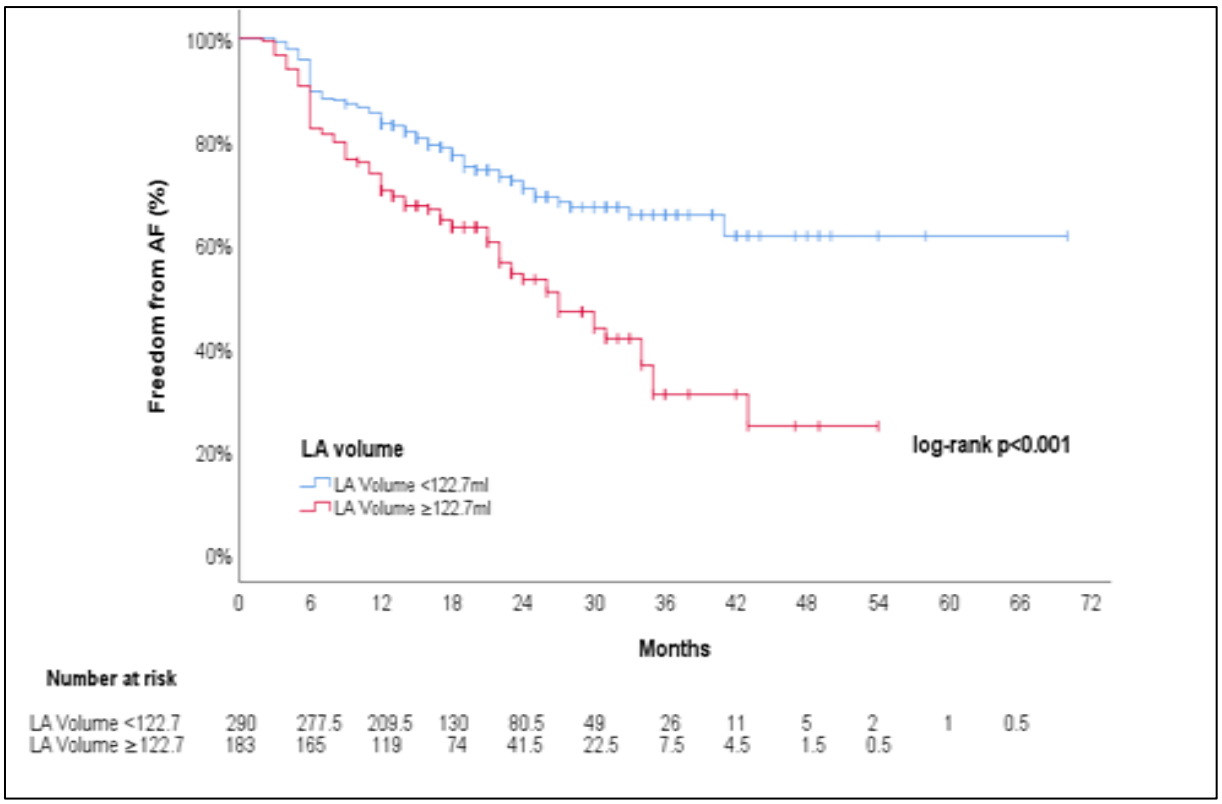

Figure 20: Kaplan-Meier-Plot regarding AF recurrence and LA volume ≥122.7 mL. Larger LA volumes demonstrated a highly significant impact on the recurrence rate of AF after cryoballoon ablation (p < 0.001).

4.9 Subanalysis of Persistent Atrial Fibrillation

As this study comprised 196 patients suffering from persistent AF, a subgroup was formed to identify the specific risk factors regarding these patients.

Compared to the paroxysmal group, patients included in the persistent cohort showed a lower percentage of females with 69 (35%) with a higher median weight of 81 (70.75; 93) kg and a higher median height of 176±0.9 cm. Moreover it could be shown that patients with persistent AF suffered from a higher rate of comorbidities such as structural heart disease in 82 (41.8%) patients, hypertensive heart disease in 51 (26%) patients, ischemic heart disease in 29 (14.8%) patients, valve disease in 18 (9.2%) patients thereof presence of mitral regurgitation ≥II° in 13 (6.6%) patients and cardiomyopathy in 9 (4.6%) patients. Valve disease, ejection fraction and structural heart disease showed a statistically significant difference between paroxysmal and persistent AF patients. The left atrial diameter was increased in patients with persistent AF with a median of 45 (41; 50) versus 42 (39; 46) in paroxysmal AF patients ($p<0.001$). Anatomical variations of pulmonary veins seems to be similar across the cohorts with 44 (22.4%) presenting a left common ostium and 31 (15.8%) presenting an additional pulmonary vein.

Baseline Characteristics	Overall n=473	Paroxysmal n=277	Persistent n=196	p-value
Age, years	66.6±9.5	66.7±9.5	65.7±9.5	0.2
Females (%)	189 (40.0)	120 (43.3)	69 (35.2)	0.08
Height, cm	175±0.09	174±0.1	176±0.1	0.2
Weight, kg	80 (70.75; 90)	80 (70; 90)	81 (71; 92.8)	0.6

BMI, kg/m²	25.96 (23.5; 28.6)	25.95 (23.4; 28.6)	25.97 (23.5; 28.6)	0.9
Mitral regurgitation ≥°II	18 (3.8)	5 (1.8)	13 (6.6)	0.01
Valve disease ≥°II	25 (5.3)	7 (2.5)	18 (9.2)	0.003
LA diameter mm	43 [40; 47]	42 [39; 46]	45 [41; 50]	<0.001
Ejection fraction **(%)**	56.88±6.1	58.51±4.2	54.61±7.7	<0.001
HHD	103 (21.8)	52 (18.7)	51 (26)	0.1
Cardiomyopathy	16 (3.4)	7 (2.6)	9 (4.6)	0.3
Ischemic heart disease	63 (13.3)	34 (12.3)	29 (14.8)	0.5
Structural heart disease	170 (35.9)	88 (31.8)	82 (41.8)	0.03
Left common ostium	101 (21.4)	57 (20.6)	44 (22.4)	0.7
Accessory veins	72 (15.2)	41 (14.8)	31 (15.8)	0.9

Table 20: Differences in Baseline Characteristics Persistent Cohort vs. Paroxysmal and Complete Population; HHD= hypertensive heart disease. Major differences identified between paroxysmal and persistent patients comprised: mitral regurgitation ≥°II, Valve disease ≥°II, LA diameter measured via transthoracic echocardiography as well as ischemic and structural heart disease. The metric data was analysed with either the student t-test when normally distributed or the Mann-Whitney U-test when non-normally distributed. Nominal data was tested for differences with Chi-Square.

The procedural results patients in persistent AF showed no difference to the overall average, with the same median procedural time of 130 (120; 160) min and fluoroscopy time of 22 (17; 28) min and a slightly higher median LA time of 95 (80; 120) min and dose area product of 1,919 (1103; 3255) cGycm2 for all $p > 0.05$.

Also, in terms of complications there were no differences in incidental rates between persistent AF patients and the paroxysmal group. Only peri-procedural complication in this subgroup were 14 phrenic nerve palsies (7.1%). The mean time until phrenic nerve palsy was 103.68±67.94 s. Post-procedural complications consisted of 9 (5%) incidents with 3 (1.5%) pericardial effusions, 2 (1%) puncture site hematomas, 1 (0.5%) fistula, 1 (0.5%) bronchitis, 1 (0.5%) respiratory tract infection, 1(0.5%) gross haematuria and 1 (0.5%) puncture site oozing. All p-values were greater than 0.05.

However, follow-up data showed that persistent AF patients experienced a higher recurrence rate compared to the paroxysmal group with 41.8% versus 30.3% (log-rank p-value = 0.001).

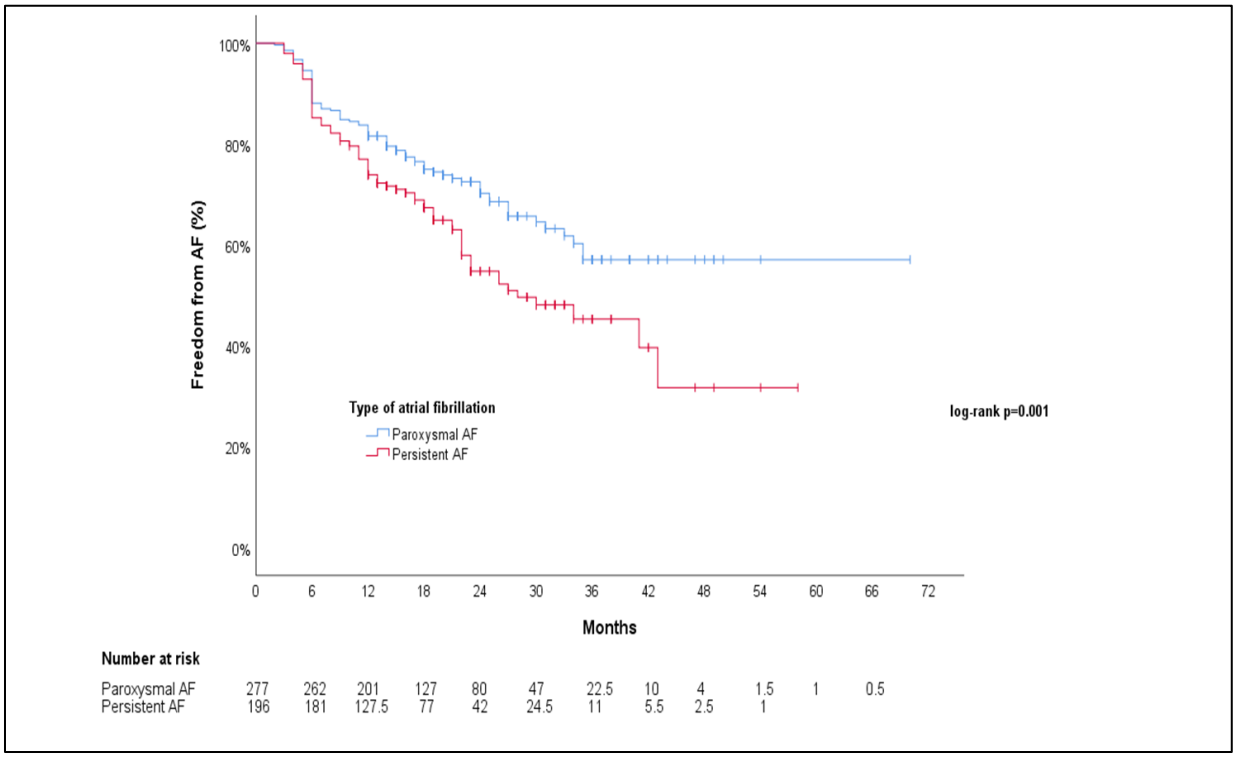

Figure 201: Kaplan-Meier-Plot regarding AF recurrence and AF type. Persistent type of AF demonstrated a significant impact on the recurrence rate of AF after cryoballoon ablation (p = 0.001).

Many of the CCTA measurement data which were predictive for AF recurrence were larger in patients with persistent AF. Important parameters included the LA and LAA volume with a median size of 124.8 (103.3; 148.5) mL versus 108.2 (92.5; 126.5) mL and 9.2 (7.2; 12.3) mL versus 8.3 (6.1; 11.2) mL. Further major parameters comprised the mean LAA ostial area with 3.7±1.4 cm^2, the median LAA ostial perimeter with 68.84 (61.98; 76.16), the median septum-orifice distance with 58 (55; 62.75) mm, the trapezoid area of the posterior LA wall with 12.76 (11.02; 15) cm^2 and the median LA depth with 40±6 mm. All statistically significant differences are illustrated in table 21.

