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Prediction of atrial fibrillation recurrence following one-year catheter ablation using atrial mechanical dispersion assessed by speckle tracking echocardiography

Dissertation

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1. Introduction

1.1 Background

Atrial Fibrillation (AF) is the most common sustained arrhythmia, defined as an uncoordinated electrical activation of the atria that can lead to ineffective atrial contraction. AF currently affects approximately 34 million individuals globally and is projected to double in old patients by 2060. This increasing incidence of AF is due in part to a greater overall life expectancy, as well as an increased survival rate of patients with other cardiovascular diseases that may predispose these patients to AF (Chugh et al. 2014; Krijthe et al. 2013). AF can seriously affect an individual's quality of life as it is associated with severe complications, such as stroke and heart failure, leading to increased morbidity and mortality and elevated healthcare costs (Anon 2022).

Clinical AF is staged based on clinical manifestation, duration, and spontaneous termination as first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (Hindricks et al. 2021). It is considered a progressive process, that is, AF often begins as a paroxysmal form of arrhythmia before progressing to a more persistent and eventually permanent condition.

Mechanisms underlying AF are 'trigger' and 'substrate' theories (Wijesurendra and Casadei 2019). A 'trigger' is a fast-firing focus outside the sinoatrial node (ectopic beats) that can act as an initiator for AF. The pulmonary vein was identified as the main source of atrial triggers in many AF cases (Haïssaguerre et al. 1998), which is the theoretical basis for pulmonary vein isolation (PVI). Other locations of triggers include inferior and superior caval veins, Marshall ligament, crista terminals, coronary sinus, the posterior free wall of left atria, and the left atrial appendage (Nattel and Dobrev 2012; Wijesurendra and Casadei 2019). The 'substrate' facilitates the maintenance of AF. This vulnerable 'substrate' is a consequence of electrical and structural remodeling, especially within the left atrium (LA). Electrical remodeling refers to altered electrical activation and conduction due to changes in ion channels (such as Ca^{2+} and K^{+} channels). Structural remodeling is characterized by modifications of myocardial structure, mainly including atrial dilatation (Nattel, Burstein, and Dobrev 2008). Atrial fibrosis seems to play a vital role in the development and progression of AF (Platonov et al. 2011). In return, AF

as well can promote fibrosis (Burstein et al. 2007), resulting in the idea that 'AF begets AF'.

Despite the increased prevalence of AF, current clinical therapies are not sufficiently effective in the long term. Current pharmaceutical approaches for AF mainly prolong the effective refractory period or extend action potential duration by targeting ion channels (Wijesurendra and Casadei 2019). Antiarrhythmic drugs have low efficacy in stopping the progression of AF and are limited by their potential adverse effects. In recent decades, catheter ablation has emerged as a mainstay in electrical rhythm control strategies outlined in current clinical guidelines (Hindricks et al. 2021). The cornerstone of AF catheter ablation is PVI, which uses heat, cold, or electrical pulse energy to electrically isolate the pulmonary veins by creating a complete circumferential lesion (Hindricks et al. 2021; Verma et al. 2023). Yet, recurrence of AF post-ablation has been estimated to occur in 20 – 45% of cases, necessitating early diagnosis in patients with a risk of AF recurrence to aid in better candidate selection and in identifying appropriate ablation strategies.

Over the past few decades, substantial technological advancements have been achieved in cardiac imaging, which can help predict catheter ablation outcomes and AF recurrence following ablation (Bax, Marsan, and Delgado 2015). Changes in the left atrium are considered a potential sign of adverse cardiovascular outcomes. By current imaging techniques involving echocardiography, cardiac magnetic resonance (CMR), and cardiac computed tomography (CCT), LA properties can be examined using a diversity of parameters. LA size, which is an indicator of the risk of stroke, as well as the likelihood of atrial fibrillation recurrence post-ablation, might be underestimated by echocardiography while it can be more precisely estimated by CMR or CCT. In addition, CMR and CCT have the capability to measure the quantity, location, size, and geometry of pulmonary veins to assist in catheter ablation (Markman, Khoshknab, and Nazarian 2021). However, CMR has several disadvantages, such as prolonged scan time, image quality that may be influenced by heart rhythm and breathing excursions, high expense, complicated operation, and claustrophobia reported in some patients, all of which limit its wider clinical application (Arnold and McCann 2020; Floria et al. 2020). The limitations of CCT include ionizing radiation, image quality vulnerable to heart rate (>60bpm), and unavailable to patients with renal insufficiency (Markman et al. 2021).

Echocardiography continues to be the primary imaging tool in the field of cardiology and is pivotal for evaluating heart conditions before catheter ablation for AF. Transthoracic echocardiography (TTE) can evaluate cardiac anatomy and function, chamber dimensions, intracardiac pressure gradients, and valvular performance, while transesophageal echocardiography (TEE) is commonly employed to identify the presence of thrombus in the left atrial appendage (LAA) before catheter ablation. Despite several advantages of CMR and CCT, echocardiography remains the fundamental and essential examination pre- and post-ablation due to its safety, low costs, practicality, and accessibility (Markman et al. 2021).

LA is in the posterior region of the heart. The LA chamber is positioned in a more posterior and superior location compared with the right atrial chamber. LA possesses a discernible appendage, which takes the appearance of a finger-like pouch that extends from the main body of the left atrium. While the majority of LA walls exhibit a smooth surface, pits and crevices are frequently observed in the area surrounding the entrance of its appendage (Ho, Cabrera, and Sanchez-Quintana 2012; Ho and McCarthy 2010). The function of the LA can be categorized into three distinct phases: reservoir, conduit, and booster pump. The reservoir phase refers to the inflow of blood from pulmonary veins during ventricular systole. The conduit phase involves passive emptying of the atrium during ventricular early diastole. The booster pump phase denotes the active emptying of the atrium during ventricular end diastole (Barbier et al. 1999). LA plays a vital role in left ventricular (LV) filling and overall cardiac performance. It dynamically interacts with both ventricular diastole and systole throughout the cardiac cycle (Bisbal et al. 2020; Legallois et al. 2022).

1.2 Imaging variables and recurrence of AF following catheter ablation

1.2.1 Left atrial size

It is widely reported that LA enlargement is a risk predictor for the recurrence of AF following ablation (Akutsu et al. 2011; Goette et al. 2002). LA anteroposterior diameter obtained in the parasternal long-axis view is generally utilized due to the repeatable results. However, it might not properly represet the true size of the atrium because of the asymmetric remodeling of LA and sometimes changes in other LA dimensions are underestimated. Researchers proposed to evaluate LA

size by LA volume (Shin et al. 2008) and given that body size is a significant factor in determining LA size, LA volume index (LAVi) is recommended as a standardized index to predict AF recurrence (Evangelista et al. 2008; Kranert et al. 2020; Roberto M. Lang et al. 2015). Incidentally, enlargement and remodeling of the right atrium (RA) are also reported to contribute to the recurrence of AF (Shin et al. 2008; Wen et al. 2017). Currently, available methods for the measurement of LA volume include the ellipsoid model biplane area-length and biplane Simpson's method, among which biplane Simpson's method is recommended. Compared with 2D echocardiography, three-dimensional (3D) echocardiography can prevent underestimating the volume of LA caused by geometric assumptions and atrial cavity foreshortening. It can estimate the volume of LA across various phases of the cardiac cycle with lower variability. However, the measurement of 3D echocardiography can be affected when arrhythmias occur, and the confined apical acoustic window hampers the precision of atrial volume measurement (Ji et al. 2022; Mor-Avi et al. 2012; Rodevan et al. 1999).

1.2.2 Left atrial ejection fraction

LA ejection fraction (LAEF) is calculated as the ratio of the difference in LA emptying volume to the maximum LA volume, which is feasible to reflect the LA function. LAEF obtained by echocardiography and CMR serves as an independent predictor for the recurrence of AF has been reported in several studies (Chou et al. 2018; Chubb et al. 2019; Habibi et al. 2016). Similar to the calculation of LVEF, LAEF is computed using the formula: LAEF = (LAVmax - LAVmin)/LAVmax (Triposkiadis et al. 1995).

1.2.3 Left atrial strain

More recently, impaired LA deformation has become an significant predictor for AF recurrence.

Strain refers to the fractional alteration of the length of each myocardial segment, representing the myocardium deformation. Several studies have shown that LA strain independently predicts AF recurrence post-ablation (Bajraktari, Bytyçi, and Henein 2020; Parwani et al. 2017). Temporal heterogeneity of LA deformation can be represented by atrial mechanical dispersion, which has been reported to be

associated with an increased risk of AF recurrence following ablation (Ciuffo et al. 2019; Kawakami et al. 2019; Sarvari et al. 2016).

Strain can be evaluated by tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE). TDI is the first used technique for strain measurement, but it's rarely applied for strain evaluation due to limitations such as susceptibility to imaging angle or signal-to-noise ratios. 2D-STE has become a widely used noninvasive technique for evaluating LA function (Yuda et al. 2016) and serves to evaluate the longitudinal deformation of the LA mechanics. Accurate tracking necessitates a high-quality grey-scale image and a frame rate ranging from 60 to 80 frames per second. The spatial displacement of each speckle (acoustic backscatter) position is tracked frame-by-frame for the whole duration of the cardiac cycle. In discontinuous areas of LA wall, such as regions that connect to the pulmonary veins or left atrial appendage, extrapolation of the epicardium and endocardium at the connection is conducted to get the ROI (Gan et al. 2018).The limitation of this technique is its incapability to examine the intricate cardiac geometry and might be affected by through-plane motion, whereas 3D-STE compensates for the shortcomings of 2D-STE, allowing for the evaluation of longitudinal, circumferential as well as radial strain. However, high requirements for image quality and low time resolution of 3D-STE restrict its clinical application (Ji et al. 2022).

1.2.4 Other left atrial parameters

Left atrial appendage (LAA) can coordinate the hemodynamics of the left atrium and a decrease in LAA contractility manifests the reduced LA function (Beigel et al. 2014). One study proved that patients with high LAA flow velocity (LAAFV) were more likely to remain in sinus rhythm 1-year post-cardioversion (Antonielli et al. 2002). On the contrary, reduced LAAFV is associated with AF recurrence after ablation (Fukushima et al. 2015; Kanda et al. 2015). LAA upward wall-motion velocity has also been reported to be a predictor for the recurrence of AF post-catheter ablation (Ariyama et al. 2015). The contraction of the left atrial appendage is typically evaluated by TEE. Other atrial functional parameters include LA stiffness index (LASI) (Machino-Ohtsuka et al. 2011) and LA sphericity (Moon et al. 2017).

1.2.5 Left ventricular parameters

Atrial fibrosis is well recognized as the hallmark of atrial remodeling and is considered the substrate for the maintenance of AF, while the ventricular myocardium may as well be affected, and ventricular fibrosis can be detected with the progression of AF (Dzeshka et al. 2015). Currently, the evaluation of ventricular fibrosis is mainly based on CMR with late-gadolinium enhancement (CMR-LGE)(Neilan et al. 2013) and T1 mapping (Florian et al. 2014). It was demonstrated that patients with increased left ventricular-LGE or native T1 time have a higher risk for AF recurrence (Kato et al. 2016; Suksaranjit et al. 2015), indicating that left ventricular fibrosis is one potential marker for AF recurrence (Kato et al. 2016).

Regarding ventricular systolic and diastolic function, the effect of left ventricular ejection fraction (LVEF) on AF recurrence is still controversial. Some studies found that individuals with AF recurrence have lower LVEF pre-ablation than those without AF recurrence, while other studies found that LVEF is not associated with AF recurrence post-ablation (Jin et al. 2018; Naruse et al. 2013; De Potter et al. 2010). Left ventricular diastolic dysfunction (LVDD) appears to have an influence on AF recurrence, as reported by numerous studies (Kosiuk et al. 2014; Onishi et al. 2018).

