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The role of cardiac computed tomography in the risk prediction of patients with atrial fibrillation

PhD Thesis

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ABBREVIATIONS

AAD	antiarrhythmic drugs
AF	atrial fibrillation
ANP	atrial natriuretic peptide
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
CMR	cardiovascular magnetic resonance imaging
CTA	computed tomography angiography
EAT	epicardial adipose tissue
ESC	European Society of Cardiology
HR	hazard ratio
ICC	inter-class correlation coefficient
ICH	intracranial hemorrhage
iLAV	body surface area-indexed left atrial volume
INR	international normalized ratio
kV	kilovolt
LA	left atrium
LAA	left atrial appendage
LAAV	left atrial appendage volume
LV	left ventricle
LVEF	left ventricle ejection fraction
MDCT	multidetector-row computed tomography
MRI	magnetic resonance imaging
NOAC	non-vitamin K antagonist oral anticoagulants
OAC	oral anticoagulants
PA	pulmonary artery
PV	pulmonary vein
RF	radiofrequency
ROC	receiver operating characteristics
SD	standard deviation

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TEE	transesophageal echocardiography
TIA	transient ischemic attack
TTE	transthoracic echocardiography
TTR	time in range therapeutic
VKA	vitamin K antagonist
vWF	von Willebrand factor

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1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia that increases the risk of stroke, heart failure and hospitalization (1-3). Around 0.4% to 1% of the general adult population has AF and this rate increases with age, especially over the age of 80 to >9% (4). The number of affected individuals is expected to double or even triple within the next twenty to thirty years (4). In the developed countries the prevalence is higher than in the developing nations (5). Moreover, the prevalence is lower in women than in men (5). The most common risk factors of AF are age, hypertension, valvular and ischemic heart disease, thyroid dysfunction, obesity, diabetes, chronic obstructive pulmonary disease, chronic kidney disease and smoking (6). Catheter ablation is an effective and safe procedure to treat AF. However in many cases recurrence occurs, approximately 20% to 45% of the patients experience recurrence of AF within 12 months after the catheter ablation (7, 8).

AF can increase the risk of stroke about five times and since elder population is constantly growing AF will have an ascendant effect on stroke morbidity and mortality (9). Moreover, stroke due to AF likely to be more severe than non-AF related (10). In the setting of AF, the left atrial appendage (LAA) is the most common source of emboli (11). Additionally, according to Di Biase, LAA morphology is related to the risk of stroke (12). Moreover, the size of the LAA orifice area and the LAA flow velocity also correspond with the incidence of stroke (13). Therefore, it is important to better understand the anatomical and functional features of the LAA to understand AF related stroke pathogenesis.

1.1. Atrial fibrillation

1.1.1. Definition of atrial fibrillation

AF is a supraventricular tachyarrhythmia presented by uncoordinated atrial activation resulting in consequent termination of atrial mechanical function (14). In the diagnosis of AF, ECG has a major rule. On ECG, AF presents with (15-18):

1. irregular R-R intervals,
2. the absence of distinguishable p-waves
3. irregular atrial activity which is less than 200 milliseconds,

The ventricular rate commonly vary between 80 to 180/min (16). AF can appear from non-symptomatic to severe symptomatic forms (19). The symptoms of AF vary on a wide range. Patients with AF may experience symptoms like palpitations, chest pain, dizziness, fatigue and dyspnea (19). AF is often associated with structural heart disease or other comorbid chronic conditions like heart failure, stroke, hypertension, diabetes and obesity (20-22).

1.1.2. Prevalence of atrial fibrillation

In the last decades, AF has become one of the biggest burdens of health care and one of the major public health issues (22). The prevalence of AF increases significantly with age. As the elder population is constantly growing, the number of affected individuals by AF will be increasing too. Nevertheless, globally the main increase of AF prevalence is 0.04 % per year (22). According to the ATRIA (AnTicoagulation and Risk Factors In Atrial Fibrillation) Study (4) the prevalence of AF ranges from 0.1% among person <55 years of age to 9.0% among person over 80 years of age. The prevalence is higher in men than in women (23). In men, the prevalence increases from 0.2% to more than 11%, while in women from 0.1% to 9.1% (4).

In the United States, the overall number of people affected by AF increases approximately 2.5-fold by 2050 (4). In the developing nations, the prevalence of AF is markedly lower than in the developed countries (23). It is probably partly because of the improved ability to diagnose AF. In 2010, the estimated incidence rates of the world population were 77.5 in men and 59.5 in women, over the age of 30 years was 181.2 per 100.000 person-years

(23). In men, the estimated number of newly discovered AF cases per year is 2.7 million and in women it is 2.0 million (23). Several concomitant conditions such as hypertension, diabetes mellitus, myocardial infarction, heath failure, obstructive sleep apnea, obesity, smoking, alcohol abuse and the lack of exercise can lead to AF (6). Some of them are potentially reversible. Therefore, it may be possible to prevent some cases of AF through risk factor modification like glucose and blood pressure control, exercising and weight loss or smoking cessation and alcohol (24).

1.1.3. Classification of atrial fibrillation

According to the American College of Cardiology Foundation, the American Heart Association and the Heart Rhythm Society, AF may be classifed, according to the duration of episodes into different groups (15). A patient may have numerous episodes of paroxysmal AF and occasional persistent AF or the reverse (17). In this case the more frequent type will be used for categorization. The terminology of lone AF is used in case of patients <60 years of age without evidence of cardiopulmonary disease and hypertension (17). We can also differentiate valvular and nonvalvular AF. Nonvalvular AF occurs with the lack of rheumatic mitral stenosis, mitral valve repair or a mechanical or bioprosthetic heart valve (17, 18, 25). The above mentioned categorization has a clinical relevance in the outcomes of therapy (17). For example, catheter ablation has a better outcome in restoring sinus rhythm in the case of paroxysmal AF than in permanent AF. After 2 or more episodes, AF is termed recurrent (17). In the setting of acute myocardial infarction, cardiac surgery, myocarditis, hyperthyroidism, pericarditis, or acute pulmonary disease, the primary problem may not be AF, therefore considered as secondary or reversible AF (26).