Measurement Data	Overall n=473	Paroxysmal n=277	Persistent n=196	p-value
LA Parameter				
LA volume, mL	115.1 (97.2; 135.2)	108.2 (92.5; 126.5)	124.8 (103.3; 148.5)	<0.000001
Septum orifice distance, mm	58 (54; 61)	57 (53; 60)	58 (55; 62.8)	<0.001
Distance from the MVA to the LA roof, mm	69 (65; 74)	68 (65; 72)	70 (66; 75)	<0.001
Roof top line, mm	35 (31; 41)	35 (31; 39)	37 (31; 42)	0.008

Roof bottom line, mm	42 (37; 46)	41 (36; 45)	43 (38; 48)	<0.001
Posterior wall box height, mm	32 (29; 35)	31 (28; 34)	33 (30; 36)	<0.0001
Trapezoid area of the posterior LA wall, cm^2	12.05 (10.32; 14.23)	11.71 (10; 13.3)	12.76 (11; 15)	<0.001
LA depth, mm	38.53±5.9	37.5±5.6	40±6	<0.001
LAA Parameter				
LAA volume, mL	8.7 (6.5; 11,6)	8.3 (6.1; 11.2)	9.2 (7.2; 12.3)	0.005
LAA ostial perimeter, mm	67.92±12.18	66.5±11.9	68.9±12.3	0.007
LAA ostial area, cm^2	3.4 (2.7; 4.3)	3.5 (2.6; 4.2)	3.5 (2.9; 4.4)	0.008

Table 21: Significant differences of CCTA measurements in the persistent vs. paroxysmal and total population. Most significant differences between paroxysmal and persistent AF patients regarding CCTA measures comprised the LA volume and its companion parameters. The metric data was analysed with either the student t-test when normally distributed or the Mann-Whitney U-test when non-normally distributed. MVA: mitral valve annulus; LA: left atrial; LAA: left atrial appendage.

Comparison of the LAA morphological distribution showed no significant differences between persistent AF patients, paroxysmal AF patients and the whole study population. Larger LAA types as windsock and chicken-wing morphology seemed to be present slightly more often in patients with persistent AF. See table 23.

LAA morphological classes	Overall n=473	Paroxysmal n=277	Persistent n=196	p-value
Chicken-Wing	98 (20.7)	55 (19.9)	43 (21.9)	0.58
Windsock	244 (51.6)	141 (50.9)	103 (52.6)	0.72
Cactus	59 (12.5)	39 (14.1)	20 (10.2)	0.21
Cauliflower	72 (15.2)	42 (15.2)	30 (15.3)	0.97

Table 22: Differences LAA morphology Persistent Cohort vs. Paroxysmal and Complete Population. There were no significant differences regarding LAA morphology in paroxysmal and persistent AF patients. Analysis was performed with the Chi-Square test.

Univariate analysis of predictors of AF recurrence in persistent AF patients showed next to similarities some major differences compared to all patients. Among baseline characteristics significant parameters included mitral regurgitation ≥°II (HR 3.09; CI [1.517-6.29], p=0.002), overall valve disease ≥°II (HR 2.693; CI [1.442-5.029]; p=0.002), left atrial diameter (HR 1.039; CI [1.010-1.068]; p=0.008), structural heart disease (HR 1.802; CI [1.163-2.793], p=0.008) and hypertensive heart disease (HR 1.679; CI [1.054-2.675]; p=0.029). As in the other group analysis of procedural results and complications could not identify any risk factors. Regarding CCTA measurement data most important parameters predicting AF recurrence in univariate regression were the LAA volume (HR 1.089; CR [1.041-1.140]; p<0.001), the LA volume (HR 1.008; CI [1.003-1.014]; p=0.003), the area of the LAA ostium (HR 1.002; CI [1.001-1.004]; p=0.004), the perimeter of the LAA ostium (HR 1.025; CI [1.007-1.044]; p=0.006), the maximal diameter of the LAA ostium (HR 1.065; CI [1.016-1.116]; p=0.009) and the septum orifice distance (HR 1.046; CI [1.010-1.082] p=0.011).

It is in line with the finding in the overall study population that also in the subgroup of persistent AF patients, LAA morphology showed no statistically significant impact on the risk of recurrence. This is illustrated in figure 22 below.

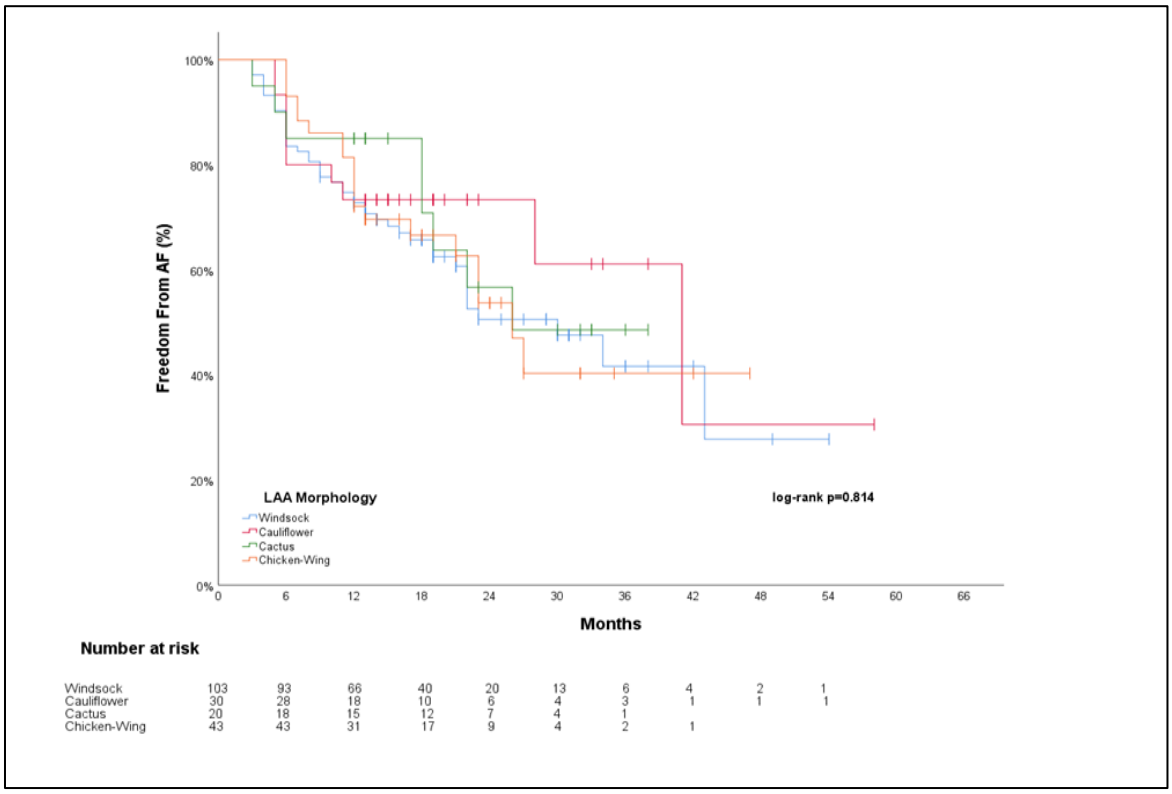

Figure 212: Kaplan-Meier-Plot regarding left atrial appendage morphologies and AF recurrence in patients with persistent AF. LAA morphology showed no statistical impact on the recurrence rate of AF after cryoballoon ablation in only persistent AF patients. The log-rank test was used to calculate the respective p-value.

Analysis of intervariable correlations in persistent AF patients showed similar results than in the overall cohort. Therefore, baseline parameters as mitral regurgitation ≥°II and the presence of overall structural heart disease were included into the multivariate model besides female gender, age, weight and height. LA measurement data could again be reduced to LA volume. However, major difference to the overall population is that LAA volume showed to be a superior predictor to LA volume in persistent AF patients as LAA volume was of higher significance compared to LA volume in

univariate analysis. LAA volume was therefore entered into the multivariate Cox regression instead of LA volume. Here final results comprised only two predictors for AF recurrence in persistent AF patients: mitral regurgitation ≥°II (HR 2.495; CI [1.207-5.126]; p=0.013) and newly the LAA volume (HR 1.082; CI [1.032-1.134]; p=0.001), whereas female sex was not an independent predictor in this subgroup.

Multivariate Analysis	HR	95%-CI	p-value
Female Sex			
Age, years			
Weight, kg			
Height, cm			
Mitral regurgitation ≥°II	2.495	1.207 - 5.126	0.013
Structural heart disease			
LAA volume, mL	1.082	1.032 - 1.134	0.001

Table 23: Multivariate Cox Regression model of persistent AF patients. To prevent problem of multicollinearity LAA volume CCTA measures were reduced to LAA volume as the most significant parameter. After stepwise multivariate regression with bidirectional elimination two parameters could be identified as independent risk factors: LAA volume and mitral regurgitation ≥ °II. The significance of the multivariate Cox regression model was p<0.001.

LAA volume was then evaluated further by determination of a cut-off value in a ROC analysis. LAA volumes ≥9.75 mL (sensitivity 0.56, specificity 0.69, area under the curve 0.64) were linked to AF recurrence (p<0.001). The Kaplan-Meier-Plot below depicts this association.

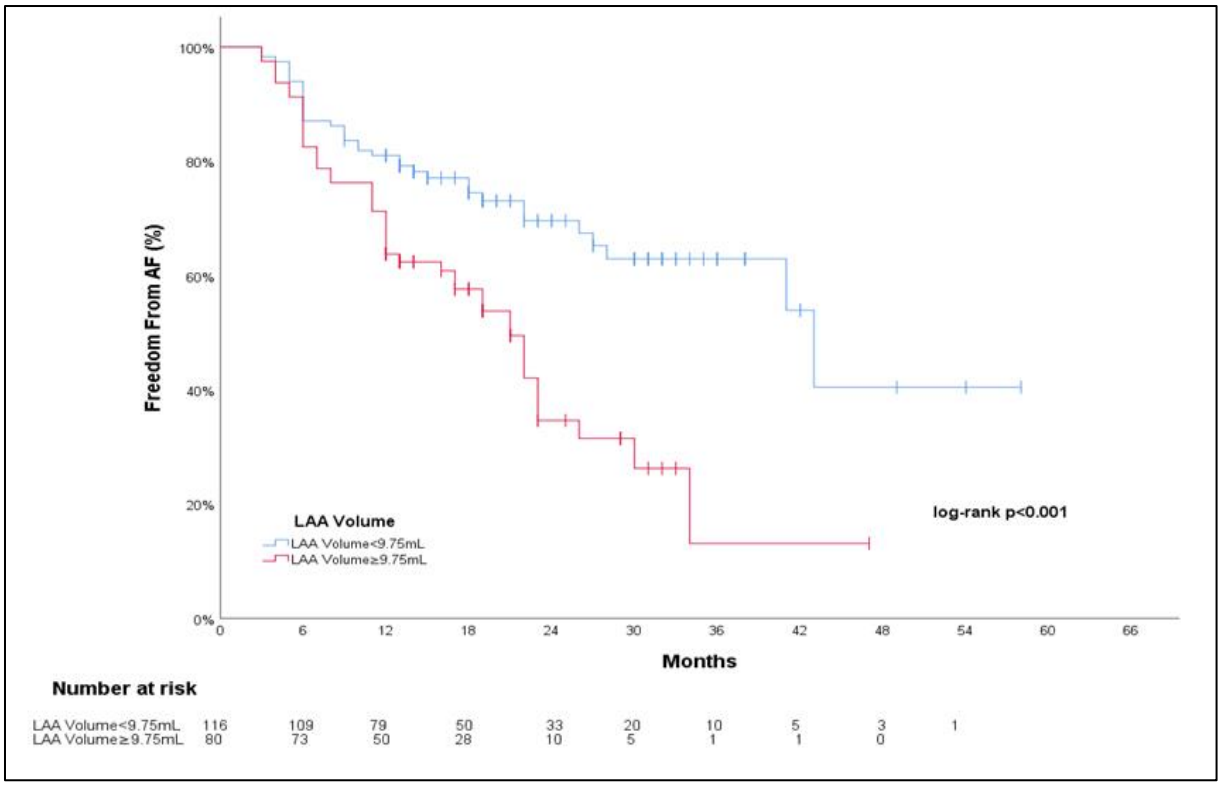

Figure 23: Kaplan-Meier-Plot regarding AF recurrence and LAA volume ≥9.75 mL. Larger LAA volumes demonstrated a highly significant impact on the recurrence rate of AF/AT after cryoballoon ablation ($p < 0.001$).