To sum up, although catheter ablation has become a major option for AF treatment, the recurrence rate is relatively high. The selection of appropriate tools for AF risk stratification and better candidate selection prior to the procedure would be of great clinical value.

2. Hypothesis

Generally, atrial fibrillation recurrences following ablation are more common in patients with an increased left atrial size, lower left atrial function, and higher left atrial fibrosis content (Bax et al. 2015; Thomas and Abhayaratna 2017). Although LA enlargement is widely recognized and used for predicting AF recurrence, AF recurrence post-ablation can also be detected in patients who do not exhibit LA enlargement, which may be clarified by the fact that functional disorder occurs before morphological alterations (Conen et al. 2013; Hong et al. 2013).

LA fibrosis is widely acknowledged as the hallmark of atrial remodeling (structural, electrical, and functional remodeling) and is common in individuals diagnosed with

AF (Dzeshka et al. 2015). It has also been reported as a predictive factor for the recurrence of AF post-ablation (Chubb et al. 2019; Marrouche et al. 2014). Left atrial fibrosis can cause atrial electrical dispersion, resulting in impaired regional myocardial contraction and Intra-atrial dyssynchrony. Minor changes of heterogeneity in atrial contraction can be detected by speckle-tracking echocardiography (STE) with atrial mechanical dispersion (AMD), which is defined as the standard deviation of the time to peak positive strain (SD-TPS) (Amlie 1997; Sarvari et al. 2016). The present study mainly concentrates on AMD as an echo parameter for predicting AF recurrence following one year of follow-up.

The aim is divided into two parts: (1) assess the association between LA mechanical dispersion and the recurrence of AF following catheter ablation and (2) evaluate LA mechanical dispersion in relation to additional new suggested imaging variables in relation to clinical variables like sex, age, and type of AF, which are evaluated in different models of AF recurrence following catheter ablation.

3. Methods

3.1 Study population

The cases utilized for the subsequent analysis are sourced from the ASTRA-AF (Atrial STrain in patients undeRgoing AtriAl Fibrillation Ablation) Pilot. Inclusion into the study was performed following written informed consent. Diagnostic of AF requires electrocardiogram (ECG) documentation that an AF episode lasting ≥ 30 s with irregular electrical rhythm (no discernible repeating P waves and irregular RR intervals) either on a 12-lead ECG or on a single-lead ECG (Hindricks et al. 2021). The initial sample contains 182 participants diagnosed with AF presenting for the first catheter ablation in the University Heart & Vascular Center Hamburg between December 2017 and January 2019. Exclusion criteria were age < 18 years old, left ventricular ejection fraction <50%, moderate to severe valvular heart disease, congenital heart disease, history of previous heart surgery, cardioversion < 4 weeks, poor imaging quality, data missing, AF at presentation, or any other arrhythmias. Persistent AF and long-lasting persistent AF were combined in one category. In this current analysis, 132 patients (59.8% men) with paroxysmal (88 patients) or persistent (44 patients) AF were finally included in our study cohort. Table 1

provides an overview of the clinical characteristics for both the entire population and individual patient groups.

3.2 Echocardiography

Transthoracic and transesophageal echocardiography (EPIQ, Philips, Holland) were conducted prior to catheter ablation. All participants were ensured to be in sinus rhythm throughout the examination. Image data processing and analysis were conducted by the software Cardiac Performance Analysis (IMAGE-COM, TOMTEC-ARENA, Tomtec Imaging System GmbH, Unterschleissheim, Germany). 2D speckle tracking echocardiography was performed following the consensus document (Badano et al. 2018). Briefly, LA endocardial border was manually traced and then the myocardium was automatically tracked during the entire cardiac cycle. Strain curves for both the global and regional left LA wall were generated by the system. Left ventricular end-diastole (the onset of QRS complex) was set as the zero-strain reference. The peak positive longitudinal strain is indicative of the atrial reservoir function, while the strain observed during early and late diastole is linked with conduit and booster function, respectively. The quantification of LA mechanical dispersion was calculated as the standard deviation of the time to peak positive strain (SD-TPS) standardized by the R-R interval. Higher values of SD-TPS indicate higher levels of mechanical dispersion and intra-atrial dyssynchrony. Conventional echocardiography was conducted following the current recommendations. The measurement technique was described previously (Kawakami et al. 2019) (Figure1). Regarding conventional echocardiography, LA ejection fraction is determined with the formula: Total emptying fraction = (LAVmax - LAVmin)/LAVmax. The additional echocardiography included LV ejection fraction, LV diastolic function, and some parameters were performed by 3D speckle tracking echocardiography as well. Measurements were according to the current recommendations (Roberto M. Lang et al. 2015) being as well applicable for strain measurements (Badano et al. 2018).

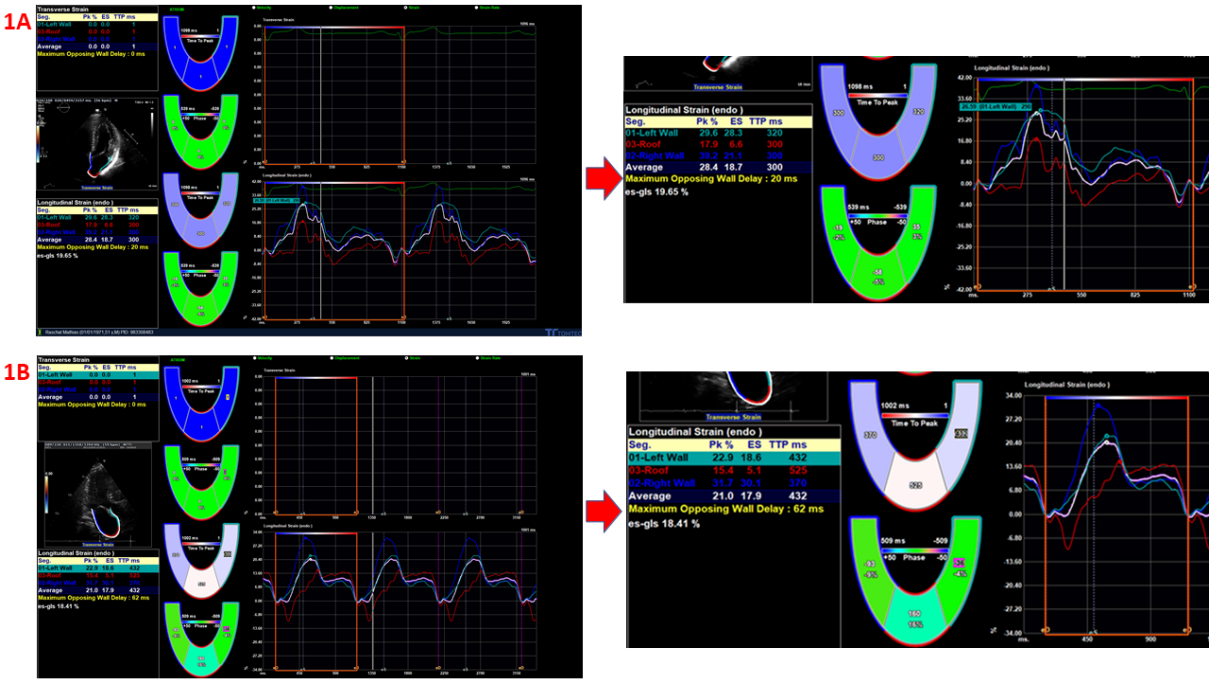

Figure 1 1A shows a patient with a low SD-TPS (9.4msec) regarding the standard deviation of the three segments left and right atrial wall and the roof of the atrium. 1B shows a patient with different time to peak and increased SD-TPS (63.7msec).

3.3 Clinical data and follow-up

The baseline data included patient characteristics (sex, age, height, weight, Body-Mass-Index [BMI], body-surface-area [BSA]), medical history (hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, previous ischemic stroke, previous myocardial infarction, previous cardioversion), medication history (oral anticoagulation and antiarrhythmic drugs), and the type of catheter ablation (radiofrequency ablation or cryoablation ablation). The CHA2DS2-VASc score was computed following current guidelines (Hindricks et al. 2021). After 12 months, all patients were invited to attend an additional echocardiography and a 24-hour Holter ECG to evaluate the recurrence of AF. Since the first three months post-ablation was the blanking time, AF recurrence was defined as an episode of atrial arrhythmia lasting for 30 seconds or longer beyond 90 days following ablation. Current antiarrhythmic drugs, anticoagulant therapy, further occurrence of stroke, or the requirement for pacemaker treatment were evaluated and documented.

Participants who were unable to make a follow-up visit were given a questionnaire and requested to provide a recent 24-hour Holter ECG.

3.4 Statistics

Continuous variables were presented as medians (25th percentile, 75th percentile), and group comparisons were conducted using the Mann-Whitney U test. Categorical variables were presented as numbers and percentages, with comparisons made using the chi-square (χ^2) test. The median follow-up time was estimated by the reverse Kaplan-Meier estimator, and the event rate was estimated by the Kaplan-Meier method. The primary endpoint is censored at one year of follow-up.

The Cox proportional hazards regression model was utilized to conduct univariate and multivariate analyses on clinical and ultrasound parameters that could potentially associated with AF recurrence and to determine the independent predictors for AF recurrence. All variables with a p-value < 0.25 in univariable regression were chosen for the multivariable model. Hazard Ratios (HR) and corresponding 95% confidence intervals (CI) are given and the respective results are displayed by forest plots. The vertical line at an HR of one is the line of no effect. A clipped CI is indicated by arrows.

The Receiver Operating Characteristic (ROC) curve analysis was established to get optimal cut-offs for the classification of the primary endpoint and assess the predictive value of risk factors. Thresholds with the maximal Youden Index are chosen for the cut-off value. The Kaplan-Meier survival curve was created based on the cut-off values. Differences between groups were tested using the log-rank test.

A p-value of <0.05 was considered statistically significant. All analyses rely on complete cases and were performed with R statistical software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

4. Results

4.1 Baseline characteristics

The study cohort consisted of 132 participants, of which 79 were male (59.8%). Paroxysmal atrial fibrillation (PAF) was diagnosed in 88 individuals, accounting for

66.7% of the cohort, whereas persistent atrial fibrillation (PersAF) was identified in 44 patients, representing 33.3% of the cohort (Table 1). The median CHA2DS2-VASc score was 2, with a range of 1 to 3. The median age of the cohort was 65.5 years, with an interquartile range (IQR) of 55 to 73. The distribution of patient characteristics was uniform throughout the cohort. The median height, weight, BMI, and BSA were 1.8m (Inter quartile range IQR: 1.7m;1.8m), 84.0kg (75.0kg, 94.6kg), 26.3 kg/ (m^2) (24.5 kg/ [m^2]), 29.0 kg/ [m^2]), and 2.0m^2 (1.9 m^2, 2.2 m^2), respectively. Cardiovascular risk factors were distributed evenly, except for a higher prevalence of smoking among patients with PersAF. There were 33 smokers (25.0%) in the cohort, 16 (18.2%) with PAF and 17 (38.6%) with PersAF. The number of individuals with hypertension, diabetes, dyslipidemia, coronary artery disease and heart failure was 78 (59.1), 7 (5.3), 18 (13.7), 15 (11.4) and 8 (6.1), respectively. 13 individuals (9.8%) had a history of ischemic stroke, while 13 patients (9.8%) had a history of myocardial infarction, and 57 (43.2%) patients had previously experienced cardioversion. Electrical cardioversion was more common in patients with PersAF (37, 84.1%) in comparison to PAF (20, 22.7%) ($p<0.001$). Oral anticoagulation was part of the medication in 67 patients with PAF, accounting for 76.1% of the total, and in 36 patients with PersAF, representing 81.8% of the total. Catheter ablation was performed using radiofrequency ablation in a total of 73 patients (40 with PAF, accounting for 45.5%, and 33 with PersAF, accounting for 75%, $p=0.002$). Additionally, cryoablation was utilized in 59 patients (48 with PAF, accounting for 54.5%, and 11 with PersAF, accounting for 25%, $p=0.002$).