1.1.4. Pathophysiology of atrial fibrillation

AF is a self-sustained cardiac arrhythmia. Several pathophysiological conditions can play a role in the development of AF. If high frequency atrial activation is maintained for at least 24 hours, ion channel remodeling occurs (27). The remodeling of ion channels contribute to sustained reentry and support the activation of triggers. There are three main

factors that can contribute to the pathogenesis of AF: trigger, substrate and systematic conditions.

a) **Trigger**: A trigger can evolve from different and these mechanisms may coexist. In focal automatic and microreentrant activity, the launching focus most often lies near to the orifices of the pulmonary veins (PVs) (28). In addition, usually sleeves of cardiac tissue extends into the PVs, which has electrical activation (29). Besides the PVs, foci that cause rapid atrial impulses can also be found in the superior vena cava, fossa ovalis, left posterior free wall, ligament of Marshall, coronary sinus and crista terminalis (30-33). These non-PV triggers usually appear after longer setting of AF and after the progression of the atrial remodeling. Furthermore, in some cases LAA can be found as the only source of arrhythmia (34).
b) **Substrate**: Substrates allows the initiation and maintenance of the reentry movements (35). Atrial remodeling results in structural and electrical changes. Substrates can develop during sinus rhythm, usually created by atrial pressure overload, atrial dilatation or ventricular remodeling. On the other hand, substrate can evolve due to tachycardia caused by AF (25). In the setting of AF, refractory period of the atrial tissue within the region of the PVs are briefer than in the rest of the atrium. This heterogenic conduction can lead to electrical remodeling and can create a substrate for AF (36).
c) **Systematic conditions**: As discussed previously, there are several concomitant conditions which predispose patients to AF. These diseases can lead to changes in myocytes and in the extracellular matrix including myocyte hypertrophy, apoptosis, necrosis, inflammatory infiltration, atrial fatty infiltration and electrical disconnection between muscle fibers (37). In some cases, AF is associated with atrial flutter which can cause atrial dilatation, pulmonary vein dilatation, reduced contractility and fibrosis. These anatomical changes explain why some of the patients with atrial flutter may have AF in a few years.

AF, especially in young patients with the lack of any other cardiovascular conditions, supposed to be associated with heritable component (38). These mutations can cause cardiomyopathies and channelopathies resulting the early-onset AF. The most important variants increase the risk of AF up to seven-fold (39). Some of these mutations are single

nucleotide polymorphisms. Due to silent AF, many of these also associated with cardioembolic or ischemic stroke (40, 41).

Previous studies have shown that AF produces changes in atrial structure and function. These findings can give possible explanation for the progressive and self-sustaining nature of this arrhythmia:

a) **Electrical remodeling** develops in the first few days of AF (42). The major impact of AF on the ion channels is the decreased activity of the L-type Ca^{2+} current and increased activity of the inward rectifier K^{+} current. This is the reason of the shortening of the atrial action potential. However, the atrial refractoriness becomes normal again within only a few days of sinus rhythm (42).
b) **Contractile remodeling** occurs after prolonged fibrillation, which leads to atrial contractile dysfunction (42). It seems mainly due to a depressed L-type Ca^{2+} current. In patients with sustained AF, contractile function was reduced by 75 % (42) .
c) **Structural remodeling** develops within weeks or months of sustained AF. AF induces structural changes in atrial myocytes such as (28):
    - growth in cell size,
    - perinuclear accumulation of glycogen,
    - myolysis,
    - modification in connexin expression and
    - alterations of mitochondrial shape.

Myolysis can be associated with increased atrial size (28). The above mentioned structural changes may be the physiological adaptation to chronic Ca^{2+} overload and metabolic stress (43). Furthermore, structural changes are predictors of failure to cardioversion (42). In addition, in the setting of chronic AF, interstitial fibrosis occurs (44). As a result of interstitial fibrosis, the left atrial function deteriorates. In the setting of sustained AF, atrial enlargement develops as a consequence (44). In the meantime, left atrial dilatation predispose patients to AF, especially in the elderly (45). Cardiovascular disease like hypertension, valvular disease or ventricular dysfunction can also cause structural remodeling in the atrium [48].

1.1.5. Therapy of atrial fibrillation

The aim of the AF patient's therapy is to reduce symptoms and prevent serious complications, like thromboembolic events (18). Management of AF patients includes antithrombotic therapy, control of ventricular rate and the treatment of underlying disease. If it is necessary, there are other additional treatments like rhythm control therapy by cardioversion, antiarrhythmic drug therapy, or catheter ablation therapy (18).

The commonly performed catheter ablation of AF has evolved from an experimental procedure in the past ten years (17, 46). Catheter ablation was developed to restore and maintain sinus rhythm by isolating or eliminating ectopic triggers of AF or by altering the arrhythmogenic substrate. This procedure seeks to electrically isolate the most common site of triggers for AF, the pulmonary veins. Moreover, the non PV triggers also can be eliminated (17). With the complete isolation of the PVs, highly experienced clinicians can achieve more efficacy than antiarrhythmic drug therapy in patients with symptomatic paroxysmal and persistent, in general as second-line treatment after refractory or intolerance to at least one class 1 or 3 antiarrhythmic medication (15, 46). In long-standing persistent AF, the most challenging part of the ablation is the extensive atrial remodeling and achieving sinus rhythm in these patients is associated with recovery of LA function (47, 48). Despite the success of restoring sinus rhythm with catheter ablation, recurrence occurs especially during the first 6 to 12 months after the procedure (17). In the meantime, the possibility of late recurrence is also high. There are several potential mechanisms of late recurrence of AF e.g., electrical reconnection of one or more PVs, previously not identified non-PV arrhythmogenic foci and atrial electrical and structural remodeling caused by older age, inflammation, heart failure, diabetes (17). In addition, Di Biase et al have been proposed that often the LAA is the source of recurrence in patients who needed repeat procedures (34). Late recurrence of AF is affected by several clinical and echocardiographic parameters such as, AF duration ≥4 years, non-paroxysmal AF, diabetes, left atrial diameter ≥45 mm, dense spontaneous echo contrast, early mitral inflow velocity and mitral annular early diastolic velocity (E/e') ≥ 10 and LAA flow velocity ≤40 cm/sec (49). The CABANA (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) Study shows a significant reduction is AF recurrence with the use of catheter ablation compared to medical therapy (50). Anticoagulation guidelines indicate that if the patient has AF for >48 hours or for