5 DISCUSSION

Success rate of catheter ablation by means of electrical PVI in AF patients is generally high but offers still room for improvement as about a third of patients experience AF recurrence [166]. Therefore, different ablation strategies like empirical lines (roof line, posterior box isolation, mitral isthmus line, cavotricuspid isthmus line), isolation of the superior vena cava, isolation of the coronary sinus, identification of triggers outside the PV, complex fractionated electrograms, and substrate modification have been evaluated. However extensive left atrial ablation procedures are associated with a higher rate of acute complications such as cardiac tamponade. Moreover, a randomized trial did show no benefit from extensive ablation as compared to PVI alone [198], and a recent meta-analysis is in line with this finding [218]. Empirical electrical LAA isolation has been proposed as a new target. However, this procedure carries a higher risk of thromboembolic events [219] with the necessity to close the LAA after electrical isolation with a LAA occluder device. Thus, the present study aimed for pre-procedural non-invasive identification of patients who might benefit from additional LAA isolation to help decrease the risk of AF recurrence and minimize unnecessary adverse events. Special focus was given to evaluate the predictive power of LAA morphology as well as other measurement data derived from pre-procedural CCTA together with baseline characteristics for AF recurrences after PVI in cryoballoon ablation technique.

The main findings of the study are summarized in the following:

1. Left atrial appendage morphology could not predict the recurrence of AF after cryoballoon ablation.
2. LAA volume correlated with LA volume and was even dependent on it. LAA volume increased by 0.70 mL per 10 mL increase in LA volume.

3. Best independent predictors of AF recurrence were LA volume, the presence of mitral regurgitation ≥°II and female sex. LAA volume and other left atrial measurement data like the septum orifice distance, the trapezoid area of the left atrial did also have a significant impact on AF recurrence but were dependent on LA volume.
4. In persistent AF, independent predictors included LAA volume and mitral regurgitation ≥°II. Surprisingly, in these patients the LAA volume showed to be a superior parameter as compared to LA volume. Sex category was of no influence here. In persistent AF, LAA morphology was also not associated with AF recurrence.
5. One target was also to objectify the rather subjective classification system of LAA morphological definitions. For this a new bounding box approach was introduced. Maximal LAA depth and the sinus alpha of this bounding box were identified to be two useful new parameters which lead to a more objective classification.

5.1 Study Population, Success Rate and Complications

Compared to epidemiologic studies and meta-analysis [8, 13, 21], the present population of this trial represents a very accurate sample of consecutive AF patients scheduled for initial AF ablation procedure, and exclusively for CBA. Merely, the presence of some of the comorbidities like arterial hypertension and ischemic heart disease was slightly lower compared to other studies [220].

Also, cryoballoon ablation success rates of the present trial were in line with other studies evaluating the outcomes of pulmonary vein isolation. Regarding the twelve-month follow-up time this study identified a success rate of about 80%. Other studies described similar success rates [221, 222].

The peri- and post-procedural complication rate with 7.4% and 4.9% was similar compared to other recently published studies [166, 223, 224]. Besides minor adverse events as transient phrenic nerve palsies or puncture side complications cryoballoon ablation represents a very safe treatment method.

5.2 Left Atrial Appendage Morphology and Pulmonary Vein Variations

This trial demonstrated that LAA morphology is not associated with AF recurrence after cryoballoon PVI, as opposed to Kocyigit et al., who revealed in a small single centre trial a correlation between the cauliflower-type and post-CBA AF recurrence [225]. Notably, the different LAA morphological types presented size differences: windsock and chicken-wing types were larger compared to cactus and cauliflower. Nevertheless, even when divided into two main groups consisting of big and small LAA morphological types no significant association could be identified. Despite having a possible impact on the formation of thrombi and a risk for embolic events as stated by di Biase et al. [212], pre-procedural evaluation of LAA morphology has no use predicting AF recurrence after cryoballoon AF.

Since the definition of the four LAA morphological types in 2010 [211], primarily designed for the LAA closure device, there were constant improvements to it because of the highly subjective classification criteria. Therefore in 2013 Kimura et al. [213] added CCTA measured parameters to reduce the inter-observer variability. However, there is still large room for further objectification. The author of this study introduced a new bounding box approach and determined two new significant parameters to differentiate between LAA morphological types. Classification can now be performed

more correctly and objectively. The necessary bounding box parameters can be measured easily by standard CCTA post-processing software and do not even require 3D reconstruction.

As mentioned previously, circumferential contact of the cryoballoon with the PV ostium is essential to achieve optimal occlusion and complete isolation of the pulmonary veins. In up to 30% of the general population there exist anatomical variations such as large common ostium or small additional pulmonary veins [226], which can be challenging in balloon based PVI. In the present study the distribution of PV anomalies was 21% common ostiae and about 15% accessory pulmonary veins. It is of interest that in this study neither of these anatomical variations was associated with AF recurrence which is in line with the findings of Khoueiry et al. [227]. Thus, individual pulmonary vein anatomy should not be considered as a major factor for the success of catheter ablation and should be approached without complex pre-procedural imaging.

5.3 Left Atrial and Left Atrial Appendage Volumes as Predictors of Atrial Fibrillation Recurrence

Of all CCTA derived results, LA volume was the best predictor of AF recurrence. This finding is in line with Hof et al. [228] and Abecasis et al. [205] who were among the first to describe a high impact of CCTA derived LA volume to predict freedom from AF following PVI. A possible underlying pathophysiologic explanation is the formation of micro-re-entries induced by atrial fibrosis, the substrate for arrhythmogenicity, the increasing left atrial enlargement and tissue stretching [34]. Atrial fibrosis can then ultimately induce complex AF triggers and is a prerequisite for the perpetuation of AF. Nevertheless, it is also important to mention that many other parameters such as the septum orifice distance, the size of the trapezoid area of the left atrial wall or the LAA volume were associated with a significant impact on the risk of recurrence. Having an

inferior prediction power than LA volume, these parameters also demonstrated strong positive correlations to LA volume. Notably, this is the first study to identify a linear dependency between LA and LAA volumes. Concerning LA volume measured by CCTA as a predictor of recurrence, the risk of recurrence increases by 10% per 10 mL increase of the LA volume.

In line with Pinto Teixeira et al. [210] who demonstrated that LAA volumes >8.825 mL should be considered as predictors for recurrence after radiofrequency catheter ablation (RFA) of AF, the present trial proofed that increased LAA volumes were also associated with a higher risk for recurrence after cryoballoon ablation. Surprisingly, in the cohort with persistent AF patients only, LAA volume was even revealed as the best available independent predictor, even superior to LA volume. Larger LAA might promote the perpetuation of AF after its initiation leading to the persistent AF type. Studies revealed that increased structural remodeling and a reduction in the number of pectinate muscles were more present in patients with AF compared to patients without AF [229]. Due to these pathophysiologic changes micro-re-entries can also originate in the LAA. Hocini et al. found proof for this as in 11% of patients undergoing ablation of persistent AF atrial tachycardia originated in the LAA and classified as localized re-entries [172].

It can be concluded that LA and LAA volumes represent the two major metrics to predict AF recurrence after CBA. Moreover, this study suggests that especially in persistent AF patients large LAA volumes are associated with AF recurrence after PVI. Due to the large size of the study population, determination of significant cut-off values for LA and LAA volumes as predictors of recurrences after second-generation CBA was possible.

5.4 Sex Specific Aspects and Age as Predictors of Atrial Fibrillation Recurrence

The results of the present trial indicated that female sex was an independent risk factor for AF recurrence after CBA in the overall study population. Possible explanation could be the increased likelihood for comorbidities and the older age of female patients by the time undergoing AF ablation [230]. There is an association between female sex and a higher burden of left atrial fibrosis in patients with AF, which might explain the increased risk of AF recurrences [231], as the arrhythmogenic activity arises from the substrate rather than the pulmonary veins. Whilst some studies indicated no significant sex-related difference with outcomes of AF ablation when comparing women to men [232], the majority of studies demonstrated that PVI in female patients has a worse success rate in paroxysmal and persistent AF [233, 234]. Ultimately, the answer to this question may lead to specific, sex-tailored AF ablation strategies.

It is also important to mention that female patients were underrepresented in the study population and showed a higher overall age in the present trial. However, although age has a significant impact as a risk factor for AF occurrence [13], it could not be identified as an independent predictor for AF recurrence after CBA which confirms the findings from Heeger et al. [235].

Notably, in patients with the persistent type of AF female sex was in this study not associated to the risk of recurrence at all, in contrast to Zhang et al. [236] who revealed a significantly lower rate of success for female patients with long-standing persistent AF. Future studies are needed to investigate the influence of female sex and AF recurrence in persistent AF patients. CBA creates wide area circumferential ablation but might miss substrate mediated AF mechanisms. Therefore, especially women

experiencing AF recurrences should be evaluated for repeat ablation procedures with an ultra-high-density electroanatomical mapping system.

5.5 Mitral Regurgitation as an Important Predictor

Besides female sex and LA volume, the presence of mitral regurgitation ≥II° was an independent predictor of AF recurrence in the present trial. This is in line with Gertz et al. who identified mitral regurgitation as an indicator for AF recurrence although dependent on LA volume as well [237]. Because an increased volume overload leads to LA enlargement, tissue stretching and ultimately to re-entry circuits, mitral regurgitation promotes the development of complex AF [238, 239]. Therefore, pre-procedural evaluation of valve disease seems to be an important selection criterion to improve the success rate of catheter ablation.

5.6 Cardiac Computed Tomography Angiography prior to Atrial Fibrillation Ablation

Another very important topic is whether pre-procedural CCTA, which exposes the patient to radiation and needs iodine contrast enhancement, is necessary prior to AF ablation procedure or if echocardiographic measurements are sufficient. Based on current literature there is no benefit for the outcome of catheter ablation [240]. However, undergoing CCTA before the initial AF ablation procedure may be helpful for intra-procedural navigation and the identification of individual LA anatomy when integrated in 3D-electro-anatomical mapping systems during the procedure [241]. It can additionally be used for the exclusion of CAD as a cause of AF or even to rule out thrombi prior to ablation as a potential alternative to transesophageal echocardiography [241, 242]. CCTA can also lead to significantly lower intra-procedural fluoroscopy times [189, 190].