4.2 Follow-up and recurrence of AF in the overall cohort

The maximum follow-up time was 1115 days, and the median follow-up time was 801 (776; 831) days. The censored follow-up time is 12 months, and AF recurrence rate was 22.7%.

Among 132 participants, 30 had recurrence of atrial fibrillation, of which 20 were diagnosed with PAF and 10 were diagnosed with PersAF. The baseline characteristics for the cohorts with and without recurrence of AF are shown in Table 2. Patients with AF recurrence had a median CHA2DS2-VASc score of 3.0 (1.9, 4.1), 1.5 times higher than the score of patients without AF recurrence (2.0 [1.0; 3.0]) ($p<0.001$). The distribution of patient characteristics was uniform except for

age being higher in AF recurrence group. The median age in AF recurrence group was 75.0 (57.9; 78.0), while 62.0 (54.9; 69.1) in the group without AF recurrence (p<0.001). Cardiovascular risks, medical and medication history, and the type of catheter ablation were distributed evenly throughout the cohort.

4.3 Imaging variables in the PAF and PersAF cohort

Imaging variables in the PAF and PersAF cohort are presented for conventional echocardiographic variables in Table 3 and for strain variables in Table 4. Regarding the LA size, the median overall LA volume indexed (LAVI) to BSA in patients with PAF (28.9ml/m² [21.2ml/m²; 35.0ml/m²]) was lower than that with PersAF (30.5ml/m² [25.9 ml/m²; 44.2ml/m²] [p=0.03]), and the same was shown for LA volume (p=0.008). The mean left ventricular ejection fraction (LVEF) was 59.0% (53.7%; 64.2%) in the overall cohort. There was a decrease in LVEF for patients with PersAF (55.5% [52.3%; 63.7%]) compared to those with PAF (60.3% [54.0%; 64.9%]) (p=0.085). In relation to the imaging parameters of diastolic dysfunction, the E/A ratio was found to be 1.2 (1.0;1.6), with no significant difference between patients with PAF and PersAF (p=0.09). Similarly, the E/e' ratio was 8.4 (6.8;10.5) with a p value of 0.29, suggesting no significant difference between the two groups. LV global longitudinal strain didn't show a difference (p=0.2), with -19.7% (-22.1%; -17.9%) for PAF and -19.4% (-21.6%; -17.8%) for PersAF. LA ejection fraction was 40.9% (32.9%; 50.1%) in the PAF cohort and 40.3% (25.7%; 48.7%) (p=0.31) in the PersAF cohort, respectively. Regarding LA strain, patients with PersAF had significantly worse LA reservoir strain (24.3% [16.4%; 32.7%] vs 29.8% [19.5%; 41.0%]) (P =0.011), conduit strain (-15.4% [-18.8%; -9.9%] vs -16.8% [-24.3%; -11.7%]) (P =0.039) and contraction strain (-7.7% [-15.7%; -4.1%] vs -12.6% [-18.5%; -6.5%]) (P =0.042) than those with PAF. There was no significant difference in SD-TPS for PAF (33.5msec [14.4msec;49.9msec]) and PersAF (38.7msec [20.6msec;68.0msec]) (p=0.09).

4.4 Imaging variables in the cohort with and without AF recurrence

Imaging variables in the cohort with and without AF recurrence are presented for conventional echocardiographic variables in Table 5 and for strain variables in Table 6. LVEF showed no significant difference between patient with AF recurrence (59.0% [52.2%, 64.1%]) and without AF recurrence (59.2% [54.0%,

64.3%])(p=0.82). Although there was no significant difference in LAVI (29.4ml/m² [22.8ml/m²;35.8ml/m²] vs 30.7ml/m² [22.7ml/m²;35.2ml/m²], p=0.74), the patients with AF recurrence showed significantly worse LAEF (34.0% [29.1%; 43.7%]) than those without AF recurrence (41.8% [33.9%; 50.5%]) (p=0.030). Regarding imaging parameters of diastolic dysfunction, the E/A ratio was 1.2 (1.0;1.6) without a relevant difference for PAF and PersAF (p=0.80) and the same was shown for E/e' with 8.4 (6.8;10.5) (p=0.24). The LV global longitudinal strain did not exhibit a significant difference between patients with AF recurrence (-19.3% [-20.9%; -17.6%]) and those without AF recurrence (-19.7% [-22.9%; -18.0%]) (p=0.15). In relation to LA strain, patients with AF recurrence had significantly decreased LA reservoir strain (19.8% [17.2%; 27.0%] vs 30.1% [21.1%; 39.5%]) (P<0.001), conduit strain (-12.9% [-15.9%; -8.1%] vs -17.1% [-23.9%; -12.0%]) (P<0.001) and contraction strain (-8.4% [-14.9%; -3.7%] vs -12.1% [-18.5%; -6.3%]) (P =0.020) compared to those without AF recurrence. The measured SD-TPS was significantly different in the cohorts without and with AF recurrence (25.3msec [12.7msec;46.5msec] vs 61.1msec [42.6msec;84.1msec] [p<0.001]).

4.5 Uni- and multivariable Cox regression analysis regarding the association with the risk of AF recurrence

Although SD-TPS (HR, 1.05 [95% CI 1.01;1.09], p=0.011) and LA ejection fraction (HR, 0.98 [95% CI 0.95;1.00], p=0.092) showed relevant associations with the risk of AF recurrence in the univariable cox regression analysis, the association of LA ejection fraction attenuated (HR, 0.98 [95% CI 0.95;1.00], p=0.11) in the multivariable analysis while the association between SD-TPS and AF recurrence risk remained stable (HR, 1.05 [95% CI 1.01;1.09], p=0.021) (Table7, Figure 2). The other included echocardiographic variables were not associated with the risk of AF recurrence.

In the univariable Cox regression analysis for clinical variables, only age was associated with the AF recurrence risk (HR, 1.07 [95% CI 1.03;1.12], p<0.001) (Table 8). In the following multivariable analysis with associated echocardiographic variables, age was the only relevant variable regarding risk of AF recurrence (HR, 1.06 [95% CI 1.02;1.11], p=0.0023) while SD-TPS did show a trend regarding the

event of AF recurrence (HR, 1.04 [95% CI 1.00;1.10]), the association was not significant (p=0.076) (Table 8, Figure 2).

4.6 Receiver operating characteristic (ROC) curve analysis and results shown in Kaplan-Meier curves regarding the association with AF recurrence

C-index of ROC curves and optimal cut-offs for the classification of AF recurrence were calculated. The C-index for SD-TPS was the highest, with a value of 0.73. In comparison, the C-index for age was 0.69, for LAVI 0.48, for LV global longitudinal strain 0.57, and for LA ejection fraction 0.60 (Table 9). The calculated cut-off for age was 71 years, for SD-TPS 38.6msec, for LAVI 27.7ml/m², for LV global longitudinal strain -22.2%, and for LA ejection fraction 35.7% (Table 9). Kaplan-Meier survival curves based on the cut-off values showed a relevant association with AF recurrence for Age (p<0.0001), SD-TPS (p<0.0001), LV global longitudinal strain (p=0.039), and LA ejection fraction (p=0.0031) (Figure 3). However, regarding LAVI results were not relevant (p=0.25). According to Kaplan-Meier curves, patients with SD-TPS>38.6msec have higher risks of AF recurrence than patients with SD-TPS≤38.6msec, and the difference between groups is statistically significant (Log-rank p<0.0001).

Table 1 Baseline characteristics of the cohort with PAF and PersAF

Variables	All (n=132)	Paroxysmal AF (n= 88)	Persistent AF (n= 44)	p-value
Male No. (%)	79 (59.8)	50 (56.8)	29 (65.9)	0.41
Age (years)	65.5 (55.0, 73.0)	65.5 (56.4, 72.0)	65.5 (55.0, 74.2)	0.72
Height (m)	1.8 (1.7, 1.8)	1.8 (1.7, 1.8)	1.8 (1.7, 1.9)	0.42
Weight (kg)	84.0 (75.0, 94.6)	84.0 (73.4, 92.6)	84.0 (76.0, 100.0)	0.22
BMI (kg/(m^2))	26.3 (24.5, 29.0)	26.2 (24.5, 29.0)	26.7 (24.5, 29.4)	0.42
BSA (m^2)	2.0 (1.9, 2.2)	2.0 (1.8, 2.2)	2.0 (1.9, 2.3)	0.23
CHA2DS2-VASc	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.29
Smoking No. (%)	33 (25.0)	16 (18.2)	17 (38.6)	0.02
Arterial hypertension No. (%)	78 (59.1)	48 (54.5)	30 (68.2)	0.19
Diabetes No. (%)	7 (5.3)	4 (4.5)	3 (6.8)	0.89
Dyslipidemia No. (%)	18 (13.6)	12 (13.6)	6 (13.6)	1.00
Coronary artery disease No. (%)	15 (11.4)	12 (13.6)	3 (6.8)	0.38
Heart failure No. (%)	8 (6.1)	3 (3.4)	5 (11.4)	0.16
Ischemic stroke No. (%)	13 (9.8)	8 (9.1)	5 (11.4)	0.92
Myocardial infarction No. (%)	13 (9.8)	9 (10.2)	4 (9.1)	1.00
Cardioversion No. (%)	57 (43.2)	20 (22.7)	37 (84.1)	<0.001
Antiarrhythmic medication No. (%)	45 (34.1)	24 (27.3)	21 (47.7)	0.008
Oral anticoagulation No. (%)	103 (78.0)	67 (76.1)	36 (81.8)	0.60
Marcumar	12 (9.1)	6 (6.8)	6 (13.6)	0.34
Apixaban	36 (27.3)	24 (27.3)	12 (27.3)	1.00
Rivaroxaban	38 (28.8)	25 (28.4)	13 (29.5)	1.00
Dabigatran	9 (6.8)	5 (5.7)	4 (9.1)	0.71
Edoxaban	8 (6.1)	7 (8.0)	1 (2.3)	0.37
Radiofrequency ablation No. (%)	73 (55.3)	40 (45.5)	33 (75.0)	0.002
Cryoablation ablation No. (%)	59 (44.7)	48 (54.5)	11 (25.0)	0.002

Table 2 Baseline characteristics of the cohort with and without AF recurrence

Variables	All (N=132)	Without AF recurrence (n=102)	With AF recurrence (n=30)	p-value
Male No. (%)	79 (59.8)	62 (60.8)	17 (56.7)	0.85
Age (years)	65.5 (55.0, 73.0)	62.0 (54.9, 69.1)	75.0 (57.9, 78.0)	<0.001
Height (m)	1.8 (1.7, 1.8)	1.8 (1.7, 1.8)	1.7 (1.6, 1.8)	0.22
Weight (kg)	84.0 (75.0, 94.6)	84.0 (75.0, 96.0)	80.0 (67.0, 90.2)	0.11
BMI (kg/(m^2))	26.3 (24.5, 29.0)	26.3 (24.6, 29.5)	26.2 (23.5, 28.0)	0.26
BSA (m^2)	2.0 (1.9, 2.2)	2.0 (1.9, 2.2)	2.0 (1.8, 2.1)	0.11
CHA2DS2-VASc	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (1.9, 4.1)	<0.001
Smoking No. (%)	33 (25.0)	26 (25.5)	7 (23.3)	1.00
Arterial hyper-tension No. (%)	78 (59.1)	54 (52.9)	24 (80.0)	0.015
Diabetes No. (%)	7 (5.3)	5 (4.9)	2 (6.7)	1.00
Dyslipidemia No. (%)	18 (13.6)	11 (10.8)	7 (23.3)	0.15
Coronary artery disease No. (%)	15 (11.4)	11 (10.8)	4 (13.3)	0.95
Heart failure No. (%)	8 (6.1)	7 (6.9)	1 (3.3)	0.78
Ischemic stroke No. (%)	13 (9.8)	9 (8.8)	4 (13.3)	0.70
Myocardial infarction No. (%)	13 (9.8)	11 (10.8)	2 (6.7)	0.75
Cardioversion No. (%)	57 (43.2)	40 (39.2)	17 (56.7)	0.14
Antiarrhythmic medication No. (%)	45 (34.1)	36 (35.3)	9 (30)	0.74
Oral anticoagulation No. (%)	103 (78.0)	77 (75.5)	26 (86.7)	0.29
Marcumar	12 (9.1)	9 (8.8)	3 (10.0)	1.00
Apixaban	36 (27.3)	25 (24.5)	11 (36.7)	0.28
Rivaroxaban	38 (28.8)	29 (28.4)	9 (30.0)	1.00
Dabigatran	9 (6.8)	7 (6.9)	2 (6.7)	1.00
Edoxaban	8 (6.1)	7 (6.9)	1 (3.3)	0.78
Radiofrequency ablation No. (%)	73 (55.3)	58 (56.9)	15 (50.0)	0.65
Cryoablation ablation No. (%)	59 (44.7)	44 (43.1)	15 (50.0)	0.65