unknown duration, 3 weeks of anticoagulation therapy is recommended. If adequate systemic anticoagulation has not been maintained, transesophageal echocardiography (TEE) should be performed before the ablation procedure (51). After ablation, systematic anticoagulation recommended to continue for patients who are at high risk of stroke according to the CHA_2DS_2-VASc score (17).

In AF patients before catheter ablation, the LA, the LAA and the PV anatomy is usually observed by cardiovascular magnetic resonance imaging (CMR) or computed tomography angiography (CTA). There are two main techniques of ablation: radiofrequency (RF) ablation and cryoablation (52). The goal of RF ablation is to isolate the PVs from the LA causing tissue necrosis and irreversible loss of conduction by heating the tissues up to 50–55 °C. These lesions can be created with circumferential or linear ablation lines. The side effects of RF ablation are rare, but serious like, cardiac tamponade, ischaemic stroke, pulmonary stenosis and esophageal fistula. Tissue necrosis and loss of conduction are the results of cryoablation as well caused by freezing the tissue around the pulmonary vein ostia low to −60 °C. Phrenic nerve palsy or injury is the most common side effect of cryoablation (52).

1.2. Preablational computed tomography angiography

In patients with AF a cardiac CTA imaging procedure should be performed before the catheter ablation in addition to determine the LA anatomy (53-55). The cardiac CTA imaging provides information to electrophysiologists to plan the procedures. In patients with sinus rhythm, prospective ECG-triggered acquisition mode is applicable. In tachyarrhythmias like AF, retrospective ECG-gating should be considered. Nonetheless, modern CT scanners provide excellent image quality with prospective ECG-triggering acquisition mode in arrhythmic patients. If the patient has a high heart rate, the use of oral or intravenous β-blocker should be considered before the imaging. The most commonly applied β-blocker is metoprolol, not just because of its low price but because it can be used in chronic obstructive pulmonary disease and congestive heart failure (56). The LAA and PV anatomy is extremely variable in the population, therefore it is particularly important to evaluate it before the PV isolation. The most common anatomic variations are extra PV ostia or common trunk. Variations on the left side of the atria are more

common than on the right side. The complex LA and PV anatomy can be pictured by volume rendered CT reconstructions. CTA can be useful in the prevention of complications after catheter ablation. To prevent a lethal complication like the atrio-esophageal fistula, we can easily evaluate the anatomical connection between the LA and the esophagus. Real-time esophageal imaging recommended to reduce the risk of injury because esophagus is a moving organ and it can shift laterally (57). With a high negative predictive value, CTA can estimate the presence of LAA thrombi which is crucial before the catheter ablation. The detection of LAA thrombi can be recognized by a low attenuation filling deficit. The determination of thrombus and pseudothrombus can be achieved by performing an affirmative delayed phase.

The location of the superior and inferior vena cava, the anatomy of fossa ovalis and any anomalies that can disturb the transseptal puncture (e.g. lipomatous hypertrophy of the interatrial septum) can be determined with cardiac CTA. The selection of the catheter can depend on the volume rendered reconstructions of the LA and PV anatomy. Moreover, with the fusion of volume rendered reconstruction and electrophysiological information, the time of the procedure can be shorter, the radiation exposure to patient and health care providers can reduce and the procedure-related complications can be minimized. (53-55)

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2. OBJECTIVES

My thesis has three main aims. Firstly, we aimed to evaluate the relationship between LAA morphology and previous stroke or TIA in two large and distinct patient populations from the Semmelweis University, Budapest, Hungary and Leiden Medical Center, Leiden, the Netherlands.

Secondly, we aimed to evaluate whether posterior LA adipose tissue attenuation, as a marker of inflammation, is associated with PVI success rate.

Thirdly, we sought to determine the independent predictors of long-term recurrence of AF after catheter ablation procedure, depending on type of AF.

3. **RESULTS**

3.1. Anatomical characteristics of the LA and LAA in relation to the risk of stroke/TIA

3.1.1. Patient characteristics

In total, 1813 patients were included in this analysis (908 patients with AF and 905 patients without known AF). All patients, gave written informed consent. The study protocol was reviewed and approved by the Local Research Ethics Committee (SE RKEB: 142/2019). Mean age of the population was 59±11 years and 42% of the patients were female. Patients with AF were significantly older (61±10 vs 56±12, $p<0.001$), predominantly male (67% vs 49%, $p<0.001$) and had a higher prevalence of hypertension (57% vs 49%, $p<0.001$), obesity (22% vs 18%, $p=0.018$), and vascular disease (10% vs 7%, $p=0.011$), as compared with patients without known AF.