However, based on the main results of the present study we cannot recommend the general use of CCTA in daily practice before PVI. Although pre-procedural CCTA allows precise measurements of LA features like the septum orifice distance or the LAA volume, LA volume represents the best predictor, and this can be approximated using LA diameter without radiation exposure by echocardiography. In a multivariate Cox-regression model without including any CCTA data, independent clinical predictors of recurrence were mitral insufficiency ≥II°, female sex, AF type and the LA diameter measured by echocardiography. Although being a weaker model compared to the Cox-regression model using CCTA measurements, it also offers the most important information for the risk assessment of AF recurrence, enables the potential benefit of ablation to be determined, and should be used in clinical practice. However, if LA volume measured by transthoracic echocardiography is equally predictive for recurrence after CBA as compared to CCTA is unknown as it was not available for all patients of this study. In persistent AF, LAA volume seems to be a superior predictor over LA volume. Echocardiographic LAA analysis is very difficult and not available in routine practice. In the future, CCTA might be an option to evaluate patients with AF recurrence after complete PVI. LAA size might identify patients who could benefit from empirical electrical LAA isolation with subsequent LAA occlusion. However, this concept has to be studied further and our data might help to create the study protocol.

In conclusion, CCTA should not be used in general practice prior to AF ablation but might be indicated in selected patients prior to complex AF ablation procedures in persistent AF patients, e.g. in those scheduled for a second AF ablation procedure. However, more research is necessary to support the concept of empirical LAA isolation.

5.7 Electrical Left Atrial Appendage Isolation as a Strategy of Atrial Fibrillation Ablation

As stated previously there exist additional strategies to further improve the success rate of catheter ablation in complex AF patients. Beyond PVI other empirical lesion techniques leads to the exclusion of LA substrate area e.g. posterior box isolation. The LAA is a potential source of extra-PV trigger and the LAA might enhance the perpetuation of AF. Thus, the LAA is a potential target for AF ablation [169-172]. Technically epicardial and endocardial approaches are possible.

1. Epicardial mechanical exclusion of the LAA via suture or clip results in an acute infarction of the tissue, leads to voltage reductions and may thus possibly eliminate all rotors and re-entries [243]. A recent trial demonstrated a significant decrease in AF burden through mechanical isolation using the LARIAT device [244]. However, amputation of LAA is a highly invasive and risky procedure. In patients with AF undergoing heart surgery for other reasons LAA ligation should be considered.
2. Empirical RF-catheter based electrical LAA isolation showed promising results in patients with long lasting persistent AF in the BELIEF trial [173]. Double the patients undergoing this treatment were recurrence free after 12 months in comparison to patients receiving only PVI. Durable LAA isolation can also be achieved with CBA [245]. Nevertheless, LAA ablation results in an impaired mechanical function and thus increases the thromboembolic risk [176]. Furthermore, operators should be extremely cautious regarding LAA perforation due to their extremely thin wall next to the thick muscle layer [173, 246]. In addition, the increased risk for left phrenic nerve paralysis as well as potential risks of the circumflex coronary artery should be considered.

Empirical isolation of the LAA is not an established treatment in AF ablation and no pre-procedural selection criterion exists. As the present study revealed that both large LA and LAA volumes are associated with a higher risk of recurrence and that patients with larger LA volumes are more likely to also have large LAA volumes, it is possible that some of those patients with large LA volumes and LAA volumes may be possible candidates for those advanced ablation methods beyond PVI in a second ablation procedure. In addition, our evidence suggests that especially patients with persistent AF and large LAA ≥9.75 mL will experience AF recurrence after PVI. However, for the primary ablation procedure “PVI only” seems to be sufficient for the majority of patients.

To further improve the success rate of catheter ablation in complex AF patients the present results suggests a randomized trial in symptomatic persistent AF patients with large LA and LAA who suffer from atrial arrhythmias despite durable PVI in the second procedure comparing substrate ablation only with substrate ablation plus electrical LAA isolation. Due to the risk and the unresolved question of the indication of LAA occlusion after LAA isolation, this study would be reserved for patients with recurrences after PVI. Ultimately, the goal must be to develop precise indication criteria of electrical LAA isolation with consecutive LAA occlusion.

5.8 Limitations

One of the main limitations lies within the study design. This was an observational single center study with the inherent limitation of generalizability due to individual department-based selection criteria, resources and protocols.

Although no patients were excluded because of CCTA findings the data are not entirely consecutive because not every patient underwent cardiac CT prior to the ablation procedure. In addition, the image quality varied quite a lot and LAA measurement data

from CCTA was not sufficient for every patient. The hydration status of the patient might also influence LA and LAA analysis [247]. All patients were in sinus rhythm for CCTA. In case of AF, they were cardioverted before the scan. Atrial stunning might have also influenced the filling of LA and LAA. Despite generally carrying out CCTA in sober patients only, the possibility of different volume loadings cannot be fully excluded. Although echocardiographic measurements included LA diameter in anterior-posterior view, echocardiographic LA volume assessment was not performed in all patients. Therefore, the predictive value of LA volume measured by echocardiography could not be evaluated.

To improve the validity of LAA morphological classification, there was a reassessment in a team of four after initial analysis. Nevertheless, LAA morphological classification is highly subjective, which is also confirmed by the greatly varying distribution of LAA morphologies in literature. There was no information available whether the LAA was arrhythmogenic or not during the CBA procedure. Thus, the incidence of LAA triggers could not be analysed with regards to LAA morphology or other CCTA derived parameters.

Another limitation is the high probability of missed asymptomatic AF recurrences as the outcome results were based on the evaluation of symptoms, clinical visits, electrocardiography and Holter studies during the routine follow-up. There were no implantable devices available for continuous and systematic monitoring.

5.9 Perspectives and Translational Outlook

During the last decade there was a remarkable progress in the interventional treatment of AF by means of catheter ablation. Besides continuous improvements of the ablation technique itself there were also multiple technical advancements of the related equipment such as the introduction of electroanatomic mapping systems or the development of new catheter designs (e.g. balloon-based single shot devices) and energy sources like CBA. But although CA shows impressive long-term results and reduces the total AF burden significantly as compared to antiarrhythmic drug treatment [248], one third is still a significant AF recurrence rate [249]. As of now there are multiple ideas of additional treatment strategies besides PVI including extensive LA linear ablation, ablation of complex fractionated electrocardiograms and ganglionated plexus ablation. However, neither of these strategies showed significant improvements [198]. Thus, the main goals in future must be a better pathophysiologic understanding of AF genesis as well as the establishment of technically more advanced diagnostic and therapeutic tools to select patients as candidates for additional ablation strategies beyond PVI.

One focus should lie upon the analysis of extra-PV triggers as they have an important role in complex AF patients and their identification and treatment are more challenging compared to standard PVI [168].

Moreover, precise pre-procedural determination of factors associated with AF recurrence could lead to further improvements of AF management. This includes the evaluation of clinical as well as anatomical parameters, biomarkers and even genetic factors. Prior to the ablation procedure, virtual computer simulations based on patient specific AF models could be used to aim for individual ablation strategies. Research will also focus on technical improvements regarding the ablation tools for PVI such as

easier intracardiac navigation or more advanced energy sources. As mentioned earlier possible alternative energy sources include laser balloons, RF balloons or electroporation, which show promising efficacy and safety data but in a limited number of patients [250-252]. Ultimately, individually tailored ablation strategies based on more advanced diagnostic and therapeutic tools will lead to the best possible outcome. This will increase the success rate and minimize complications.

6 SUMMARY

AF is the most common sporadic arrhythmia worldwide with still increasing incidence and prevalence. In case of failing basic AF therapies in symptomatic patients such as pharmacological approaches or cardioversion, PVI by means of CA is a well-established treatment option with remarkable long-term outcomes and symptom improvement. Nevertheless, about one third of patients undergoing such ablation procedures experience at least one episode of AF recurrence and might require additional treatment strategies. Recently, studies suggested empirical LAA isolation as it might be an important region for AF triggers not related to the pulmonary veins. However, this approach is controversially discussed. To help improve the long-term outcome and develop new treatment strategies for complex AF patients the main objective of this study was the identification of predictors of recurrence after second generation cryoballoon PVI with special focus on LAA anatomy and dimensions derived from pre-procedural CCTA.

Thus, a prospective observational single center study was conducted with a blinded retrospective evaluation of pre-procedural cardiac CT images via a 3D mapping system. Besides baseline characteristics, procedural results and follow-up data, multiple measurement parameters regarding the left atrium, pulmonary veins and LAA were assessed and statistically analyzed. As the substrate of persistent AF patients is often complex and PVI only in persistent AF has only recently been accepted, this subgroup was analyzed further.

In total, this study comprised 1,103 patients undergoing second generation cryoballoon PVI from 2012 to 2016. CCTA was available for 725 patients with 473 having a sufficient CCTA image quality for the acquisition of measurement data. Patients had a

mean age of 66 years. Persistent AF was present in 196 patients. Median follow-up time was 19 months. Overall, 166 (35.1%) patients experienced AF recurrence. Independent predictors of recurrence were LA volume, female gender and mitral regurgitation ≥°II. In the subgroup of persistent AF, independent predictors were LAA volume and mitral regurgitation ≥°II. An association between LAA morphology and AF recurrence was neither identified for the overall study population nor for the persistent AF subgroup. LAA volume was revealed to have a linear dependency on LA volume. LAA morphological classification can be further improved by the introduction of two new parameters: maximal LAA depth and sinus alpha of a newly introduced bounding box approach. Cut-off values were determined for the overall population for LA volume and for the subgroup for LAA volume.

In most patients PVI only was sufficient in the first ablation procedure. LA volume is the most powerful predictor for AF recurrence overall, whereas LAA volume was superior in the persistent cohort. In conclusion, LAA volume may be an important pre-procedural selection parameter in persistent AF patients for additional ablation procedures such as LAA isolation. Nevertheless, the results of this study might support the initiation of further trials to determine the benefit of electrical LAA isolation with consecutive LAA occlusion in selected patients.

7 ZUSAMMENFASSUNG

Vorhofflimmern (AF) ist weltweit die häufigste Arrhythmie mit stetig zunehmender Inzidenz und Prävalenz. Aufgrund der individuell ausgeprägten, teilweise stark belastenden Symptomatik sowie der potentiell schwerwiegenden Komplikationen ist AF seit vielen Jahren ein zentraler Bereich der kardiologischen Forschung. Seit nun schon über 15 Jahren hat sich neben den klassischen symptomatischen Therapieverfahren wie der pharmakologischen Behandlung oder der Elektrokardioversion eine neue und erstmals kausale Therapieoption durchgesetzt: die Katheter geführte Pulmonalvenenisolation. Trotz bemerkenswerter Langzeiterfolgsraten kommt es doch in etwa einem Drittel der Patienten zu einem Vorhofflimmerrezidiv. Die Entwicklung weiterführender Behandlungsstrategien ist daher essentiell. Vor kurzem erst wurde die Hypothese postuliert, neben den Pulmonalvenen auch das linke Vorhofohr (LAA) elektrisch zu isolieren, da es eine weitere wichtige Quelle für AF Trigger darstellt. Aufgrund diverser Komplikationen und Risiken wird dieses Verfahren kontrovers diskutiert, weshalb die Frage welche Patienten für eine Vorhofohrisolation in Frage kommen derzeit noch unklar ist. Daher war es das Hauptziel dieser Studie die Rolle des LAA hinsichtlich Vorhofflimmerrezidive nach Pulmonalvenenisolation (PVI) in Kryoballontechnik zu untersuchen. Das sekundäre Ziel war die Analyse von Prädiktoren für das Wiederauftreten von Vorhofflimmern nach Katheterablation.