Table 3 Conventional echocardiographic variables of the cohort with PAF and PersAF

Variables	All (n=132)	Paroxysmal AF (n= 88)	Persistent AF (n= 44)	p-value
LA Volumen (ml)	57.0 (45.8, 74.8)	56.0 (43.7, 70.3)	64.7 (49.6, 88.8)	0.008
LA volume indexed to BSA (ml/m²)	29.6 (22.9, 35.7)	28.9 (21.2, 35.0)	30.5 (25.9, 44.2)	0.03
Left ventricular enddiastolic volume 3d	86.0 (67.2, 110.8)	83.5 (64.0, 105.4)	95.3 (71.0, 119.2)	0.11
endsystolic volume 3d Messung (ml)	38.0 (29.0, 47.0)	36.5 (28.6, 43.1)	40.8 (30.0, 55.3)	0.046
LV ejection fraction 3d (%)	56.0 (53.0, 60.1)	57.0 (53.0, 60.9)	55.8 (52.5, 58.1)	0.19
LV ejection fraction 2d (Simpson) (%)	59.0 (53.7, 64.2)	60.3 (54.0, 64.9)	55.5 (52.3, 63.7)	0.085
Stroke volume 3d (ml)	48.0 (36.0, 62.4)	47.0 (34.6, 60.9)	51.5 (40.9, 70.1)	0.18
LA ejection fraction 2d (Simpson) (%)	40.6 (31.9, 49.7)	40.9 (32.9, 50.1)	40.3 (25.7, 48.7)	0.31
Stroke volume Atrium 2d (ml)	33.1 (22.6, 45.3)	36.0 (22.2, 46.3)	29.6 (24.9, 41.0)	0.61
PW Doppler Mitral valve E (m/s)	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)	0.26
PW Doppler Mitral valve A (m/s)	0.6 (0.5, 0.7)	0.6 (0.5, 0.8)	0.6 (0.4, 0.7)	0.02
E/A	1.2 (1.0, 1.6)	1.2 (1.0, 1.5)	1.3 (1.0, 1.8)	0.09
Tissue Doppler imaging E (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.0, 0.1)	0.01
Tissue Doppler imaging A (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.0, 0.1)	<0.001
Tissue Doppler imaging S (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.01
Tissue Doppler imaging lateral E (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.06
Tissue Doppler imaging lateral A (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.005
Tissue Doppler imaging lateral S (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.04
E/e' (average of septal and lateral tissue Doppler)	8.4 (6.8, 10.5)	8.0 (6.8, 10.3)	8.6 (7.3, 10.7)	0.29

Table 4 Strain variables of the cohort with PAF and PersAF

Variables	All (n=132)	Paroxysmal AF (n= 88)	Persistent AF (n= 44)	p-value
LV global longitudinal strain (%)	-19.6 (-22.1, -17.8)	-19.7 (-22.1, -17.9)	-19.4 (-21.6, -17.8)	0.2
LV strain 3d (%)	-18.0 (-21.0, -15.0)	-18.0 (-21.1, -14.9)	-18.0 (-20.6, -15.4)	0.84
Reservoir Strain LA (%)	27.7 (18.8, 36.9)	29.8 (19.5, 41.0)	24.3 (16.4, 32.7)	0.011
Conduit Strain LA (%)	-16.1 (-22.1, -11.1)	-16.8 (-24.3, -11.7)	-15.4 (-18.8, -9.9)	0.039
Contraction Strain LA (%)	-11.1 (-17.8, -5.4)	-12.6 (-18.5, -6.5)	-7.7 (-15.7, -4.1)	0.042
SD-TPS (msec)	33.9 (16.3, 56.0)	33.5 (14.4, 49.9)	38.7 (20.6, 68.0)	0.09
Time-to-peak left wall (msec)	399.0 (357.3, 444.5)	383.5 (340.0, 431.6)	439.0 (372.2, 499.8)	0.003
Time-to-peak roof (msec)	409.0 (340.2, 479.0)	399.0 (340.0, 438.0)	441.0 (350.5, 538.8)	0.001
Time-to-peak right wall (msec)	399.0 (340.0, 457.0)	396.5 (340.0, 439.0)	419.0 (359.0, 502.0)	0.04
Maximum opposing wall delay (msec)	40.0 (20.0, 80.0)	36.0 (19.4, 78.6)	46.0 (20.0, 98.8)	0.14

Table 5 Conventional imaging variables of the cohort with and without AF recurrence

Variables	All (n=132)	Without AF recurrence (n=102)	With AF recurrence (n=30)	p-value
LA Volumen (ml)	57.0 (45.8, 74.8)	56.9 (46.0, 75.4)	58.5 (43.7, 72.3)	0.86
LA volume indexed to BSA (ml/m²)	29.6 (22.9, 35.7)	29.4 (22.8, 35.8)	30.7 (22.7, 35.2)	0.74
Left ventricular enddiastolic volume 3d	86.0 (67.2, 110.8)	89.0 (70.9, 114.1)	78.5 (54.7, 105.4)	0.030
endsystolic volume 3d Messung (ml)	38.0 (29.0, 47.0)	39.0 (30.0, 48.5)	32.2 (26.4, 42.4)	0.044
LV ejection fraction 3d (%)	56.0 (53.0, 60.1)	56.0 (53.3, 60.0)	57.3 (52.0, 62.1)	0.57
LV ejection fraction 2d (Simpson) (%)	59.0 (53.7, 64.2)	59.2 (54.0, 64.3)	59.0 (52.2, 64.1)	0.82
Stroke volume 3d (ml)	48.0 (36.0, 62.4)	48.9 (40.4, 63.8)	47.5 (28.0, 52.2)	0.031
LA ejection fraction 2d (Simpson) (%)	40.6 (31.9, 49.7)	41.8 (33.9, 50.5)	34.0 (29.1, 43.7)	0.030
Stroke volume Atrium 2d (ml)	33.1 (22.6, 45.3)	33.5 (22.9, 48.0)	31.0 (21.7, 41.0)	0.22
PW Doppler Mitral valve E (m/s)	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)	0.99
PW Doppler Mitral valve A (m/s)	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.6 (0.4, 0.8)	0.68
E/A	1.2 (1.0, 1.6)	1.2 (1.0, 1.5)	1.2 (1.0, 1.8)	0.80
Tissue Doppler imaging E (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.0, 0.1)	0.033
Tissue Doppler imaging A (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.13
Tissue Doppler imaging S (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.21
Tissue Doppler imaging lateral E (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.73
Tissue Doppler imaging lateral A (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.71
Tissue Doppler imaging lateral S (m/s)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.092
E/e' (average of septal and lateral tissue Doppler)	8.4 (6.8, 10.5)	8.3 (6.8, 10.1)	9.0 (7.4, 11.1)	0.24

Table 6 Strain variables of the cohort with and without AF recurrence

Variables	All (n=132)	Without AF recurrence (n=102)	With AF recurrence (n=30)	p-value
LV global longitudinal strain (%)	-19.6 (-22.1, -17.8)	-19.7 (-22.9, -18.0)	-19.3 (-20.9, -17.6)	0.15
LV strain 3d (%)	-18.0 (-21.0, -15.0)	-18.0 (-20.3, -14.5)	-19.1 (-23.0, -15.7)	0.12
Reservoir Strain LA (%)	27.7 (18.8, 36.9)	30.1 (21.1, 39.5)	19.8 (17.2, 27.0)	<0.001
Conduit Strain LA (%)	-16.1 (-22.1, -11.1)	-17.1 (-23.9, -12.0)	-12.9 (-15.9, -8.1)	<0.001
Contraction Strain LA (%)	-11.1 (-17.8, -5.4)	-12.1 (-18.5, -6.3)	-8.4 (-14.9, -3.7)	0.020
SD-TPS (msec)	33.9 (16.3, 56.0)	25.3 (12.7, 46.5)	61.1 (42.6, 84.1)	<0.001
Time-to-peak left wall (msec)	399.0 (357.3, 444.5)	400.0 (357.0, 451.0)	385.5 (357.5, 432.6)	0.54
Time-to-peak roof (msec)	409.0 (340.2, 479.0)	409.0 (341.0, 465.7)	394.5 (320.9, 481.6)	0.68
Time-to-peak right wall (msec)	399.0 (340.0, 457.0)	400.0 (340.0, 451.0)	384.0 (339.0, 467.1)	0.73
Maximum opposing wall delay (msec)	40.0 (20.0, 80.0)	33.0 (19.7, 79.3)	43.0 (31.9, 100.7)	0.072

Table 7 Univariable and multivariable Cox regression of echocardiographic parameters for AF recurrence

	Univariable		Multivariable	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
LV global longitudinal strain	1.02 (0.96, 1.09)	0.51		
LA volume indexed	1.01 (0.97, 1.04)	0.61		
SD-TPS (per 10 msec)	1.05 (1.01, 1.09)	0.011	1.05 (1.01, 1.09)	0.021
LA ejection fraction 2D	0.98 (0.95, 1.00)	0.092	0.98 (0.95, 1.00)	0.11

Table 8 Univariable and multivariable Cox regression of clinical parameters for AF recurrence

	Univariable		Multivariable	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.07 (1.03, 1.12)	<0.001	1.06 (1.02, 1.11)	0.0023
Male	0.86 (0.42, 1.77)	0.68		
Persistent AF	0.97 (0.46, 2.08)	0.95		
LA volume indexed	1.01 (0.97, 1.04)	0.61		
SD-TPS (per 10 msec)	1.05 (1.01, 1.09)	0.011	1.04 (1.00, 1.10)	0.076