3.1.2. Anatomic characteristics of the LA and LAA according to AF status

Mean LA and LAA volumes were 94±31 and 7.7±4.3 mL, respectively in the overall population. In patients with AF, LA and LAA volumes were significantly larger compared with patients without known AF (LA volume: 109±32 vs 78±20 mL, and LAAV: 8.8±5.3 vs 6.6±2.5 mL, both $p<0.001$). Cauliflower was the most prevalent LAA morphology (53%) in the overall study population, followed by windsock (32%), chicken wing (11%), and swan LAA morphology (4%). No significant difference was found in LAA morphology between patients with vs without known AF, as it can be seen in ***Figure 1***.

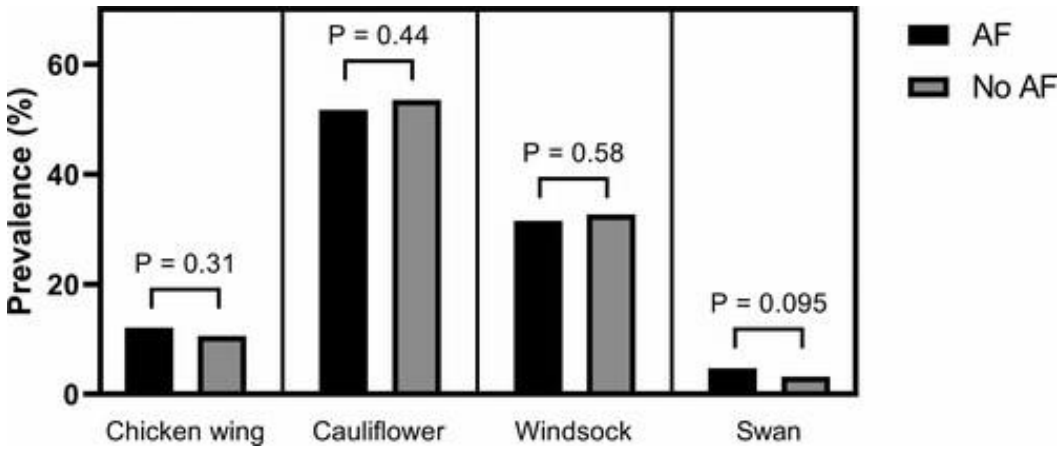

Figure 1. *Distribution of the four different types of LAA morphology in patients with and without known AF.*

3.1.3. Anatomic characteristics of the LA and LAA according to prior stroke/TIA

In total, 120 patients had a history of stroke or TIA (73 patients with AF and 47 patients without known AF). In patients with AF, LA and LAA volume were not significantly different between patients with and without prior stroke/TIA. In patients without known AF, LA volume was significantly higher in patients with prior stroke/TIA (86±23 vs 78±20 mL, p=0.011), while no significant difference was found for LAAV. Both in patients with and without known AF, the prevalence of chicken wing, cauliflower, and windsock LAA morphology was not significantly different between patients with and without prior stroke/TIA. In contrast, swan LAA morphology was significantly more prevalent in patients with prior stroke/TIA, both in patients with (11% vs 4%, p=0.009) and without known AF (11% vs 3%, p=0.003).

3.1.4. LAA morphology in relation to prior stroke/TIA

The stroke/TIA rate was the highest in patients with swan LAA morphology in the overall study population, as well as in patients with AF and without known AF, as it can be seen in ***Figure 2.***

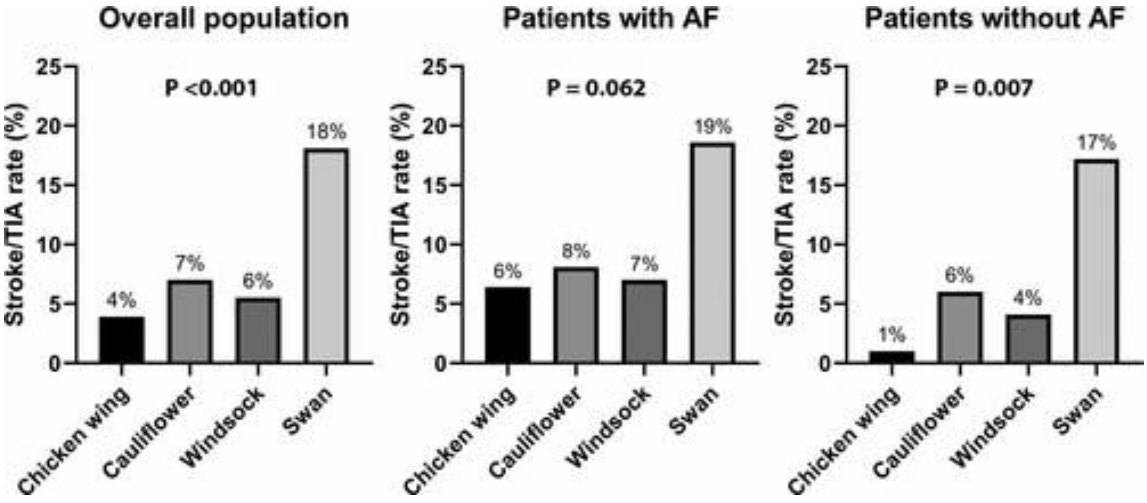

Figure 2. *The stroke/TIA rate in the overall patient population and in patients with and without known AF.*

Multivariable analysis showed an independent association between swan LAA morphology and prior stroke/TIA in the overall study population (odds ratio [OR]=3.40, p<0.001), and in patients with (OR=2.88, p=0.012) and without known AF (OR=3.96, p=0.011). Also, swan morphology remained significantly associated with prior stroke/TIA corrected for the CHA2DS2-VASc score (excluding prior stroke or TIA) in the overall study population (OR=3.50, p<0.001), as well as for patients with (OR=2.92, p=0.010) and without known AF (OR=4.29, p=0.006).