Dazu wurde eine prospektive, monozentrische Beobachtungsstudie mit einer verblindeten, retrospektiven Auswertung von präprozeduralen kardialen CT Aufnahmen durchgeführt. Neben den Patienteneigenschaften, den prozeduralen Ergebnissen und den Ergebnissen der Nachbeobachtungzeit wurden mehrere Messparameter bezüglich des linken Vorhofs (LA), der Pulmonalvenen und des LAA

erhoben und statistisch analysiert. Da persistierende Vorhofflimmerpatienten oftmals besonders schwierig zu behandeln sind und für diese Gruppe die alleinige Pulmonalvenenisolation ohne zusätzliche Ablationsverfahren erst vor kurzem als Behandlungskonzept akzeptiert wurde, ist diese Patientengruppe als spezielle Subanalyse zusätzlich ausgewertet worden.

Insgesamt umfasste die vorliegende Studie 1.103 Patienten über den Zeitraum von 2012 bis 2016, bei denen eine Pulmonalvenenisolation in Kryoballontechnik mit einem Ballon der zweiten Generation durchgeführt wurde. Für 725 Patienten erfolgten präprozedurale kardiale Computertomographieaufnahmen. Von diesen hatten wiederum 473 Patienten eine ausreichende Bildqualität für die Bestimmung der zusätzlichen, studienspezifischen Messdaten. Die Patienten hatten ein Durchschnittsalter von 66 Jahren. Bei 196 Patienten bestand ein persistierendes AF. Die mediane Nachbeobachtungszeit betrug 19 Monate. Bei 166 (35,1%) Patienten trat ein Vorhofflimmerrezidiv auf. Unabhängige Prädiktoren für ein Rezidiv waren das LA-Volumen, das weibliches Geschlecht und eine Mitralklappeninsuffizienz ≥°II. In der Subanalyse der persistierenden Vorhofflimmerpatienten waren die unabhängigen Prädiktoren das LAA-Volumen und eine Mitralklappeninsuffizienz ≥°II. Es konnte kein Zusammenhang zwischen der LAA-Morphologie und einem AF Rezidiv identifiziert werden. Des Weiteren wurde eine lineare Abhängigkeit des LAA-Volumens vom LA-Volumen festgestellt. Die morphologische LAA-Klassifizierung konnte durch die Einführung von zwei neuen Parametern weiter verbessert werden: die maximale LAA-Tiefe und der Sinus Alpha eines neu eingeführten „bounding box“-Verfahrens. Außerdem wurden Cut-off-Werte für das LA Volumen in der gesamten Studienpopulation bestimmt. Für die Untergruppe der persistierenden Vorhofflimmerpatienten wurden Grenzwerte für das LAA Volumen ermittelt.

Bei den meisten Patienten scheint die PVI als erstes Ablationsverfahren effektiv und sicher zu sein. LA Volumen zeigte sich als stärkster Prädiktor in der gesamten Studienpopulation für AF-Rezidive, wohingegen sich das LAA-Volumen in der Untergruppe der persistierenden VHF-Patienten als statistisch überlegen erwies. Daraus lässt sich folgern, dass das LAA Volumen in dieser Kohorte einen wichtigen präprozeduralen Selektionsparameter für zusätzliche Ablationsverfahren wie die LAA-Isolierung darstellen könnte. Die Ergebnisse dieser Studie kann außerdem die Konzeption weiterer Studien unterstützen, die die Frage der Indikation zur elektrischen Isolation und konsekutiver Okklusion des Vorhofohrs untersuchen.

8 APPENDIX

8.1 List of Figures and Figure Legend

8.2 List of Tables and Table Legend

8.3 References

[1] Lip GY, Beevers DG. ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. BMJ. 1995;311(7016):1361-3.

[2] Bedford DE. The ancient art of feeling the pulse. Br Heart J. 1951;13(4):423-37.

[3] Adams R. Cases of diseases of the Heart, accompanied with Pathological Observations. Dublin1827. 100 p. (pp. 353-453). p.

[4] Schweitzer P, Keller S. A history of atrial fibrillation. Vnitr Lek. 2002;48 Suppl 1:24-6.

[5] Einthoven W. Le télécardiogramme. Arch Intern Physiol. 1906;4:pp. 132-64.

[6] Bootsma BK, Hoelsen AJ, Strackee J, Meijler FL. Analysis of R-R intervals in patients with atrial fibrillation at rest and during exercise. Circulation. 1970;41(5):783-94.

[7] Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med. 1982;306(17):1018-22.

[8] Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837-47.

[9] Chugh SS, Roth GA, Gillum RF, Mensah GA. Global burden of atrial fibrillation in developed and developing nations. Glob Heart. 2014;9(1):113-9.

[10] Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006;27(8):949-53.

[11] Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. Am J Cardiol. 2013;112(8):1142-7.

[12] Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. Am J Cardiol. 2009;104(11):1534-9.

[13] Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet. 2015;386(9989):154-62.

[14] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-8.

[15] Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 1998;32(3):695-703.

[16] Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm. 2010;7(4):433-7.

[17] Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98(10):946-52.

[18] DeVore AD, Hellkamp AS, Becker RC, Berkowitz SD, Breithardt G, Hacke W, et al. Hospitalizations in patients with atrial fibrillation: an analysis from ROCKET AF. Europace. 2016;18(8):1135-42.

[19] Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. Am J Med. 2006;119(5):448 e1-19.

[20] Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC, et al. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. Int J Cardiol. 2012;161(1):39-44.

[21] Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nat Rev Cardiol. 2016;13(6):321-32.

[22] Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. J Am Coll Cardiol. 2007;49(5):572-7.

[23] Ball J, Carrington MJ, Wood KA, Stewart S, Investigators S. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). PLoS One. 2013;8(5):e65795.

[24] Hinojosa-Laborde C, Chapa I, Lange D, Haywood JR. Gender differences in sympathetic nervous system regulation. Clin Exp Pharmacol Physiol. 1999;26(2):122-6.

[25] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016;18(11):1609-78.

[26] Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. Circulation. 2007;115(24):3050-6.

[27] Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res. 2014;114(9):1453-68.

[28] Voigt N, Heijman J, Wang Q, Chiang DY, Li N, Karck M, et al. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. Circulation. 2014;129(2):145-56.

[29] Wakili R, Voigt N, Kaab S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. J Clin Invest. 2011;121(8):2955-68.

[30] Nattel S. New ideas about atrial fibrillation 50 years on. Nature. 2002;415(6868):219-26.

[31] Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999;100(1):87-95.

[32] Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol. 2008;1(1):62-73.

[33] Yue L, Xie J, Nattel S. Molecular determinants of cardiac fibroblast electrical function and therapeutic implications for atrial fibrillation. Cardiovasc Res. 2011;89(4):744-53.

[34] McManus DD, Xanthakis V, Sullivan LM, Zachariah J, Aragam J, Larson MG, et al. Longitudinal tracking of left atrial diameter over the adult life course: Clinical correlates in the community. Circulation. 2010;121(5):667-74.

[35] Cardin S, Li D, Thorin-Trescases N, Leung TK, Thorin E, Nattel S. Evolution of the atrial fibrillation substrate in experimental congestive heart failure: angiotensin-dependent and -independent pathways. Cardiovasc Res. 2003;60(2):315-25.

[36] Boldt A, Wetzel U, Weigl J, Garbade J, Lauschke J, Hindricks G, et al. Expression of angiotensin II receptors in human left and right atrial tissue in atrial fibrillation with and without underlying mitral valve disease. J Am Coll Cardiol. 2003;42(10):1785-92.

[37] Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, et al. The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. Europace. 2009;11(4):423-34.

[38] Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82(8A):2N-9N.

[39] Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, et al. Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation. 2015;132(8):624-32.

[40] Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994;89(2):724-30.

[41] Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Jr., Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327(10):685-91.

[42] Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35.

[43] Van den Berg MP, Tuinenburg AE, Crijns HJ, Van Gelder IC, Gosselink AT, Lie KI. Heart failure and atrial fibrillation: current concepts and controversies. Heart. 1997;77(4):309-13.

[44] Tomaselli GF, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res. 1999;42(2):270-83.

[45] Nattel S, Li D. Ionic remodeling in the heart: pathophysiological significance and new therapeutic opportunities for atrial fibrillation. Circ Res. 2000;87(6):440-7.

[46] Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. J Am Coll Cardiol. 2010;55(21):2299-307.

[47] Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet. 2014;384(9961):2235-43.

[48] Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, et al. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. J Am Coll Cardiol. 2012;59(18):1598-603.

[49] van den Berg NW, de Groot JR. Myocardial infarction, atrial fibrillation and mortality: timing is everything. Neth Heart J. 2015;23(9):428-9.

[50] Lokshyn S, Mewis C, Kuhlkamp V. Atrial fibrillation in coronary artery disease. Int J Cardiol. 2000;72(2):133-6.

[51] Weijs B, Pisters R, Haest RJ, Kragten JA, Joosen IA, Versteylen M, et al. Patients originally diagnosed with idiopathic atrial fibrillation more often suffer from insidious coronary artery disease compared to healthy sinus rhythm controls. Heart Rhythm. 2012;9(12):1923-9.

[52] Kralev S, Schneider K, Lang S, Suselbeck T, Borggrefe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. PLoS One. 2011;6(9):e24964.

[53] Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Rooij FJ, Lip GY, et al. Subclinical atherosclerosis and risk of atrial fibrillation: the rotterdam study. Arch Intern Med. 2007;167(4):382-7.

[54] Xiong Z, Liu T, Tse G, Gong M, Gladding PA, Smaill BH, et al. A Machine Learning Aided Systematic Review and Meta-Analysis of the Relative Risk of Atrial Fibrillation in Patients With Diabetes Mellitus. Front Physiol. 2018;9:835.

[55] Lamberts RR, Lingam SJ, Wang HY, Bollen IA, Hughes G, Galvin IF, et al. Impaired relaxation despite upregulated calcium-handling protein atrial myocardium from type 2 diabetic patients with preserved ejection fraction. Cardiovasc Diabetol. 2014;13:72.

[56] Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. Heart Rhythm. 2013;10(1):90-100.

[57] Li B, Pan Y, Li X. Type 2 Diabetes Induces Prolonged P-wave Duration without Left Atrial Enlargement. J Korean Med Sci. 2016;31(4):525-34.

[58] Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, et al. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). Am J Cardiol. 2014;114(8):1217-22.

[59] Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, et al. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes

mellitus: a population-based dynamic cohort and in vitro studies. Cardiovasc Diabetol. 2014;13:123.

[60] Tsang TS, Barnes ME, Miyasaka Y, Cha SS, Bailey KR, Verzosa GC, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J. 2008;29(18):2227-33.

[61] Berkovitch A, Kivity S, Klempfner R, Segev S, Milwidsky A, Erez A, et al. Body mass index and the risk of new-onset atrial fibrillation in middle-aged adults. Am Heart J. 2016;173:41-8.

[62] Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013;310(19):2050-60.

[63] Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007;49(5):565-71.

[64] Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J. 2003;21(6):1012-6.

[65] Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. Am J Respir Crit Care Med. 2001;163(7):1632-6.

[66] Hall MJ, Ando S, Floras JS, Bradley TD. Magnitude and time course of hemodynamic responses to Mueller maneuvers in patients with congestive heart failure. J Appl Physiol (1985). 1998;85(4):1476-84.

[67] Schafer H, Hasper E, Ewig S, Koehler U, Latzelsberger J, Tasci S, et al. Pulmonary haemodynamics in obstructive sleep apnoea: time course and associated factors. Eur Respir J. 1998;12(3):679-84.