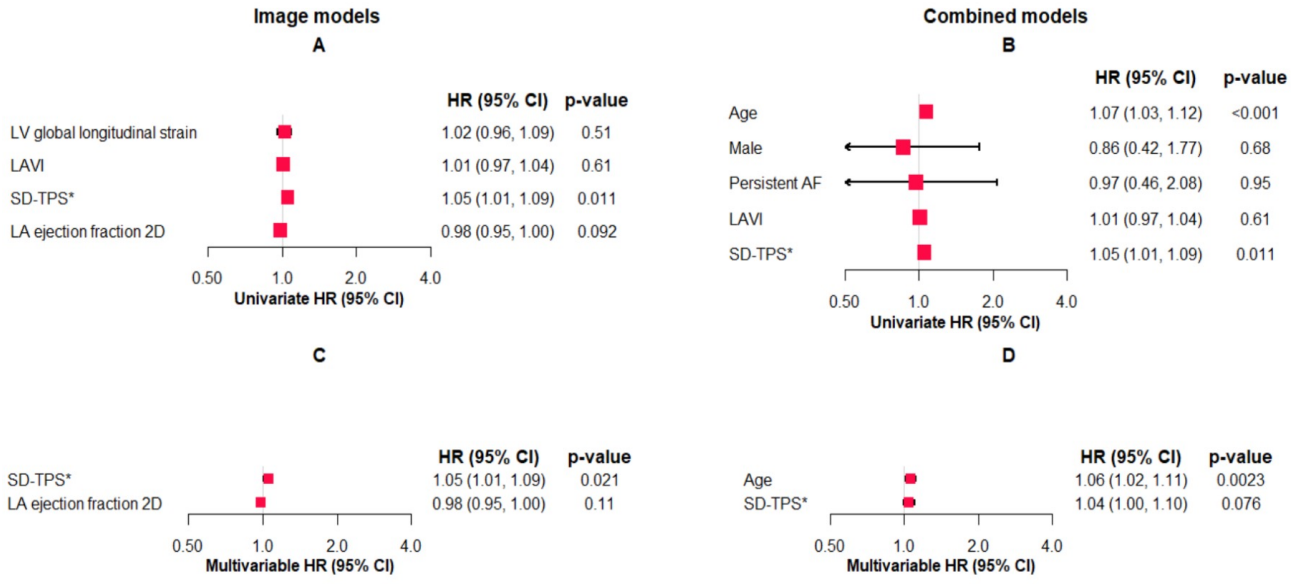

Figure 2 Forest plots showing the results of univariate and multivariable Cox regression analysis regarding the imaging and clinical variables. A)univariate analysis for the imaging variables, B)univariate analysis for the clinical variables, C)multivariable analysis for the imaging variables and D) multivariable analysis including all variables of the clinical model

Table 9 ROC curves for AF recurrence

Variables	Cut.off	C-index (original)	C-index (corrected)
Age	71	0.69	0.69
SD-TPS	38.6	0.73	0.73
LAVI	27.7	0.52	0.48
LV global longitudinal strain	-22.2	0.59	0.57
LA ejection fraction 2D	35.73	0.62	0.60

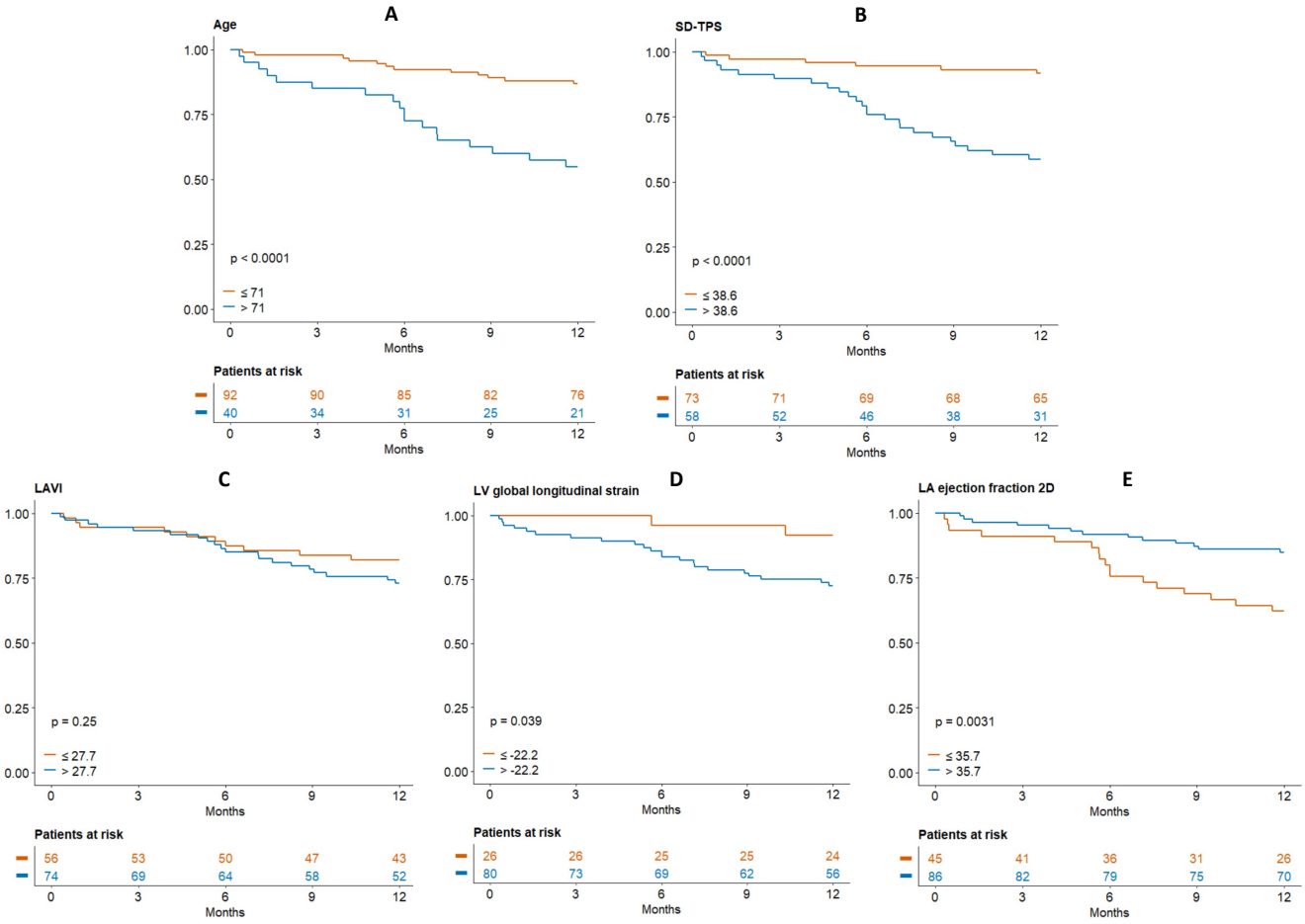

Figure 3 Kaplan-Meier curves regarding the association of clinical and imaging variables with the risk of AF recurrence for A) Age, B) SD-TPS, C) LAVI, D) LV global longitudinal strain, and E) LA ejection fraction 2D

5. Discussion:

The current study indicated (1) that catheter ablation with either radiofrequency or cryo-balloon ablation resulted in a low AF recurrence rate of 22.7% after 1 year of follow-up; (2) LAVI was not different distributed in patients with AF recurrence; (3) atrial mechanical dispersion (SD-TPS) was associated with the risk of AF recurrence; (4) a cut-off of SD-TPS of 38.6msec might be able to identify patients with an increased risk of AF recurrence; (5) multivariable analysis identified age as the most relevant variable regarding risk of AF recurrence in a model including SD-TPS as the most relevant of the imaging variables and age, sex, type of AF and LAVI during follow-up.

Catheter ablation has become a major treatment option for AF and is widely recognized as the predominant cardiac ablation technique. Pulmonary vein isolation (PVI) is the cornerstone of AF catheter ablation. According to current guidelines, it is recommended to perform the procedure on patients who cannot tolerate or do not respond well to antiarrhythmic drugs (class IIa) and on selected patients with symptomatic paroxysmal AF (class IIa) or persistent AF (class IIb) (Hindricks et al. 2021). Some studies have provided evidence of the superior effectiveness of catheter ablation compared to antiarrhythmic medication therapy in the maintenance of sinus rhythm. However, the recurrence of AF after ablation is relatively high and has been estimated to occur in 20 – 45% of cases (Dretzke et al. 2020). In our cohort study, 30 out of 132 individuals who underwent catheter ablation had AF recurrence after 1 year of follow-up. The recurrence rate (22.7%) appears to be relatively low compared with currently available data.

While re-ablation is an option for AF-recurrence patients, ablations may result in surgical complications, and they are associated with reduced LA size and decreased atrial pumping function that is proportional to the volume of the inflicted scar (Wylie et al. 2008). Thus, more accurate risk stratification with suitable parameters and better patient selection prior to the procedure is critical. The risk factors linked to AF recurrence post-ablation are not thoroughly established, yet they are likely to involve age, AF duration, cardiac structural and functional changes (Darby 2016). In the present study, we examined a cohort without structural heart disease or severely reduced cardiac function to concentrate on new suggested

imaging variables in addition to common clinical variables for predicting AF recurrence after ablation.

5.1 LA size and recurrence of AF following catheter ablation

LA size measured as LA diameter or left atrial volume (indexed) is commonly employed as a predictor for AF recurrence after catheter ablation. LA diameter includes anteroposterior diameter, medial-lateral diameter and superior-inferior diameter, among which the anteroposterior diameter obtained in the parasternal long axis is commonly utilized in clinical practice and research endeavors (Roberto M Lang et al. 2015). LA anteroposterior diameter >50-55 mm indicates higher recurrence risk and poor benefit of ablation therapy (Calkins et al. 2012). LA volume can be obtained by the Simpson method and then normalized by body surface area to get the LA volume index (LAVI). Increased LA volumes are known to facilitate new episodes of AF and recurrence following a therapeutic intervention (Njoku et al. 2018). However, AF recurrence can be detected in patients who do not exhibit LA enlargement, which is also observed in our study. In the cohort of patients with AF recurrence and without AF recurrence, there was no significant difference in LA volume ($p=0.90$) or LAVI ($p=0.54$), and LAVI (29.3 ml/m² vs 30.8 ml/m²) was not increased above the threshold of 34ml/m² which is often related to diastolic dysfunction (Thomas et al. 2019).

5.2 LA function and recurrence of AF following catheter ablation

Despite the finding of normal LAVI for the study cohort, LA ejection fraction and SD-TPS showed significant differences among patients with and without AF recurrence in the univariable analysis, which is consistent with the notion that functional disorder occurs before morphological alterations.

5.2.1 LA ejection fraction and recurrence of AF following catheter ablation

The suggested LA ejection fraction is a new parameter that is calculated according to the formula as equivalent to the LV ejection fraction (Roberto M Lang et al. 2015) and is termed the total emptying fraction (Thomas et al. 2020) reflecting the global function of the LA and thus might be an indicator of a poor outcome in AF patients. It has already been reported that LAEF is an independent predictor for AF recurrence (Chou et al. 2018; Chubb et al. 2019; Habibi et al. 2016). In our study,

LA ejection fraction was associated with a higher risk of AF recurrence and lower values of LAEF indicate a reduced total emptying fraction which might as well indicate a decreased function of the LA. However, the association of LA ejection fraction attenuated in the multivariate analysis with other image imaging variables. Our study calculated LA ejection fraction with a cut-off of 35.7% being lower than the suggested threshold in the literature, whereas this might be due to differences in the study cohorts the values were derived from (Thomas et al. 2019).

5.2.2 LA Strain and recurrence of AF following catheter ablation

LA fibrosis is widely acknowledged as the hallmark of atrial remodeling (structural, electrical, and functional remodeling) and is common in individuals diagnosed with atrial fibrillation (Dzeshka et al. 2015). One prospective multicenter study involving patients diagnosed with AF undergoing catheter ablation revealed that atrial fibrosis was independently associated with the risk of recurrent arrhythmia (Marrouche et al. 2014). Tissue fibrosis can not only impair myocardial deformation but also trigger reentry and electrical dispersion, leading to atrial mechanical dispersion and desynchronized motion (Nguyen, Qu, and Weiss 2014; Verheule and Schotten 2021). Apart from CMR, speckle-tracking echocardiography (STE) can assess regional myocardial function with greater accessibility and lower cost. It enables the quantification of both the amplitude and timing of atrial deformation. The amplitude of LA deformation is measured as atrial longitudinal strain in 2D images, which is represented by LA reservoir strain, conduit strain and contraction strain. In our cohort, LA longitudinal strain showed a significant difference among patients with and without AF recurrence. However, it's not the main aim of this manuscript and will be discussed elsewhere. What we focused on here is the temporal heterogeneity of LA deformation, which is measured as mechanical dispersion by calculating time-to-peak strain standard deviation (SD-TPS). A previous cohort has also shown that SD-TPS is a marker for recurrence of AF following catheter ablation. However, this study did only include patients with PAF, and catheter ablation was done in all patients with radiofrequency ablation (Sarvari et al. 2016), thus the investigated study cohort more closely reflects the real-world population presenting for catheter ablation (Hindricks et al. 2021). The current study did show larger SD-TPS in patients with AF recurrence in the first year following catheter ablation and

the significant difference remained stable in the multivariate analysis with other image imaging variables.