3.2. Posterior LA adipose tissue attenuation and AF recurrence

3.2.1. Patient characteristics

A total of 460 patients (66% male, age 61±10 years) were included in the analysis. All patients, gave written informed consent. The study protocol was reviewed and approved by the Local Research Ethics Committee (SE RKEB: 142/2019). There were 168 (37%) patients that developed AF recurrence after catheter ablation during a median follow-up period of 18 months (IQR: 6–32). Patients with AF recurrence after catheter ablation were older (62±10 vs 60±10 years; p=0.038), more often females (42% vs 30%, p=0.012), and had more often persistent AF (33% vs 18%, p<0.001).

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3.2.2. The association between posterior LA adipose tissue attenuation and AF recurrence

Patients with higher posterior LA adipose tissue attenuation had more cumulative recurrence rates of AF than patients with lower posterior LA adipose tissue attenuation as it can be seen in ***Figure 3.***

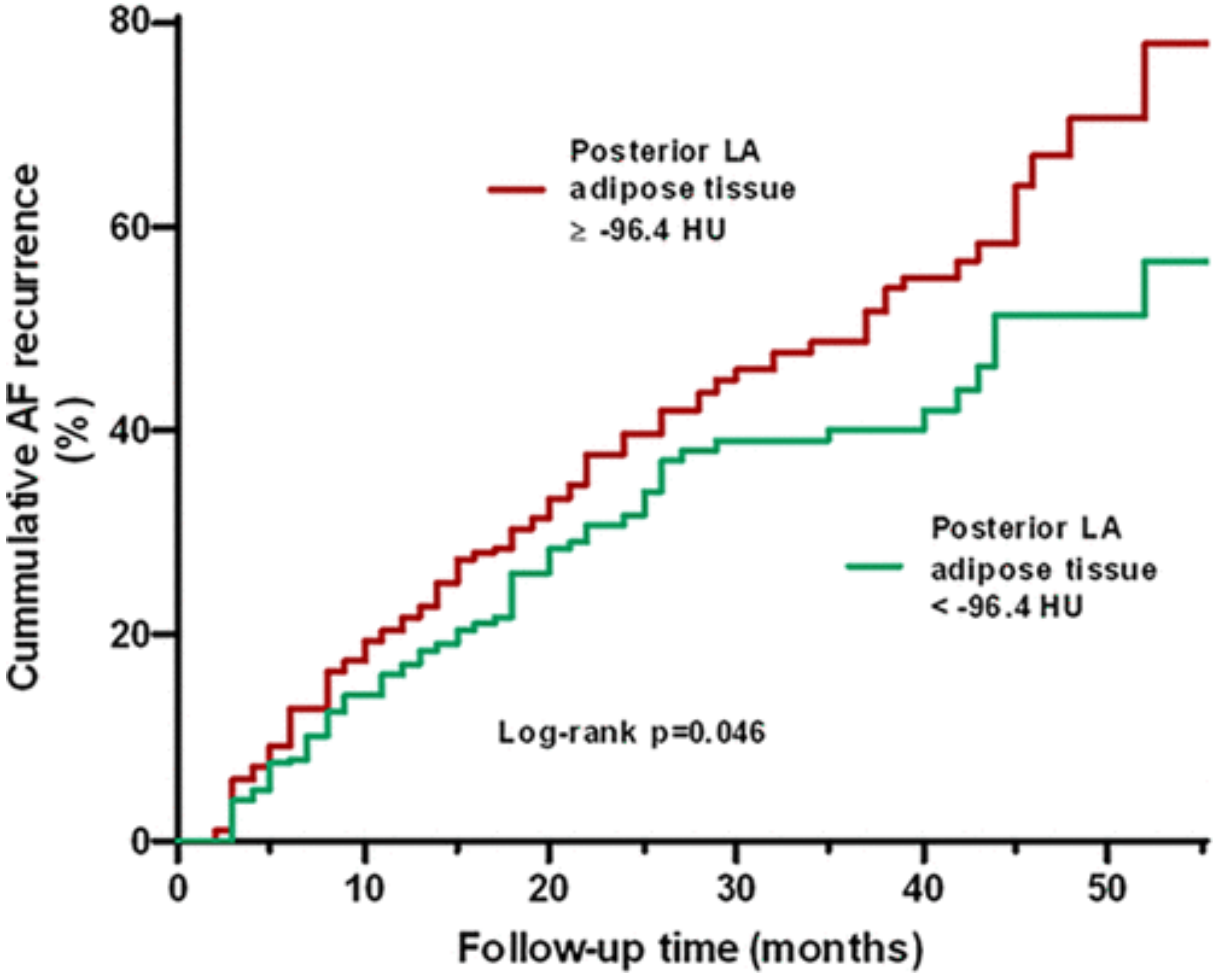

Figure 3. *Kaplan-Meier curve for AF recurrence after catheter ablation according to posterior LA adipose tissue attenuation.*

Table 1 summarizes the Cox regression analysis of the posterior LA adipose tissue mass and attenuation for AF recurrence. After correcting for known associates of AF, recurrence posterior LA adipose tissue attenuation (hazard ratio [HR]=1.26, *p*=0.181) remained a promising predictor of AF recurrence following catheter ablation.

Table 1. *Uni- and multivariable Cox regression analysis for AF recurrence after catheter ablation.* Abbreviations: CI=confidence intervall; HR=hazard ratio; HU=Hounsfield unit; LA=left atrium.