[68] Roche F, Xuong AN, Court-Fortune I, Costes F, Pichot V, Duverney D, et al. Relationship among the severity of sleep apnea syndrome, cardiac arrhythmias, and autonomic imbalance. Pacing Clin Electrophysiol. 2003;26(3):669-77.

[69] Stevenson IH, Roberts-Thomson KC, Kistler PM, Edwards GA, Spence S, Sanders P, et al. Atrial electrophysiology is altered by acute hypercapnia but not hypoxemia: implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. Heart Rhythm. 2010;7(9):1263-70.

[70] Ogi H, Nakano Y, Niida S, Dote K, Hirai Y, Suenari K, et al. Is structural remodeling of fibrillated atria the consequence of tissue hypoxia? Circ J. 2010;74(9):1815-21.

[71] Terzano C, Romani S, Conti V, Paone G, Oriolo F, Vitarelli A. Atrial fibrillation in the acute, hypercapnic exacerbations of COPD. Eur Rev Med Pharmacol Sci. 2014;18(19):2908-17.

[72] Kirkham PA, Barnes PJ. Oxidative stress in COPD. Chest. 2013;144(1):266-73.

[73] Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59(7):574-80.

[74] Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003;42(5):1050-65.

[75] Hart RG, Eikelboom JW, Brimble KS, McMurtry MS, Ingram AJ. Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol. 2013;29(7 Suppl):S71-8.

[76] Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol. 2011;4(1):26-32.

[77] Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence. Eur Heart J. 2006;27(5):512-8.

[78] Schlaich MP, Socratous F, Hennebry S, Eikelis N, Lambert EA, Straznicky N, et al. Sympathetic activation in chronic renal failure. J Am Soc Nephrol. 2009;20(5):933-9.

[79] Chen PS, Tan AY. Autonomic nerve activity and atrial fibrillation. Heart Rhythm. 2007;4(3 Suppl):S61-4.

[80] Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. 2012;345:e7895.

[81] Auer J, Eber B. [Subclinical hyperthyroidism and atrial fibrillation]. Acta Med Austriaca. 2003;30(4):98-9.

[82] Chen YC, Chen SA, Chen YJ, Chang MS, Chan P, Lin CI. Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes. J Am Coll Cardiol. 2002;39(2):366-72.

[83] Chamberlain AM, Agarwal SK, Folsom AR, Duval S, Soliman EZ, Ambrose M, et al. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. Heart Rhythm. 2011;8(8):1160-6.

[84] Zevin S, Saunders S, Gourlay SG, Jacob P, Benowitz NL. Cardiovascular effects of carbon monoxide and cigarette smoking. J Am Coll Cardiol. 2001;38(6):1633-8.

[85] Goette A, Lendeckel U, Kuchenbecker A, Bukowska A, Peters B, Klein HU, et al. Cigarette smoking induces atrial fibrosis in humans via nicotine. Heart. 2007;93(9):1056-63.

[86] Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. J Am Coll Cardiol. 2014;64(3):281-9.

[87] Denison H, Jern S, Jagenburg R, Wendestam C, Wallerstedt S. Influence of increased adrenergic activity and magnesium depletion on cardiac rhythm in alcohol withdrawal. Br Heart J. 1994;72(6):554-60.

[88] Maki T, Toivonen L, Koskinen P, Naveri H, Harkonen M, Leinonen H. Effect of ethanol drinking, hangover, and exercise on adrenergic activity and heart rate variability in patients with a history of alcohol-induced atrial fibrillation. Am J Cardiol. 1998;82(3):317-22.

[89] Preedy VR, Siddiq T, Why H, Richardson PJ. The deleterious effects of alcohol on the heart: involvement of protein turnover. Alcohol Alcohol. 1994;29(2):141-7.

[90] Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. J Interv Card Electrophysiol. 2000;4(2):369-82.

[91] Levy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. Circulation. 1999;99(23):3028-35.

[92] Sears SF, Serber ER, Alvarez LG, Schwartzman DS, Hoyt RH, Ujhelyi MR. Understanding atrial symptom reports: objective versus subjective predictors. Pacing Clin Electrophysiol. 2005;28(8):801-7.

[93] Goette A, Bukowska A, Dobrev D, Pfeiffenberger J, Morawietz H, Strugala D, et al. Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles. Eur Heart J. 2009;30(11):1411-20.

[94] Range FT, Schafers M, Acil T, Schafers KP, Kies P, Paul M, et al. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation. Eur Heart J. 2007;28(18):2223-30.

[95] Skinner NS, Jr., Mitchell JH, Wallace AG, Sarnoff SJ. Hemodynamic Consequences of Atrial Fibrillation at Constant Ventricular Rates. Am J Med. 1964;36:342-50.

[96] Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. J Am Coll Cardiol. 1997;30(4):1039-45.

[97] Daoud EG, Weiss R, Bahu M, Knight BP, Bogun F, Goyal R, et al. Effect of an irregular ventricular rhythm on cardiac output. Am J Cardiol. 1996;78(12):1433-6.

[98] van den Berg MP, Hassink RJ, Tuinenburg AE, Lefrandt JD, de Kam PJ, Crijns HJ. Impaired autonomic function predicts dizziness at onset of paroxysmal atrial fibrillation. Int J Cardiol. 2001;81(2-3):175-80.

[99] Bao Z, Chen H, Yang B, Shehata M, Ju W, Zhang F, et al. Prolonged Sinus Pauses upon Termination of Paroxysmal Atrial Fibrillation: Abnormal Right Atrial Electrophysiologic and Electroanatomic Findings. Tex Heart Inst J. 2017;44(2):107-14.

[100] Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. Am Heart J. 2006;152(6):1097-103.

[101] Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. Neurology. 2013;80(17):1546-50.

[102] Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120-9.

[103] Winter Y, Wolfram C, Schaeg M, Reese JP, Oertel WH, Dodel R, et al. Evaluation of costs and outcome in cardioembolic stroke or TIA. J Neurol. 2009;256(6):954-63.

[104] Bruggenjurgen B, Rossnagel K, Roll S, Andersson FL, Selim D, Muller-Nordhorn J, et al. The impact of atrial fibrillation on the cost of stroke: the berlin acute stroke study. Value Health. 2007;10(2):137-43.

[105] Wasilewska M, Gosk-Bierska I. Thromboembolism associated with atrial fibrillation as a cause of limb and organ ischemia. Adv Clin Exp Med. 2013;22(6):865-73.

[106] European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31(19):2369-429.

[107] Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500-10.

[108] Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med. 2013;158(5 Pt 1):338-46.

[109] Thacker EL, McKnight B, Psaty BM, Longstreth WT, Jr., Sitlani CM, Dublin S, et al. Atrial fibrillation and cognitive decline: a longitudinal cohort study. Neurology. 2013;81(2):119-25.

[110] Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. Stroke. 1980;11(1):35-8.

[111] Zito M, Muscari A, Marini E, Di Iorio A, Puddu GM, Abate G. Silent lacunar infarcts in elderly patients with chronic non valvular atrial fibrillation. Aging (Milano). 1996;8(5):341-6.

[112] Houmsse M, Tyler J, Kalbfleisch S. Supraventricular tachycardia causing heart failure. Curr Opin Cardiol. 2011;26(3):261-9.

[113] Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12(10):1360-420.

[114] Gutierrez C, Blanchard DG. Atrial fibrillation: diagnosis and treatment. Am Fam Physician. 2011;83(1):61-8.

[115] Gutierrez C, Blanchard DG. Diagnosis and Treatment of Atrial Fibrillation. Am Fam Physician. 2016;94(6):442-52.

[116] Cooke G, Doust J, Sanders S. Is pulse palpation helpful in detecting atrial fibrillation? A systematic review. J Fam Pract. 2006;55(2):130-4.

[117] Davis RC, Hobbs FD, Kenkre JE, Roalfe AK, Iles R, Lip GY, et al. Prevalence of atrial fibrillation in the general population and in high-risk groups: the ECHOES study. Europace. 2012;14(11):1553-9.

[118] Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost. 2013;110(2):213-22.

[119] Sabzwari SRA, Garg L, Lakkireddy D, Day J. Ten Lifestyle Modification Approaches to Treat Atrial Fibrillation. Cureus. 2018;10(5):e2682.

[120] Heeringa J, Kors JA, Hofman A, van Rooij FJ, Witteman JC. Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. Am Heart J. 2008;156(6):1163-9.

[121] Kayrak M, Gul EE, Aribas A, Akilli H, Alibasic H, Abdulhalikov T, et al. Self-reported sleep quality of patients with atrial fibrillation and the effects of cardioversion on sleep quality. Pacing Clin Electrophysiol. 2013;36(7):823-9.

[122] Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol. 2015;65(20):2159-69.

[123] Lampert R, Jamner L, Burg M, Dziura J, Brandt C, Liu H, et al. Triggering of symptomatic atrial fibrillation by negative emotion. J Am Coll Cardiol. 2014;64(14):1533-4.

[124] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857-67.

[125] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with

warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.

[126] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.

[127] Olesen JB, Sorensen R, Hansen ML, Lamberts M, Weeke P, Mikkelsen AP, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. Europace. 2015;17(2):187-93.

[128] Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med. 1999;131(7):492-501.

[129] Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206-14.

[130] Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol. 1995;25(2):452-9.

[131] Holmes DR, Jr., Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, et al. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. J Am Coll Cardiol. 2015;65(24):2614-23.

[132] Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, Hoosien M, et al. Utilization and adverse outcomes of percutaneous left atrial appendage closure for stroke prevention in atrial fibrillation in the United States: influence of hospital volume. Circ Arrhythm Electrophysiol. 2015;8(1):42-8.

[133] Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. Eur J Cardiothorac Surg. 2015;47(5):847-54.

[134] Umana E, Solares CA, Alpert MA. Tachycardia-induced cardiomyopathy. Am J Med. 2003;114(1):51-5.

[135] Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, et al. The evidence regarding the drugs used for ventricular rate control. J Fam Pract. 2000;49(1):47-59.

[136] Siu CW, Lau CP, Lee WL, Lam KF, Tse HF. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. Crit Care Med. 2009;37(7):2174-9; quiz 80.

[137] Kotecha D, Kirchhof P. What's new in the 2016 ESC Guidelines on atrial fibrillation? Eur Heart J. 2016;37(38):2851-2.

[138] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol (Engl Ed). 2016;69(12):1167.

[139] Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. Am J Cardiol. 1998;81(5):594-8.

[140] Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010;362(15):1363-73.

[141] Lundstrom T, Ryden L. Ventricular rate control and exercise performance in chronic atrial fibrillation: effects of diltiazem and verapamil. J Am Coll Cardiol. 1990;16(1):86-90.

[142] Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? J Am Coll Cardiol. 2003;42(11):1944-51.

[143] Lip GY, Tello-Montoliu A. Management of atrial fibrillation. Heart. 2006;92(8):1177-82.

[144] Lim KT, Davis MJ, Powell A, Arnolda L, Moulden K, Bulsara M, et al. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. Europace. 2007;9(7):498-505.

[145] Queiroga A, Marshall HJ, Clune M, Gammage MD. Ablate and pace revisited: long term survival and predictors of permanent atrial fibrillation. Heart. 2003;89(9):1035-8.

[146] Garcia B, Clementy N, Benhenda N, Pierre B, Babuty D, Olshansky B, et al. Mortality After Atrioventricular Nodal Radiofrequency Catheter Ablation With Permanent Ventricular Pacing in Atrial Fibrillation: Outcomes From a Controlled Nonrandomized Study. Circ Arrhythm Electrophysiol. 2016;9(7).