The calculated cut-off in our study with 38.6msec is close to the previously published mean SD-TPS of 38msec in patients with AF recurrence (Sarvari et al. 2016), however the cut-off originating from our cohort is data-driven and thus cannot be recommended for general use. The results show that even in a cohort including PAF and PersAF with normal LAVI, SD-TPS can be applied to detect changes of the atrial tissue facilitating AF recurrence in terms of prolongation of the SD-TPS (Kawakami et al. 2019; Sarvari et al. 2016).

5.3 LV strain and recurrence of AF following catheter ablation

Additional strain parameters assessed in the study cohort include the LV global longitudinal strain. Ventricular fibrosis can be detected with the progression of AF and left ventricular fibrosis derived from LGE is associated with a higher risk of mortality in patients with AF (Dzeshka et al. 2015; Neilan et al. 2013). It has been demonstrated that LV fibrosis is an independent predictor of AF recurrence post ablation in AF patients (Kato et al. 2016). LV global longitudinal strain was impaired in AF patients (Kuo et al. 2020) and was described to be associated with the presence of AF in patients with cryptogenic stroke (Kawakami et al. 2020). However, In our study, LV global longitudinal strain was not associated with the risk of AF recurrence in the univariable analysis.

Regarding the LV global longitudinal strain with the suggested cut-off from our analysis of -22.2% this value is more negative than the suggested -20% for a healthy individual which might not reflect the comorbidities of most of the patients (Kawakami et al. 2020; Roberto M Lang et al. 2015).

5.4 Clinical variables and recurrence of AF following catheter ablation

Age and sex are not only risk factors for the development of AF (Hindricks et al. 2021; Magnussen et al. 2017) but are also the most common variables used for predicting AF recurrence (Dretzke et al. 2020). Other widely used clinical variables include the type of AF (paroxysmal and persistent AF), which might also reflect the alterations of the atrial myocardial tissue (Dretzke et al. 2020; Fabritz et al. 2021). However, in the univariable analysis of clinical variables, only age ($p<0.001$)

showed a significant difference. Male sex (p=0.68) and Persistent AF (p=0.95) were distributed evenly throughout the cohort.

5.5 Appraisal of the combining imaging and clinical variables

Age and SD-TPS were chosen for the overall multivariable analysis including the clinical variables and the imaging variable. Only age remained associated with the risk of AF recurrence (p= 0.0023), while the association of SD-TPS attenuated (p= 0.076). However, considering that age is a given factor in AF treatment, the utilization of SD-TPS could be considered to assess the treatment decision for patients with AF. Besides, the C-index of SD-TPS (0.73) is the largest among parameters (Table 9), indicating high predictive power.

Some blood biomarkers involving ANP (atrial natriuretic peptide), BNP (B-type natriuretic peptide), NT-proBNP (N-terminal pro-brain natriuretic peptide), galectin-3 (Gal-3), IL-6 (interleukin-6), CRP (C-reactive protein) could also be implied to predict AF recurrence after ablation (Jiang et al. 2017; Wu et al. 2015). However, these biomarkers would require extra resources from the healthcare system and may not be widely accessible.

The main point indicating at the approach of combining imaging variables and clinical variables to predict the risk of AF recurrence following treatment with catheter ablation is that echocardiography is recommended with class I according to the current guidelines in AF patients (Hindricks et al. 2021) and in addition, the clinical variables with age, sex and type of AF are available in the patient upon treatment. While LAVI is still a routine parameter employed as the imaging variable for risk stratification and treatment decision-making in patients with AF, it may be beneficial to involve additional imaging parameters, such as atrial mechanical dispersion, into a comprehensive assessment that includes clinical variables. Atrial mechanical dispersion obtained by speckle tracking echocardiography is an emerging technique with potential value for the identification of early atrial dysfunction and prediction of atrial fibrillation recurrence following one-year catheter ablation.

5.6 Limitations

The current study exhibits several limitations. Firstly, the cohort size is relatively small, and the result especially the suggested cut-off value should be further validated by a larger and multi-center study, which is integral to our upcoming research endeavors. Secondly, the count of AF patients in our cohort might be underestimated, as asymptomatic AF episodes could be overlooked due to the inability to continuously monitor patients throughout the follow-up period. Thirdly, the exclusion of some patient data due to missing values or unclear images introduces the potential for selection bias.

6. Summary

Atrial fibrillation (AF) is the most common arrhythmia, contributing to decreased life quality and increased healthcare costs. Catheter ablation has become the cornerstone for electrical rhythm control in current guidelines. However, the recurrence rate of AF post-ablation is relatively high and re-ablation may result in certain complications, underscoring the importance of early diagnosis in patients with high recurrence risk for optimizing candidate selection and guiding the choice of suitable treatment strategies.

As a progressive disease, AF sustains itself through the mechanism of atrial remodeling (structural, electrical and functional remodeling). Although left atrial size including left atrial volume or left atrial diameter in the parasternal long axis is still a routine parameter, AF recurrence can also be detected in patients who don't exhibit left atrial enlargement, which may be explained by the fact that functional disorder occurs before morphological alterations. Intra-atrial dyssynchrony is reported to be a predictor for AF recurrence after ablation and subtle changes of heterogeneity in atrial contraction can be represented by atrial mechanical dispersion which is defined as the standard deviation of the time to peak positive strain (SD-TPS). The present study concentrates on atrial mechanical dispersion as an echo parameter regarding its association with AF recurrence following one-year after catheter ablation.

132 participants diagnosed with AF (PAF or PersAF) presenting for the first catheter ablation in the University Heart & Vascular Center Hamburg between December 2017 and January 2019 were retrospectively analyzed. Transthoracic and transesophageal echocardiography were performed before catheter ablation. After 12 months, all patients were invited to attend an additional echocardiography and a 24-hour Holter ECG to evaluate the recurrence of AF.

Our study showed (1) that catheter ablation with either radiofrequency or cryo-balloon ablation resulted in a low AF recurrence rate of 22.7% after 1 year of follow-up; (2) Left atrial volume index (LAVi) was not differently distributed in patients with AF recurrence; (3) atrial mechanical dispersion was associated with the risk of AF recurrence; (4) a cut-off of SD-TPS of 38.6msec might be able to identify patients with an increased risk of AF recurrence; (5) multivariable analysis identified age as the most relevant variable regarding risk of AF recurrence in a model including SD-

TPS as the most relevant of the imaging variables and age, sex, type of AF and LAVI during follow-up.

The results indicated that, even within a cohort displaying normal LAVI, SD-TPS can identify alterations in atrial tissue facilitating detection of AF recurrence. It's beneficial to involve atrial mechanical dispersion as additional imaging parameters into a comprehensive assessment that includes common imaging and clinical variables. Atrial mechanical dispersion obtained by speckle tracking echocardiography is an emerging technique with potential value for the identification of early atrial dysfunction and prediction of AF recurrence following one-year after catheter ablation. The calculated cut-off in our study is close to the previously published mean SD-TPS of 38msec in patients with AF recurrence, however it needs to be further evaluated by larger, multicenter studies.

7. Zusammenfassung

Vorhofflimmern (AF) ist die häufigste Arrhythmie, die zu einer verminderten Lebensqualität und erhöhten Kosten im Gesundheitswesen beiträgt. Die Katheterablation ist in den aktuellen Leitlinien zum Eckpfeiler der elektrischen Rhythmuskontrolle geworden. Die Rezidivrate von Vorhofflimmern nach einer Ablation ist jedoch relativ hoch, und eine erneute Ablation kann zu bestimmten Komplikationen führen. Dies unterstreicht die Bedeutung einer frühzeitigen Diagnose bei Patienten mit hohem Rezidivrisiko, um die Auswahl der Kandidaten zu optimieren und die Wahl der geeigneten Behandlungsstrategien zu steuern.

Das Vorhofflimmern ist eine fortschreitende Erkrankung, die sich durch den Mechanismus des Vorhofumbaus (struktureller, elektrischer und funktioneller Umbau) selbst erhält. Obwohl die Größe des linken Vorhofs, einschließlich des Volumens oder des Durchmessers des linken Vorhofs in der parasternalen Längsachse, nach wie vor ein Routineparameter ist, um ein erhöhtes Risiko für das Auftreten von Vorhofflimmern zu detektieren, kann ein Vorhofflimmern auch bei Patienten festgestellt werden, die keine Vergrößerung des linken Vorhofs aufweisen. Dieser Zusammenhang lässt sich dadurch erklären, dass eine funktionelle Störung vor morphologischen Veränderungen auftritt. Die intraatriale Dyssynchronie gilt als Prädiktor für das Wiederauftreten von Vorhofflimmern nach einer Ablation, und subtile Veränderungen der Heterogenität der Vorhofkontraktion können durch die mechanische Dispersion des Vorhofs dargestellt werden, die als Standardabweichung der Zeit bis zur positiven Spitzenverkürzung (SD-TPS) definiert ist. Die vorliegende Studie konzentriert sich auf die mechanische Dispersion des Vorhofs als Echoparameter und seiner Assoziation mit dem Wiederauftreten von Vorhofflimmern nach einer Katheterablation innerhalb eines Jahres.

132 Teilnehmer mit der Diagnose Vorhofflimmern (PAF oder PersAF), die zwischen Dezember 2017 und Januar 2019 zur ersten Katheterablation im Universitären Herz- und Gefäßzentrum Hamburg vorgestellt wurden, wurden retrospektiv analysiert. Vor der Katheterablation wurden eine transthorakale und transösophageale Echokardiographie durchgeführt. Nach 12 Monaten wurden alle Patienten zu einer weiteren Echokardiographie und einem 24-Stunden-Holter-EKG eingeladen, um das Wiederauftreten von Vorhofflimmern zu beurteilen.

Unsere Studie zeigte, dass (1) die Katheterablation entweder mit Radiofrequenz- oder mit Kryoballonablation zu einer niedrigen Vorhofflimmer-Rezidivrate von 22.7% nach einem Jahr Nachbeobachtung führte; (2) der Volumenindex des linken Vorhofs (LAVi) bei Patienten mit Vorhofflimmer-Rezidiv nicht unterschiedlich verteilt war; (3) die mechanische Dispersion des Vorhofs mit dem Risiko eines Vorhofflimmer-Rezidivs verbunden war; (4) ein Cut-off-Wert für SD-TPS von 38.6 ms könnte in der Lage sein, Patienten mit einem erhöhten Risiko für ein Wiederauftreten von Vorhofflimmern zu identifizieren; (5) eine multivariable Analyse identifizierte das Alter als die relevanteste Variable in Bezug auf das Risiko eines Wiederauftretens von Vorhofflimmern in einem Modell, das SD-TPS als die relevanteste der bildgebenden Variablen und Alter, Geschlecht, Art des Vorhofflimmerns und LAVI während der Nachbeobachtung einschloss.

Die Ergebnisse deuten darauf hin, dass die SD-TPS selbst in einer Kohorte mit normalem LAVI Veränderungen im Vorhofgewebe erkennen kann, die ein Wiederauftreten von Vorhofflimmern begünstigen. Es ist von Vorteil, die mechanische Dispersion des Vorhofs als zusätzlichen bildgebenden Parameter in eine umfassende Bewertung einzubeziehen, die allgemeine bildgebende und klinische Variablen umfasst. Die mittels Speckle-Tracking-Echokardiographie ermittelte mechanische Dispersion des Vorhofs ist eine neue Technik mit potenziellem Wert für die Identifizierung einer frühen atrialen Dysfunktion und die Vorhersage des Wiederauftretens von Vorhofflimmern nach einer Katheterablation nach einem Jahr. Der in unserer Studie berechnete Cut-off-Wert liegt nahe an dem zuvor veröffentlichten mittleren SD-TPS-Wert von 38 ms bei Patienten mit einem Vorhofflimmern-Rezidiv, muss jedoch in größeren, multizentrischen Studien weiter untersucht werden.