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Posterior LA adipose tissue mass (per one unit increase)	1.00 (0.97-1.03)	0.970	1.01 (0.97-1.04)	0.759
Posterior LA adipose tissue attenuation ≥-96.4 HU	1.37 (1.00-1.86)	0.047	1.26 (0.90-1.76)	0.181

3.3. Independent predictors of AF recurrence after radiofrequency catheter ablation in patients with paroxysmal and persistent AF

3.3.1. Patient characteristics

A total of 561 patients were included in the current analysis. All patients, gave written informed consent. The study protocol was reviewed and approved by the Local Research Ethics Committee (SE RKEB: 142/2019). Mean age was 62± 10 years and 34.9% of the patients were female. Recurrence of AF was reported in 40.8% of the patients (34.6% in patients with paroxysmal and 53.5% in those with persistent AF). Median recurrence-free time was 22.7 (IQR: 9.3–43.1) months (21.8 [9.4–43.2] months in paroxysmal and 23.6 [9.0–42.6] months in persistent AF). The proportion of individuals aged >65 years (40.7% vs 49.3%; p=0.046), female gender (30% vs 41.9%; p=0.005), persistent AF (25.9% vs 43.2%; p<0.001), and LVEF <50% (6.9% vs 21.0%; p<0.001) were significantly higher in patients with AF recurrence. Moreover, patients with AF recurrence had significantly higher iLAV (54.4±19.3 mL/m^2 vs 61.8±23.9 mL/m^2; p<0.001), LAAV (7.6±3.2 mL vs 8.8±5.2 mL; p=0.002) and LAA orifice area (387.6 ± 140.5 mm^2 vs 454.4±167.7 mm^2; p<0.001).

We also examined the differences of the clinical and imaging parameters between patients with paroxysmal and persistent AF. Those patients with persistent AF had significantly higher proportion of age > 65 years (41.0% vs 50.8%; p=0.030), hypertension (67% vs 85.9%; p<0.001) and LVEF<50% (6.6% vs 24.9%; p<0.001). Regarding the CT parameters, we measured significantly higher iLAV (51.0±15.9 mL/m^2 vs 70.4±25.6 mL/m^2; p<0.001), LAAV (7.4±3.0 mL vs 9.5±5.6 mL; p=0.002), LAA orifice area (385.2±132.8 mm^2 vs 475.2±179.7 mm^2; p<0.001) and lower LAA flow velocity

(35.3±13.4 cm/s vs 31.7±12.0 cm/s; p<0.001). Detailed data on the clinical and imaging parameters by AF type can be seen in ***Figure 4.***

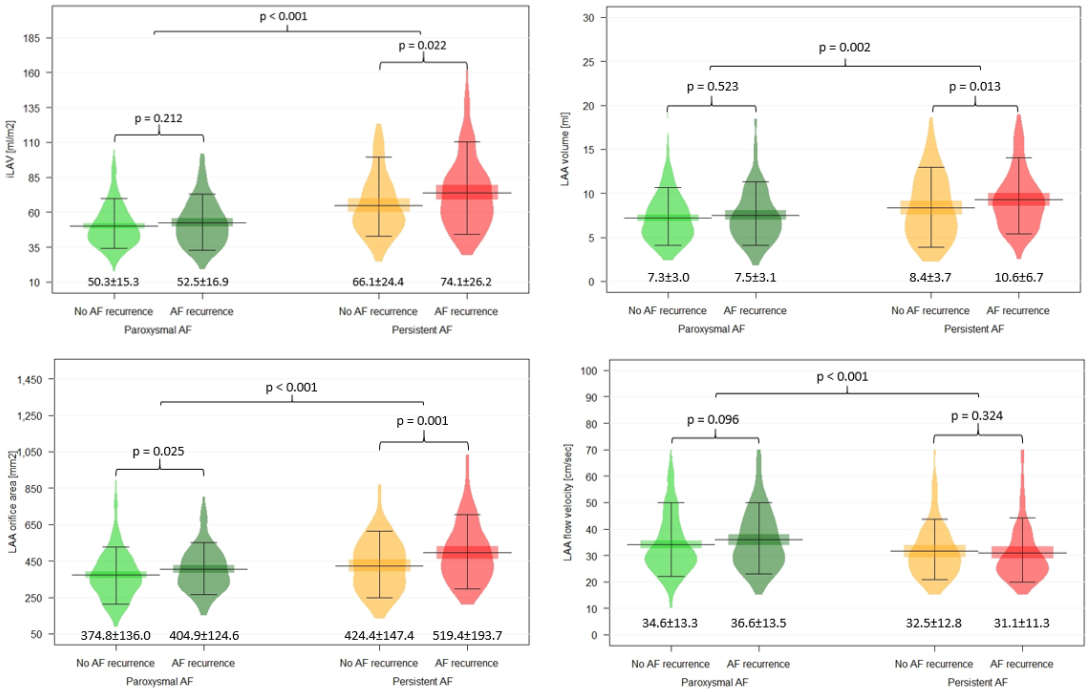

Figure 4. *Comparison of LA and LAA parameters between patients with and without AF recurrence, as stratified by AF type.*

3.3.2. Predictors of AF recurrence

Significantly higher iLAV and LAAV values were measured in patients with persistent AF recurrences, and larger LAA orifice area values were measured both in paroxysmal and persistent recurrences. To explore the associations between the various examined parameters and AF recurrence, Cox proportional hazards regression analyses were performed, as stratified by AF type. After adjustment LVEF <50% (HR=2.17, p<0.001) and LAAV (HR=1.06, p=0.029) remained a significant predictor of AF recurrence in patients with persistent AF, while in paroxysmal AF no independent predictors could be identified in the multivariate analysis. Kaplan–Meier curves of AF recurrence-free survival in persistent AF stratified by LVEF and LAAV can be seen in ***Figure 5.***