[147] Gitt AK, Smolka W, Michailov G, Bernhardt A, Pittrow D, Lewalter T. Types and outcomes of cardioversion in patients admitted to hospital for atrial fibrillation: results of the German RHYTHM-AF Study. Clin Res Cardiol. 2013;102(10):713-23.

[148] Mittal S, Ayati S, Stein KM, Schwartzman D, Cavlovich D, Tchou PJ, et al. Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. Circulation. 2000;101(11):1282-7.

[149] Mann CJ, Kendall S, Lip GY, Guideline Development Group for the Ncgftmoaf. Acute management of atrial fibrillation with acute haemodynamic instability and in the postoperative setting. Heart. 2007;93(1):45-7.

[150] Schadlich PK, Schmidt-Lucke C, Huppertz E, Lehmacher W, Nixdorff U, Stellbrink C, et al. Economic evaluation of enoxaparin for anticoagulation in early cardioversion of persisting nonvalvular atrial fibrillation: a statutory health insurance perspective from Germany. Am J Cardiovasc Drugs. 2007;7(3):199-217.

[151] Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med. 2001;344(19):1411-20.

[152] Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2012(5):CD005049.

[153] Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. Pacing Clin Electrophysiol. 2013;36(1):122-33.

[154] Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, et al. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. Lancet. 2012;380(9838):238-46.

[155] Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med. 1995;333(2):77-82.

[156] Harris L, McKenna WJ, Rowland E, Holt DW, Storey GC, Krikler DM. Side effects of long-term amiodarone therapy. Circulation. 1983;67(1):45-51.

[157] Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med. 2005;352(18):1861-72.

[158] Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med. 2007;357(10):987-99.

[159] Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med. 2009;360(7):668-78.

[160] Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20(1):e1-e160.

[161] Haissaguerre M, Gencel L, Fischer B, Le Metayer P, Poquet F, Marcus FI, et al. Successful catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 1994;5(12):1045-52.

[162] Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two

systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009;2(4):349-61.

[163] Noheria A, Kumar A, Wylie JV, Jr., Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review. Arch Intern Med. 2008;168(6):581-6.

[164] Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2(2):e004549.

[165] Sanchez-Quintana D, Lopez-Minguez JR, Pizarro G, Murillo M, Cabrera JA. Triggers and anatomical substrates in the genesis and perpetuation of atrial fibrillation. Curr Cardiol Rev. 2012;8(4):310-26.

[166] Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N Engl J Med. 2016;374(23):2235-45.

[167] Callans DJ, Gerstenfeld EP, Dixit S, Zado E, Vanderhoff M, Ren JF, et al. Efficacy of repeat pulmonary vein isolation procedures in patients with recurrent atrial fibrillation. J Cardiovasc Electrophysiol. 2004;15(9):1050-5.

[168] Lin D, Santangeli P, Zado ES, Bala R, Hutchinson MD, Riley MP, et al. Electrophysiologic findings and long-term outcomes in patients undergoing third or more catheter ablation procedures for atrial fibrillation. J Cardiovasc Electrophysiol. 2015;26(4):371-7.

[169] Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, et al. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. Eur Heart J. 2006;27(23):2871-8.

[170] Knecht S, Hocini M, Wright M, Lellouche N, O'Neill MD, Matsuo S, et al. Left atrial linear lesions are required for successful treatment of persistent atrial fibrillation. Eur Heart J. 2008;29(19):2359-66.

[171] Di Biase L, Burkhardt JD, Mohanty P, Sanchez J, Mohanty S, Horton R, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation. 2010;122(2):109-18.

[172] Hocini M, Shah AJ, Nault I, Sanders P, Wright M, Narayan SM, et al. Localized reentry within the left atrial appendage: arrhythmogenic role in patients undergoing ablation of persistent atrial fibrillation. Heart Rhythm. 2011;8(12):1853-61.

[173] Di Biase L, Burkhardt JD, Mohanty P, Mohanty S, Sanchez JE, Trivedi C, et al. Left Atrial Appendage Isolation in Patients With Longstanding Persistent AF Undergoing Catheter Ablation: BELIEF Trial. J Am Coll Cardiol. 2016;68(18):1929-40.

[174] Verma N, Knight BP. Left atrial appendage isolation at the time of atrial fibrillation ablation. Heart Rhythm. 2018;15(12):1754-5.

[175] Di Biase L, Natale A, Romero J. Thrombogenic and Arrhythmogenic Roles of the Left Atrial Appendage in Atrial Fibrillation. Circulation. 2018;138(18):2036-50.

[176] Heeger CH, Rillig A, Geisler D, Wohlmuth P, Fink T, Mathew S, et al. Left Atrial Appendage Isolation in Patients Not Responding to Pulmonary Vein Isolation. Circulation. 2019;139(5):712-5.

[177] Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, et al. Complications of catheter ablation of atrial fibrillation: a systematic review. Circ Arrhythm Electrophysiol. 2013;6(6):1082-8.

[178] Khairy P, Chauvet P, Lehmann J, Lambert J, Macle L, Tanguay JF, et al. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation. 2003;107(15):2045-50.

[179] Reddy VY, Sediva L, Petru J, Skoda J, Chovanec M, Chitovova Z, et al. Durability of Pulmonary Vein Isolation with Cryoballoon Ablation: Results from the Sustained PV Isolation with Arctic Front Advance (SUPIR) Study. J Cardiovasc Electrophysiol. 2015;26(5):493-500.

[180] Dorwarth U, Schmidt M, Wankerl M, Krieg J, Straube F, Hoffmann E. Pulmonary vein electrophysiology during cryoballoon ablation as a predictor for procedural success. J Interv Card Electrophysiol. 2011;32(3):205-11.

[181] Hoffmann E, Straube F, Wegscheider K, Kuniss M, Andresen D, Wu LQ, et al. Outcomes of cryoballoon or radiofrequency ablation in symptomatic paroxysmal or persistent atrial fibrillation. Europace. 2019.

[182] Kuck KH, Albenque JP, Chun KJ, Furnkranz A, Busch M, Elvan A, et al. Repeat Ablation for Atrial Fibrillation Recurrence Post Cryoballoon or Radiofrequency Ablation in the FIRE AND ICE Trial. Circ Arrhythm Electrophysiol. 2019;12(6):e007247.

[183] Knecht S, Sticherling C, von Felten S, Conen D, Schaer B, Ammann P, et al. Long-term comparison of cryoballoon and radiofrequency ablation of paroxysmal atrial fibrillation: a propensity score matched analysis. Int J Cardiol. 2014;176(3):645-50.

[184] Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol. 2008;52(4):273-8.

[185] Knecht S, Nault I, Wright M, Matsuo S, Lellouche N, Somasundaram PE, et al. Imaging in catheter ablation for atrial fibrillation: enhancing the clinician's view. Europace. 2008;10 Suppl 3:iii2-7.

[186] O'Neill MD, Jais P, Hocini M, Sacher F, Klein GJ, Clementy J, et al. Catheter ablation for atrial fibrillation. Circulation. 2007;116(13):1515-23.

[187] De Ponti R, Zardini M, Storti C, Longobardi M, Salerno-Uriarte JA. Trans-septal catheterization for radiofrequency catheter ablation of cardiac arrhythmias. Results and safety of a simplified method. Eur Heart J. 1998;19(6):943-50.

[188] Schmidt M, Straube F, Ebersberger U, Dorwarth U, Wankerl M, Krieg J, et al. [Cardiac computed tomography and ablation of atrial fibrillation]. Herzschrittmacherther Elektrophysiol. 2012;23(4):281-8.

[189] Sra J, Narayan G, Krum D, Malloy A, Cooley R, Bhatia A, et al. Computed tomography-fluoroscopy image integration-guided catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2007;18(4):409-14.

[190] Dong J, Calkins H, Solomon SB, Lai S, Dalal D, Lardo AC, et al. Integrated electroanatomic mapping with three-dimensional computed tomographic images for real-time guided ablations. Circulation. 2006;113(2):186-94.

[191] Niinuma H, George RT, Arbab-Zadeh A, Lima JA, Henrikson CA. Imaging of pulmonary veins during catheter ablation for atrial fibrillation: the role of multi-slice computed tomography. Europace. 2008;10 Suppl 3:iii14-21.

[192] Jongbloed MR, Bax JJ, Lamb HJ, Dirksen MS, Zeppenfeld K, van der Wall EE, et al. Multislice computed tomography versus intracardiac echocardiography to evaluate the pulmonary veins before radiofrequency catheter ablation of atrial fibrillation: a head-to-head comparison. J Am Coll Cardiol. 2005;45(3):343-50.

[193] Sharma K, Brinker JA, Henrikson CA. Computed Tomography Imaging in Atrial Fibrillation Ablation. J Atr Fibrillation. 2011;4(1):319.

[194] Nedios S, Sommer P, Bollmann A, Hindricks G. Advanced Mapping Systems To Guide Atrial Fibrillation Ablation: Electrical Information That Matters. J Atr Fibrillation. 2016;8(6):1337.

[195] Knackstedt C, Schauerte P, Kirchhof P. Electro-anatomic mapping systems in arrhythmias. Europace. 2008;10 Suppl 3:iii28-34.

[196] Hoffmann E, Nimmermann P, Reithmann C, Elser F, Remp T, Steinbeck G. New mapping technology for atrial tachycardias. J Interv Card Electrophysiol. 2000;4 Suppl 1:117-20.

[197] Reithmann C, Hoffmann E, Dorwarth U, Remp T, Steinbeck G. Electroanatomical mapping for visualization of atrial activation in patients with incisional atrial tachycardias. Eur Heart J. 2001;22(3):237-46.

[198] Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19):1812-22.

[199] Sultan A, Luker J, Andresen D, Kuck KH, Hoffmann E, Brachmann J, et al. Predictors of Atrial Fibrillation Recurrence after Catheter Ablation: Data from the German Ablation Registry. Sci Rep. 2017;7(1):16678.

[200] Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol. 2011;108(1):47-51.

[201] Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005;45(2):285-92.

[202] Cha YM, Friedman PA, Asirvatham SJ, Shen WK, Munger TM, Rea RF, et al. Catheter ablation for atrial fibrillation in patients with obesity. Circulation. 2008;117(20):2583-90.

[203] Oral H, Chugh A, Scharf C, Hall B, Cheung P, Veerareddy S, et al. Pulmonary vein isolation for vagotonic, adrenergic, and random episodes of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2004;15(4):402-6.

[204] Themistoclakis S, Schweikert RA, Saliba WI, Bonso A, Rossillo A, Bader G, et al. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. Heart Rhythm. 2008;5(5):679-85.

[205] Abecasis J, Dourado R, Ferreira A, Saraiva C, Cavaco D, Santos KR, et al. Left atrial volume calculated by multi-detector computed tomography may predict successful pulmonary vein isolation in catheter ablation of atrial fibrillation. Europace. 2009;11(10):1289-94.

[206] Miyazaki S, Kuwahara T, Kobori A, Takahashi Y, Takei A, Sato A, et al. Preprocedural predictors of atrial fibrillation recurrence following pulmonary vein antrum isolation in patients with paroxysmal atrial fibrillation: long-term follow-up results. J Cardiovasc Electrophysiol. 2011;22(6):621-5.

[207] Berruezo A, Tamborero D, Mont L, Benito B, Tolosana JM, Sitges M, et al. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. Eur Heart J. 2007;28(7):836-41.

[208] Dilaveris PE, Gialafos EJ, Andrikopoulos GK, Richter DJ, Papanikolaou V, Poralis K, et al. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. Pacing Clin Electrophysiol. 2000;23(3):352-8.