8. References

Akutsu, Yasushi, Kyouichi Kaneko, Yusuke Kodama, Jumpei Suyama, Hui-Ling Li, Yuji Hamazaki, Kaoru Tanno, Takehiko Gokan, and Youichi Kobayashi. 2011. "Association between Left and Right Atrial Remodeling with Atrial Fibrillation Recurrence after Pulmonary Vein Catheter Ablation in Patients with Paroxysmal Atrial Fibrillation: A Pilot Study." *Circulation. Cardiovascular Imaging* 4(5):524–31. doi: 10.1161/CIRCIMAGING.110.962761.

Amlie, J. P. 1997. "Dispersion of Repolarization. A Basic Electrophysiological Mechanism behind Malignant Arrhythmias." *European Heart Journal* 18(8):1200–1202. doi: 10.1093/oxfordjournals.eurheartj.a015426.

Anon. 2022. "Atrial Fibrillation." *Nature Reviews. Disease Primers* 8(1):20. doi: 10.1038/s41572-022-00354-w.

Antonielli, Emanuele, Alfredo Pizzuti, Attila Pálinkás, Mattia Tanga, Noèmi Gruber, Claudio Michelassi, Albert Varga, Alessandro Bonzano, Nicola Gandolfo, László Halmai, Antonia Bassignana, Muhammad Babar Imran, Fabrizio Delnevo, Miklós Csanády, and Eugenio Picano. 2002. "Clinical Value of Left Atrial Appendage Flow for Prediction of Long-Term Sinus Rhythm Maintenance in Patients with Nonvalvular Atrial Fibrillation." *Journal of the American College of Cardiology* 39(9):1443–49. doi: 10.1016/s0735-1097(02)01800-4.

Ariyama, Miyuki, Ritsushi Kato, Makoto Matsumura, Harumi Yoshimoto, Yoshie Nakajima, Shintaro Nakano, Takatoshi Kasai, Jun Tanno, Takaaki Senbonmatsu, Kazuo Matsumoto, and Shigeyuki Nishimura. 2015. "Left Atrial Appendage Wall-Motion Velocity Associates with Recurrence of Nonparoxysmal Atrial Fibrillation after Catheter Ablation." *Echocardiography (Mount Kisco, N.Y.)* 32(2):272–80. doi: 10.1111/echo.12647.

Arnold, Jayanth Ranjit, and Gerry P. McCann. 2020. "Cardiovascular Magnetic Resonance: Applications and Practical Considerations for the General Cardiologist." *Heart (British Cardiac Society)* 106(3):174–81. doi: 10.1136/heartjnl-2019-314856.

Badano, Luigi P., Theodore J. Kolias, Denisa Muraru, Theodore P. Abraham, Gerard Aurigemma, Thor Edvardsen, Jan D'Hooge, Erwan Donal, Alan G. Fraser, Thomas Marwick, Luc Mertens, Bogdan A. Popescu, Partho P. Sengupta, Patrizio Lancellotti, James D. Thomas, Jens-Uwe Voigt, Industry representatives, and Reviewers: This document was reviewed by members of the 2016–2018 EACVI Scientific Documents Committee. 2018. "Standardization of Left Atrial, Right Ventricular, and Right Atrial Deformation Imaging Using Two-Dimensional Speckle Tracking Echocardiography: A Consensus Document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging." *European Heart Journal. Cardiovascular Imaging* 19(6):591–600. doi: 10.1093/ehjci/jey042.

Bajraktari, Gani, Ibadete Bytyçi, and Michael Y. Henein. 2020. "Left Atrial Structure and Function Predictors of Recurrent Fibrillation after Catheter Ablation: A Systematic Review and Meta-Analysis." *Clinical Physiology and Functional Imaging* 40(1):1–13. doi: 10.1111/cpf.12595.

Barbier, P., S. B. Solomon, N. B. Schiller, and S. A. Glantz. 1999. "Left Atrial Relaxation and Left Ventricular Systolic Function Determine Left Atrial Reservoir Function." *Circulation* 100(4):427–36. doi: 10.1161/01.cir.100.4.427.

Bax, Jeroen J., Nina Ajmone Marsan, and Victoria Delgado. 2015. “Non-Invasive Imaging in Atrial Fibrillation: Focus on Prognosis and Catheter Ablation.” *Heart (British Cardiac Society)* 101(2):94–100. doi: 10.1136/heartjnl-2013-305150.

Beigel, Roy, Nina C. Wunderlich, Siew Yen Ho, Reza Arsanjani, and Robert J. Siegel. 2014. “The Left Atrial Appendage: Anatomy, Function, and Noninvasive Evaluation.” *JACC. Cardiovascular Imaging* 7(12):1251–65. doi: 10.1016/j.jcmg.2014.08.009.

Bisbal, Felipe, Adrian Baranchuk, Eugene Braunwald, Antoni Bayés de Luna, and Antoni Bayés-Genís. 2020. “Atrial Failure as a Clinical Entity: JACC Review Topic of the Week.” *Journal of the American College of Cardiology* 75(2):222–32. doi: 10.1016/j.jacc.2019.11.013.

Burstein, Brett, Xiao-Yan Qi, Yung-Hsin Yeh, Angelino Calderone, and Stanley Nattel. 2007. “Atrial Cardiomyocyte Tachycardia Alters Cardiac Fibroblast Function: A Novel Consideration in Atrial Remodeling.” *Cardiovascular Research* 76(3):442–52. doi: 10.1016/j.cardiores.2007.07.013.

Calkins, Hugh, Karl Heinz Kuck, Riccardo Cappato, Josep Brugada, A. John Camm, Shih-Ann Chen, Harry J. G. Crijns, Ralph J. Damiano, D. Wyn Davies, John DiMarco, James Edgerton, Kenneth Ellenbogen, Michael D. Ezekowitz, David E. Haines, Michel Haissaguerre, Gerhard Hindricks, Yoshito Iesaka, Warren Jackman, Jose Jalife, Pierre Jais, Jonathan Kalman, David Keane, Young-Hoon Kim, Paulus Kirchhof, George Klein, Hans Kottkamp, Koichiro Kumagai, Bruce D. Lindsay, Moussa Mansour, Francis E. Marchlinski, Patrick M. McCarthy, J. Lluis Mont, Fred Morady, Koonlawee Nademanee, Hiroshi Nakagawa, Andrea Natale, Stanley Nattel, Douglas L. Packer, Carlo Pappone, Eric Prystowsky, Antonio Raviele, Vivek Reddy, Jeremy N. Ruskin, Richard J. Shemin, Hsuan-Ming Tsao, and David Wilber. 2012. “2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design.” *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 14(4):528–606. doi: 10.1093/europace/eus027.

Chou, Chung-Chuan, Hui-Ling Lee, Po-Cheng Chang, Hung-Ta Wo, Ming-Shien Wen, San-Jou Yeh, Fen-Chiung Lin, and Yi-Ting Hwang. 2018. “Left Atrial Emptying Fraction Predicts Recurrence of Atrial Fibrillation after Radiofrequency Catheter Ablation.” *PloS One* 13(1):e0191196. doi: 10.1371/journal.pone.0191196.

Chubb, Henry, Rashed Karim, Rahul Mukherjee, Steven E. Williams, John Whitaker, James Harrison, Steven A. Niederer, Wieland Staab, Jaspal Gill, Tobias Schaeffter, Matthew Wright, Mark O’Neill, and Reza Razavi. 2019. “A Comprehensive Multi-Index Cardiac Magnetic Resonance-Guided Assessment of Atrial Fibrillation Substrate Prior to Ablation: Prediction of Long-Term Outcomes.” *Journal of Cardiovascular Electrophysiology* 30(10):1894–1903. doi: 10.1111/jce.14111.

Chugh, Sumeet S., Rasmus Havmoeller, Kumar Narayanan, David Singh, Michiel Rienstra, Emelia J. Benjamin, Richard F. Gillum, Young-Hoon Kim, John H. McAnulty, Zhi-Jie Zheng, Mohammad H. Forouzanfar, Mohsen Naghavi,

George A. Mensah, Majid Ezzati, and Christopher J. L. Murray. 2014. "Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study." *Circulation* 129(8):837–47. doi: 10.1161/CIRCULATIONAHA.113.005119.

Ciuffo, Luisa, Susumu Tao, Esra Gucuk Ipek, Tarek Zghaib, Muhammad Balouch, Joao A. C. Lima, Saman Nazarian, David D. Spragg, Joseph E. Marine, Ronald D. Berger, Hugh Calkins, and Hiroshi Ashikaga. 2019. "Intra-Atrial Dyssynchrony During Sinus Rhythm Predicts Recurrence After the First Catheter Ablation for Atrial Fibrillation." *JACC. Cardiovascular Imaging* 12(2):310–19. doi: 10.1016/j.jcmg.2017.11.028.

Conen, David, Robert J. Glynn, Roopinder K. Sandhu, Usha B. Tedrow, and Christine M. Albert. 2013. "Risk Factors for Incident Atrial Fibrillation with and without Left Atrial Enlargement in Women." *International Journal of Cardiology* 168(3):1894–99. doi: 10.1016/j.ijcard.2012.12.060.

Darby, Andrew E. 2016. "Recurrent Atrial Fibrillation After Catheter Ablation: Considerations For Repeat Ablation And Strategies To Optimize Success." *Journal of Atrial Fibrillation* 9(1):1427. doi: 10.4022/jafib.1427.

Dretzke, Janine, Naomi Chuchu, Ridhi Agarwal, Clare Herd, Winnie Chua, Larissa Fabritz, Susan Bayliss, Dipak Kotecha, Jonathan J. Deeks, Paulus Kirchhof, and Yemisi Takwoingi. 2020. "Predicting Recurrent Atrial Fibrillation after Catheter Ablation: A Systematic Review of Prognostic Models." *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 22(5):748–60. doi: 10.1093/europace/euaa041.

Dzeshka, Mikhail S., Gregory Y. H. Lip, Viktor Snezhitskiy, and Eduard Shantsila. 2015a. "Cardiac Fibrosis in Patients With Atrial Fibrillation: Mechanisms and Clinical Implications." *Journal of the American College of Cardiology* 66(8):943–59. doi: 10.1016/j.jacc.2015.06.1313.

Evangelista, Arturo, Frank Flachskampf, Patrizio Lancellotti, Luigi Badano, Rio Aguilar, Mark Monaghan, José Zamorano, Petros Nihoyannopoulos, and European Association of Echocardiography. 2008. "European Association of Echocardiography Recommendations for Standardization of Performance, Digital Storage and Reporting of Echocardiographic Studies." *European Journal of Echocardiography : The Journal of the Working Group on Echocardiography of the European Society of Cardiology* 9(4):438–48. doi: 10.1093/ejechocard/jen174.

Fabritz, Larissa, Harry J. G. M. Crijns, Eduard Guasch, Andreas Goette, Karl Georg Häusler, Dipak Kotecha, Thorsten Lewalter, Christian Meyer, Tatjana S. Potpara, Michiel Rienstra, Renate B. Schnabel, Stephan Willems, Guenter Breithardt, A. John Camm, Anthony Chan, Winnie Chua, Mirko de Melis, Christina Dimopoulou, Dobromir Dobrev, Christina Easter, Lars Eckardt, Doreen Haase, Stephane Hatem, Jeff S. Healey, Jordi Heijman, Stefan H. Hohnloser, Thomas Huebner, Bushra Saeed Ilyas, Aaron Isaacs, Ingo Kutschka, Christophe Leclercq, Gregory Y. H. Lip, Elena Andreassi Marinelli, Jose L. Merino, Lluís Mont, Michael Nabauer, Jonas Oldgren, Helmut Pürerfellner, Ursula Ravens, Irina Savelieva, Moritz F. Sinner, Alice Sitch, Rüdiger Smolnik, Jan Steffel, Kenneth Stein, Monika Stoll, Emma Svennberg, Dierk Thomas, Isabelle C. Van Gelder, Burcu Vardar, Reza Wakili, Mattias Wieloch, Stef

Zeemering, Paul D. Ziegler, Hein Heidbuchel, Gerhard Hindricks, Ulrich Schotten, and Paulus Kirchhof. 2021. “Dynamic Risk Assessment to Improve Quality of Care in Patients with Atrial Fibrillation: The 7th AFNET/EHRA Consensus Conference.” *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 23(3):329–44. doi: 10.1093/europace/euaa279.