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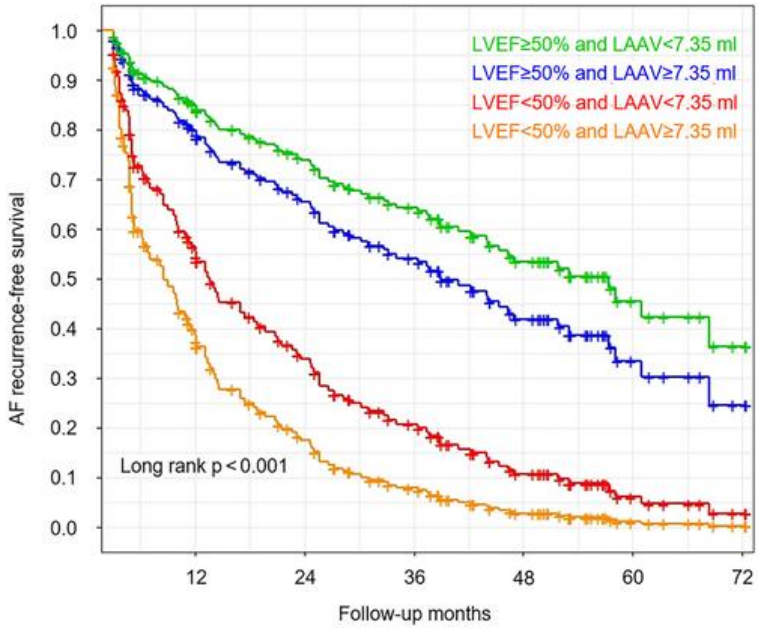

Figure 5. *Adjusted AF recurrence-free survival according to LVEF and LAAV in patients with persistent AF*

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4. **DISCUSSION**

We showed in two large and distinct patient cohorts that LAA swan morphology is associated with higher prevalence of stroke and/or TIA. Moreover, higher posterior LA adipose tissue attenuation is linked with increased risk of AF recurrence following AF catheter ablation. We demonstrated that beyond impaired LVEF, a larger LAAV is an independent predictor of AF recurrence in patients with persistent AF. Interestingly, this association was not present in patients with paroxysmal AF.

The LAA represents a frequent site of thrombus formation, since this part of the heart is prone to dysfunction, structural changes of the endothelium and abnormal blood stasis and homeostasis (58). The anatomic morphology of the LAA is highly variable. Previous studies have reported contradictory results regarding the association between LAA morphology and the risk of ischemic stroke. While Di Biase et al suggested that non-chicken wing morphology might be associated with increased risk of stroke, other authors reported that cauliflower morphology is more common in patients with ischemic stroke (59-61). However, these studies categorized LAA morphologies into cauliflower, windsock, chicken wing and cactus shapes, while we used other classification of cauliflower, windsock, chicken wing and swan morphologies, as previously applied by van Rosendael et al (62). In our study, we found swan morphology of the LAA to be independently associated with prior stroke and/or TIA, both in patients with and without known AF. It could be hypothesized that swan LAA morphology, due to its curved structure, is associated with a lower flow velocity compared to other morphologies. As a consequence, swan LAA morphology may be prone to stasis of blood, leading to thrombus formation and the occurrence of stroke and/or TIA. Although conceptually attractive, further studies are needed to investigate the echocardiographic flow pattern in

swan LAA morphology and its relationship to thrombus formation and subsequent thrombo-embolism.

Obesity has been recognized as an important, and modifiable risk factor for AF development (63-67). Several studies demonstrated a linear relationship between BMI and AF risk (63, 64). Importantly, BMI as a marker of general adiposity incorporates both subcutaneous and visceral adipose tissue, although both structures are distinct (68). Of note, higher levels of proinflammatory adipokines are secreted by visceral adipose tissue as compared to subcutaneous adipose tissue, and visceral adipose tissue has been associated with a greater risk for cardiovascular diseases (68-70). EAT, the adipose tissue within the visceral layer of the pericardium, has demonstrated to be an important source of adipokines (70). Since there are no direct barriers between the EAT and the myocardium, a direct crosstalk between the two structures exists (70). Total EAT is a stronger predictor for the presence of AF as compared to BMI (71, 72). More specifically, the relation between peri-atrial EAT and AF was examined in a population of 618 patients in sinus rhythm or with AF. Although, peri-atrial EAT thickness was higher in patients with AF compared to those in sinus rhythm, posterior LA adipose tissue thickness had the strongest correlation with the occurrence of AF of all LA adipose tissue pads (73). Moreover, Batal et al. reported that only posterior LA adipose tissue thickness was significantly associated with AF burden (74). Subsequently, Rosendael and colleagues quantified the posterior LA adipose tissue and found that each gram increase in posterior LA adipose tissue mass was associated with an increase of 32% in the risk of AF (75). Using electroanatomic mapping of the LA, Mahajan et al. reported that low voltage areas were predominantly observed in the posterior and inferior regions of the LA, which corresponded to the location of EAT as detected with cardiac magnetic resonance (76).

While some studies also demonstrated a relation between peri-atrial EAT assessed on CT and late AF recurrence after ablation, others could not confirm this relation (77-81). This discrepancy could be explained by methodological differences in assessment of peri-atrial EAT. In the current study we could not demonstrate an association between the posterior LA adipose tissue mass and AF recurrence, which could be related to the large posterior LA adipose tissue mass (mean 10.1 gram for the total population). The higher BMI in the current population, compared to populations in previous studies, suggest higher adiposity and higher peri-atrial EAT in the current population. It may be that the posterior LA adipose tissue mass has reached the maximum mass in both the recurrence and no-recurrence groups. This is further supported by the higher total EAT in the current population compared to previous studies (77, 81).

Assessment of the posterior LA adipose tissue attenuation on CT is a novel and easily accessible tissue specific biomarker of inflammation prior to AF catheter ablation. Moreover, attenuation of peri-vascular EAT assessed from CT could be a marker to track response to anti-inflammatory therapy (82). In addition, several studies have demonstrated that anti-inflammatory therapy reduces the risk for AF (83, 84). Assessment of posterior LA adipose tissue attenuation may potentially guide/personalize the use of anti-inflammatory therapy to reduce AF recurrences.