[209] Letsas KP, Weber R, Burkle G, Mihas CC, Minners J, Kalusche D, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. Europace. 2009;11(2):158-63.

[210] Pinto Teixeira P, Martins Oliveira M, Ramos R, Rio P, Silva Cunha P, Delgado AS, et al. Left atrial appendage volume as a new predictor of atrial fibrillation recurrence after catheter ablation. J Interv Card Electrophysiol. 2017;49(2):165-71.

[211] Wang Y, Di Biase L, Horton RP, Nguyen T, Morhanty P, Natale A. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. J Cardiovasc Electrophysiol. 2010;21(9):973-82.

[212] Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol. 2012;60(6):531-8.

[213] Kimura T, Takatsuki S, Inagawa K, Katsumata Y, Nishiyama T, Nishiyama N, et al. Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS2 scores. Heart Rhythm. 2013;10(6):921-5.

[214] Straube F, Dorwarth U, Schmidt M, Wankerl M, Ebersberger U, Hoffmann E. Comparison of the first and second cryoballoon: high-volume single-center safety and efficacy analysis. Circ Arrhythm Electrophysiol. 2014;7(2):293-9.

[215] Straube F, Dorwarth U, Vogt J, Kuniss M, Heinz Kuck K, Tebbenjohanns J, et al. Differences of two cryoballoon generations: insights from the prospective multicentre, multinational FREEZE Cohort Substudy. Europace. 2014;16(10):1434-42.

[216] Schmidt M, Dorwarth U, Straube F, Daccarett M, Rieber J, Wankerl M, et al. Cryoballoon in AF ablation: impact of PV ovality on AF recurrence. Int J Cardiol. 2013;167(1):114-20.

[217] Avelar E, Durst R, Rosito GA, Thangaroopan M, Kumar S, Tournoux F, et al. Comparison of the accuracy of multidetector computed tomography versus two-dimensional echocardiography to measure left atrial volume. Am J Cardiol. 2010;106(1):104-9.

[218] Clarnette JA, Brooks AG, Mahajan R, Elliott AD, Twomey DJ, Pathak RK, et al. Outcomes of persistent and long-standing persistent atrial fibrillation ablation: a systematic review and meta-analysis. Europace. 2018;20(FI_3):f366-f76.

[219] Rillig A, Tilz RR, Lin T, Fink T, Heeger CH, Arya A, et al. Unexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation After Electrical Isolation of the Left Atrial Appendage for the Treatment of Atrial Tachyarrhythmias. Circ Arrhythm Electrophysiol. 2016;9(5):e003461.

[220] Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One. 2013;8(5):e63479.

[221] Vogt J, Heintze J, Gutleben KJ, Muntean B, Horstkotte D, Nolker G. Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. J Am Coll Cardiol. 2013;61(16):1707-12.

[222] Aryana A, Singh SM, Kowalski M, Pujara DK, Cohen AI, Singh SK, et al. Acute and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using the Second-Generation Cryoballoon versus Open-Irrigated Radiofrequency: A Multicenter Experience. J Cardiovasc Electrophysiol. 2015;26(8):832-9.

[223] Knight BP, Novak PG, Sangrigoli R, Champagne J, Dubuc M, Adler SW, et al. Long-Term Outcomes After Ablation for Paroxysmal Atrial Fibrillation Using the Second-Generation Cryoballoon: Final Results From STOP AF Post-Approval Study. JACC Clin Electrophysiol. 2019;5(3):306-14.

[224] Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3(1):32-8.

[225] Kocyigit D, Yalcin MU, Gurses KM, Turk G, Ardali S, Canpolat U, et al. Impact of anatomical features of the left atrial appendage on outcomes after cryoablation for atrial fibrillation. J Cardiovasc Comput Tomogr. 2019;13(2):105-12.

[226] Kaseno K, Tada H, Koyama K, Jingu M, Hiramatsu S, Yokokawa M, et al. Prevalence and characterization of pulmonary vein variants in patients with atrial fibrillation determined using 3-dimensional computed tomography. Am J Cardiol. 2008;101(11):1638-42.

[227] Khoueiry Z, Albenque JP, Providencia R, Combes S, Combes N, Jourda F, et al. Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy. Europace. 2016;18(9):1343-51.

[228] Hof I, Chilukuri K, Arbab-Zadeh A, Scherr D, Dalal D, Nazarian S, et al. Does left atrial volume and pulmonary venous anatomy predict the outcome of catheter ablation of atrial fibrillation? J Cardiovasc Electrophysiol. 2009;20(9):1005-10.

[229] Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: Implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol. 2000;9(2):95-101.

[230] Beck H, Curtis AB. Sex Differences In Outcomes Of Ablation Of Atrial Fibrillation. J Atr Fibrillation. 2014;6(6):1024.

[231] Akoum N, Mahnkopf C, Kholmovski EG, Brachmann J, Marrouche NF. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. Europace. 2018;20(7):1086-92.

[232] Singh SM, D'Avila A, Aryana A, Kim YH, Mangrum JM, Michaud GF, et al. Persistent Atrial Fibrillation Ablation in Females: Insight from the MAGIC-AF Trial. J Cardiovasc Electrophysiol. 2016;27(11):1259-63.

[233] Zylla MM, Brachmann J, Lewalter T, Hoffmann E, Kuck KH, Andresen D, et al. Sex-related outcome of atrial fibrillation ablation: Insights from the German Ablation Registry. Heart Rhythm. 2016;13(9):1837-44.

[234] Avgil Tsadok M, Gagnon J, Joza J, Behlouli H, Verma A, Essebag V, et al. Temporal trends and sex differences in pulmonary vein isolation for patients with atrial fibrillation. Heart Rhythm. 2015;12(9):1979-86.

[235] Heeger CH, Bellmann B, Fink T, Bohnen JE, Wissner E, Wohlmuth P, et al. Efficacy and safety of cryoballoon ablation in the elderly: A multicenter study. Int J Cardiol. 2019;278:108-13.

[236] Zhang XD, Tan HW, Gu J, Jiang WF, Zhao L, Wang YL, et al. Efficacy and safety of catheter ablation for long-standing persistent atrial fibrillation in women. Pacing Clin Electrophysiol. 2013;36(10):1236-44.

[237] Gertz ZM, Raina A, Mountantonakis SE, Zado ES, Callans DJ, Marchlinski FE, et al. The impact of mitral regurgitation on patients undergoing catheter ablation of atrial fibrillation. Europace. 2011;13(8):1127-32.

[238] Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, et al. Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation. 1976;53(2):273-9.

[239] Messika-Zeitoun D, Bellamy M, Avierinos JF, Breen J, Eusemann C, Rossi A, et al. Left atrial remodelling in mitral regurgitation--methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. Eur Heart J. 2007;28(14):1773-81.

[240] Kistler PM, Earley MJ, Harris S, Abrams D, Ellis S, Sporton SC, et al. Validation of three-dimensional cardiac image integration: use of integrated CT image into electroanatomic mapping system to perform catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2006;17(4):341-8.

[241] Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and

surgical ablation of atrial fibrillation: Executive summary. Heart Rhythm. 2017;14(10):e445-e94.

[242] Pathan F, Hecht H, Narula J, Marwick TH. Roles of Transesophageal Echocardiography and Cardiac Computed Tomography for Evaluation of Left Atrial Thrombus and Associated Pathology: A Review and Critical Analysis. JACC Cardiovasc Imaging. 2018;11(4):616-27.

[243] Han FT, Bartus K, Lakkireddy D, Rojas F, Bednarek J, Kapelak B, et al. The effects of LAA ligation on LAA electrical activity. Heart Rhythm. 2014;11(5):864-70.

[244] Lakkireddy D, Sridhar Mahankali A, Kanmanthareddy A, Lee R, Badhwar N, Bartus K, et al. Left Atrial Appendage Ligation and Ablation for Persistent Atrial Fibrillation: The LAALA-AF Registry. JACC Clin Electrophysiol. 2015;1(3):153-60.

[245] Bordignon S, Chen S, Perrotta L, Bologna F, Nagase T, Konstantinou A, et al. Durability of cryoballoon left atrial appendage isolation: Acute and invasive remapping electrophysiological findings. Pacing Clin Electrophysiol. 2019;42(6):646-54.

[246] Cabrera JA, Ho SY, Climent V, Sanchez-Quintana D. The architecture of the left lateral atrial wall: a particular anatomic region with implications for ablation of atrial fibrillation. Eur Heart J. 2008;29(3):356-62.

[247] Spencer RJ, DeJong P, Fahmy P, Lempereur M, Tsang MYC, Gin KG, et al. Changes in Left Atrial Appendage Dimensions Following Volume Loading During Percutaneous Left Atrial Appendage Closure. JACC Cardiovasc Interv. 2015;8(15):1935-41.

[248] Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012;367(17):1587-95.

[249] Kumar P, Mounsey JP. Atrial Substrate Modification for Atrial Fibrillation: Striving to Get Smarter. Circ Arrhythm Electrophysiol. 2017;10(11).

[250] Reddy VY, Schilling R, Grimaldi M, Horton R, Natale A, Riva S, et al. Pulmonary Vein Isolation With a Novel Multielectrode Radiofrequency Balloon

Catheter That Allows Directionally Tailored Energy Delivery: Short-Term Outcomes From a Multicenter First-in-Human Study (RADIANCE). Circ Arrhythm Electrophysiol. 2019;12(12):e007541.

[251] Dukkipati SR, Neuzil P, Kautzner J, Petru J, Wichterle D, Skoda J, et al. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. Heart Rhythm. 2012;9(6):919-25.

[252] Reddy VY, Neuzil P, Koruth JS, Petru J, Funosako M, Cochet H, et al. Pulsed Field Ablation for Pulmonary Vein Isolation in Atrial Fibrillation. J Am Coll Cardiol. 2019;74(3):315-26.

8.4 Abbreviations and acronyms

AF	Atrial fibrillation
ACT	Activated clotting time
AV	Atrioventricular
ASA	Acetylsalicylic acid
BMI	Body Mass Index
CA	Catheter Ablation
CAD	Coronary artery disease
CBA	Cryoballoon ablation
CCTA	Cardiac computed tomography angiography
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CS	Coronary sinus
DAD	Delayed afterdepolarizations
DM	Diabetes mellitus
EAM	Electroanatomical mapping
ECG	Electrocardiography
EHRA	European Hearth Rhythm Association
ESC	European society of cardiology
HF	Heart Failure

ICE	Intracardiac echocardiography
LA	Left atrium
LAA	Left atrial appendage
LAO	Left anterior oblique
LIPV	Left inferior pulmonary vein
LSPV	Left superior pulmonary vein
MACCE	Major adverse cardiovascular and cerebrovascular events
NOAC	New oral anticoagulants
NYHA	New York Heart Association
OAC	Oral anticoagulation
OSA	Obstructive sleep apnea
PN	Phrenic nerve
PV	Pulmonary veins
PVI	Pulmonary vein isolation
QoL	Quality of Life
RAO	Right anterior oblique
RAAS	Renin-Angiotensin-Aldosterone system
RFA	Radiofrequency ablation
RIPV	Right inferior pulmonary vein
ROC	Receiver operating characteristics

RSPV	Right superior pulmonary vein
SD	Standard deviations
TEE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
TTI	Time to isolation
VKA	Vitamin K antagonist

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Eidesstattliche Versicherung

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema

Impact of left atrial appendage morphology on the recurrence of atrial fibrillation after cryoballoon ablation and detailed analysis of pre-procedural computed tomography

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München, 09.12.2021 Janis Mario Pongratz