AF is a complex disease with many incompletely understood mechanisms. Although significant progress has been made in the last two decades, the therapy remains suboptimal, particularly in persistent AF. Success rate of catheter ablation varies between 60 and 90% (85-87). Previous studies have shown that the majority of AF recurrence occurred in the first two years after catheter ablation (88). So far, persistent AF, LA enlargement, hypertension, diabetes mellitus, aging, obesity, heart failure, chronic renal

insufficiency and preprocedural amiodarone failure have been reported as independent predictors of AF recurrence (88-93). However, the data are controversial and the conclusions of previous studies are inconsistent. Several studies aimed to investigate the role of different scoring systems in the prediction of rhythm outcomes after AF ablation. While the HATCH score was found to have no value in the prediction of AF recurrence after catheter ablation, R_2CHADS_2 and CHA_2DS_2-VASc scores were associated with rhythm outcomes (94, 95). Since APPLE score proved to be superior to the CHA_2DS_2-VASc score for the prediction of rhythm outcome after catheter ablation, we incorporated its factors into our multivariable models (96). Due to inconsistent definition of recurrence, estimation of the AF ablation success is challenging (89, 90). Current guidelines of the European Society of Cardiology define AF recurrence as the occurrence of atrial tachyarrhythmia that last for more than 30 sec (89, 90). In the current studies, we have also applied this definition. Moreover, previous studies have reported a wide range of recurrent AF duration time following various ablation strategies. In our study, we included AF patients who underwent point-by-point catheter ablation procedure after 2014 in order to provide more useful information to the current clinical practice. Moreover, since efficacy of radiofrequency catheter ablation varies greatly between paroxysmal and persistent AF, we analyzed the outcomes separately by type of AF. Since radiofrequency catheter ablation procedure became more widely performed, clinical studies regarding the long-term effectiveness are warranted, especially in patients with persistent AF. In our study population the recurrence rate after point-by-point catheter ablation was 53.5% in persistent AF and 34.6% in paroxysmal AF after a single procedure. These findings suggest that catheter ablation in patient with persistent AF should be chosen very cautiously due to the low success rate. In the present study, left

ventricular systolic dysfunction and higher LAAV were identified as significant predictors of AF recurrence in patients with persistent AF who underwent point-by-point catheter ablation.

Di Biase et al have reported that LAA appears to be responsible for recurrence of AF/tachycardia in at least 27% of patients undergoing repeated ablation, especially in persistent AF cases (97). Moreover, electric isolation of the LAA was associated with a decreased AF burden (98). Despite the increasing evidence of the role of LAA in triggering atrial arrhythmias, the literature is scarce regarding the contributing mechanisms and factors. Previous smaller studies including both paroxysmal and persistent AF patients undergoing catheter ablation have shown that larger LAAV is associated with a higher risk of AF recurrence (99, 100). The LAA is known to be more compliant than the LA, and therefore may play an important role in the modulation of LA pressure and LAAV measurement could be a reliable tool in determining the structural and functional conditions of LA from the early stage of AF (101). In line with these findings, our results also suggest that LAAV may be a surrogate of increased LAA arrhythmogenicity. LAA has a complex anatomy and LAA enlargement might result in longer activation pathways and development of re-entry through interstitial fibrosis (102). Previous studies have reported that preserved LAA flow velocity plays a role in the maintenance of sinus rhythm after catheter ablation (103-105). In our study LAA flow velocity did not prove to be associated with AF outcome after ablation.

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5. **CONCLUSIONS**

We showed in two large and distinct cohorts of patients with and without documented AF that LAA swan morphology is associated with higher prevalence of stroke and/or TIA. We also aimed to determine the predictors of AF recurrence after catheter ablation procedure. Based on our results, posterior LA adipose tissue attenuation is a promising novel and tissue-specific biomarker of AF recurrence. Higher attenuation of the posterior LA adipose tissue might signal local inflammation and serve as an imaging biomarker of increased risk of AF recurrence. We have also demonstrates that beyond left ventricular systolic dysfunction, LAA enlargement is an independent predictor of AF recurrence after catheter ablation in persistent AF. Our results suggest that preprocedural assessment of LVEF and LAAV might contribute to optimal patient selection and aid to improve long-term results of ablation procedures in patients with persistent AF.

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6. SUMMARY

AF is the most common sustained rhythm disorder worldwide that is associated with 5-fold increased risk of stroke or TIA. Therefore risk prediction in these patients is essential. LAA is an important source of cardiac thrombus and appears important in the contribution of thromboembolism in patients with AF. In patients with AF, cardiac CTA imaging procedure should be performed before catheter ablation in addition to determine LA anatomy. Cardiac CTA provides information to the elctrophysiologists to plan the procedure. CTA has been shown to be an accurate imaging technique to assess LAA morphology. We showed in two large and distinct patient cohorts that LAA swan morphology is independetly associated with higher prevalence of stroke and/or TIA in the overall study population, (OR=3.5, p<0.001), as well as in patients with AF (OR=2.9, p=0.010) and without known AF (OR=4.3, p=0.006).

In case of drug-refractory symptomatic AF, cathater ablation of the PV orifices proved to be an effective solution for rhythm control. However, success rates of catheter ablation after 1 year is between 60% to 90%. We aimed to determine the predictors of AF recurrence after catheter ablation procedure. Based on our results, posterior LA adipose tissue attenuation is a promising novel and tissue-specific biomarker of AF recurrence (HR=1.3, p=0.181 for posterior LA adipose tissue attenuation ≥-96.4 HU). Higher attenuation of the posterior LA adipose tissue might signal local inflammation and serve as an imaging biomarker of increased risk of AF recurrence.

We have also demonstrated that beyond left ventricular systolic dysfunction (HR=2.2, p<0.001 for LVEF <50%), LAA enlargement is an independent predictor of AF recurrence after catheter ablation in persistent AF (HR=1.1, p=0.029 per 1 ml increase in LAAV). Our results suggest that preprocedural assessment of LVEF and LAAV might contribute to optimal patient selection and aid to improve long-term results of ablation procedures in patients with persistent AF.

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