Floria, Mariana, Smaranda Radu, Evelina Maria Gosav, Dragos Cozma, Ovidiu Mitu, Anca Ouatu, Daniela Maria Tanase, Viorel Scripcariu, and Lacramioara Ionela Serban. 2020. “Left Atrial Structural Remodelling in Non-Valvular Atrial Fibrillation: What Have We Learnt from CMR?” *Diagnostics (Basel, Switzerland)* 10(3). doi: 10.3390/diagnostics10030137.

Florian, Anca, Anna Ludwig, Sabine Rösch, Handan Yildiz, Udo Sechtem, and Ali Yilmaz. 2014. “Myocardial Fibrosis Imaging Based on T1-Mapping and Extracellular Volume Fraction (ECV) Measurement in Muscular Dystrophy Patients: Diagnostic Value Compared with Conventional Late Gadolinium Enhancement (LGE) Imaging.” *European Heart Journal. Cardiovascular Imaging* 15(9):1004–12. doi: 10.1093/ehjci/jeu050.

Fukushima, Keiko, Noritoshi Fukushima, Koichiro Ejima, Ken Kato, Yasuto Sato, Shoko Uematsu, Kotaro Arai, Tetsuyuki Manaka, Atsushi Takagi, Kyomi Ashihara, Morio Shoda, and Nobuhisa Hagiwara. 2015. “Left Atrial Appendage Flow Velocity and Time from P-Wave Onset to Tissue Doppler-Derived A’ Predict Atrial Fibrillation Recurrence after Radiofrequency Catheter Ablation.” *Echocardiography (Mount Kisco, N.Y.)* 32(7):1101–8. doi: 10.1111/echo.12823.

Gan, Gary C. H., Aaisha Ferkh, Anita Boyd, and Liza Thomas. 2018. “Left Atrial Function: Evaluation by Strain Analysis.” *Cardiovascular Diagnosis and Therapy* 8(1):29–46. doi: 10.21037/cdt.2017.06.08.

Goette, Andreas, Gina Juenemann, Brigitte Peters, Helmut U. Klein, Albert Roessner, Christof Huth, and Christoph Röcken. 2002. “Determinants and Consequences of Atrial Fibrosis in Patients Undergoing Open Heart Surgery.” *Cardiovascular Research* 54(2):390–96. doi: 10.1016/s0008-6363(02)00251-1.

Habibi, Mohammadali, Joao A. C. Lima, Esra Gucuk Ipek, Stefan L. Zimmerman, Vadim Zipunnikov, David Spragg, Hiroshi Ashikaga, John Rickard, Joseph E. Marine, Ronald D. Berger, Hugh Calkins, and Saman Nazarian. 2016. “The Association of Baseline Left Atrial Structure and Function Measured with Cardiac Magnetic Resonance and Pulmonary Vein Isolation Outcome in Patients with Drug-Refractory Atrial Fibrillation.” *Heart Rhythm* 13(5):1037–44. doi: 10.1016/j.hrthm.2016.01.016.

Haïssaguerre, M., P. Jaïs, D. C. Shah, A. Takahashi, M. Hocini, G. Quiniou, S. Garrigue, A. Le Mouroux, P. Le Métayer, and J. Clémenty. 1998. “Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins.” *The New England Journal of Medicine* 339(10):659–66. doi: 10.1056/NEJM199809033391003.

Hindricks, Gerhard, Tatjana Potpara, Nikolaos Dagres, Jeroen J. Bax, Giuseppe Boriani, Gheorghe Andrei Dan, Laurent Fauchier, Jonathan M. Kalman, Deirdre A. Lane, Maddalena Lettino, Fausto J. Pinto, G. Neil Thomas, Marco Valgimigli, Bart P. Van Putte, Paulus Kirchhof, Michael Kühne, Victor Aboyans, Anders Ahlsson, Pawel Balsam, Johann Bauersachs, Stefano Benussi, Axel Brandes, Frieder Braunschweig, A. John Camm, Davide Capodanno,

Barbara Casadei, David Conen, Harry J. G. M. Crijns, Victoria Delgado, Dobromir Dobrev, Heinz Drexel, Lars Eckardt, Donna Fitzsimons, Thierry Folliguet, Chris P. Gale, Bulent Gorenek, Karl Georg Haeusler, Hein Heidbuchel, Bernard Iung, Hugo A. Katus, Dipak Kotecha, Ulf Landmesser, Christophe Leclercq, Basil S. Lewis, Julia Mascherbauer, Jose Luis Merino, Béla Merkely, Lluís Mont, Christian Mueller, Klaudia V. Nagy, Jonas Oldgren, Nikola Pavlović, Roberto F. E. Pedretti, Steffen E. Petersen, Jonathan P. Piccini, Bogdan A. Popescu, Helmut Pürerfellner, Dimitrios J. Richter, Marco Roffi, Andrea Rubboli, Daniel Scherr, Renate B. Schnabel, Iain A. Simpson, Evgeny Shlyakhto, Moritz F. Sinner, Jan Steffel, Miguel Sousa-Uva, Piotr Suwalski, Martin Svetlosak, Rhian M. Touyz, Elena Arbelo, Carina Blomström-Lundqvist, Manuel Castella, Polychronis E. Dilaveris, Gerasimos Filippatos, Mark La Meir, Jean Pierre Lebeau, Gregory Y. H. Lip, G. Neil Thomas, Isabelle C. Van Gelder, and Caroline L. Watkins. 2021. "2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)." *European Heart Journal* 42(5):373–498.

Ho, Siew Yen, José Angel Cabrera, and Damian Sanchez-Quintana. 2012. "Left Atrial Anatomy Revisited." *Circulation. Arrhythmia and Electrophysiology* 5(1):220–28. doi: 10.1161/CIRCEP.111.962720.

Ho, Siew Yen, and Karen P. McCarthy. 2010. "Anatomy of the Left Atrium for Interventional Electrophysiologists." *Pacing and Clinical Electrophysiology : PACE* 33(5):620–27. doi: 10.1111/j.1540-8159.2009.02659.x.

Hong, Jin, Xiaoyan Gu, Ping An, Taiyang Luo, Qiang Lv, Junping Kang, Yihua He, Rong Hu, Xiaohui Liu, and Changsheng Ma. 2013. "Left Atrial Functional Remodeling in Lone Atrial Fibrillation: A Two-Dimensional Speckle Tracking Echocardiographic Study." *Echocardiography (Mount Kisco, N.Y.)* 30(9):1051–60. doi: 10.1111/echo.12200.

Ji, Mengmeng, Lin He, Lang Gao, Yixia Lin, Mingxing Xie, and Yuman Li. 2022. "Assessment of Left Atrial Structure and Function by Echocardiography in Atrial Fibrillation." *Diagnostics (Basel, Switzerland)* 12(8). doi: 10.3390/diagnostics12081898.

Jiang, Hui, Weizong Wang, Cong Wang, Xinxing Xie, and Yinglong Hou. 2017. "Association of Pre-Ablation Level of Potential Blood Markers with Atrial Fibrillation Recurrence after Catheter Ablation: A Meta-Analysis." *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 19(3):392–400. doi: 10.1093/europace/euw088.

Jin, Xiao, Jianke Pan, Huanlin Wu, and Danping Xu. 2018. "Are Left Ventricular Ejection Fraction and Left Atrial Diameter Related to Atrial Fibrillation Recurrence after Catheter Ablation?: A Meta-Analysis." *Medicine* 97(20):e10822. doi: 10.1097/MD.0000000000010822.

Kanda, Takashi, Masaharu Masuda, Akihiro Sunaga, Masashi Fujita, Osamu Iida, Shin Okamoto, Takayuki Ishihara, Tetsuya Watanabe, Mitsuyoshi Takahara, Yasushi Sakata, and Masaaki Uematsu. 2015. "Low Left Atrial Appendage Flow Velocity Predicts Recurrence of Atrial Fibrillation after Catheter Ablation of Persistent Atrial Fibrillation." *Journal of Cardiology* 66(5):377–81. doi: 10.1016/j.jjcc.2015.04.009.

Kato, Shingo, Murilo Foppa, Sébastien Roujol, Tamer Basha, Sophie Berg, Kraig V Kissinger, Beth Goddu, Warren J. Manning, and Reza Nezafat. 2016. "Left Ventricular Native T1 Time and the Risk of Atrial Fibrillation Recurrence after Pulmonary Vein Isolation in Patients with Paroxysmal Atrial Fibrillation." *International Journal of Cardiology* 203:848–54. doi: 10.1016/j.ijcard.2015.11.073.

Kawakami, Hiroshi, Satish Ramkumar, Mark Nolan, Leah Wright, Hong Yang, Kazuaki Negishi, and Thomas H. Marwick. 2019. "Left Atrial Mechanical Dispersion Assessed by Strain Echocardiography as an Independent Predictor of New-Onset Atrial Fibrillation: A Case-Control Study." *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography* 32(10):1268-1276.e3. doi: 10.1016/j.echo.2019.06.002.

Kawakami, Hiroshi, Satish Ramkumar, Faraz Pathan, Leah Wright, and Thomas H. Marwick. 2020. "Use of Echocardiography to Stratify the Risk of Atrial Fibrillation: Comparison of Left Atrial and Ventricular Strain." *European Heart Journal. Cardiovascular Imaging* 21(4):399–407. doi: 10.1093/ehjci/jez240.

Kosiuk, Jedrzej, Ole-A. Breithardt, Kerstin Bode, Jelena Kornej, Arash Arya, Christopher Piorkowski, Thomas Gaspar, Philipp Sommer, Daniela Husser, Gerhard Hindricks, and Andreas Bollmann. 2014. "The Predictive Value of Echocardiographic Parameters Associated with Left Ventricular Diastolic Dysfunction on Short- and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation." *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 16(8):1168–74. doi: 10.1093/europace/eut415.

Kranert, Malte, Tetyana Shchetynska-Marinova, Volker Liebe, Christina Doesch, Theano Papavassiliu, Ibrahim Akin, Martin Borggrefe, and Anna Hohneck. 2020. "Recurrence of Atrial Fibrillation in Dependence of Left Atrial Volume Index." *In Vivo (Athens, Greece)* 34(2):889–96. doi: 10.21873/invivo.11854.

Krijthe, Bouwe P., Anton Kunst, Emelia J. Benjamin, Gregory Y. H. Lip, Oscar H. Franco, Albert Hofman, Jacqueline C. M. Witteman, Bruno H. Stricker, and Jan Heeringa. 2013. "Projections on the Number of Individuals with Atrial Fibrillation in the European Union, from 2000 to 2060." *European Heart Journal* 34(35):2746–51. doi: 10.1093/eurheartj/eht280.

Kuo, Jen-Yuan, Sheng-Hsiung Chang, Kuo-Tzu Sung, Po-Ching Chi, Jo-Nan Liao, Tze-Fan Chao, Cheng-Huang Su, Hung-I. Yeh, and Chung-Lieh Hung. 2020. "Left Ventricular Dysfunction in Atrial Fibrillation and Heart Failure Risk." *ESC Heart Failure* 7(6):3694–3706. doi: 10.1002/ehf2.12920.

Lang, Roberto M., Luigi P. Badano, Victor Mor-Avi, Jonathan Afilalo, Anderson Armstrong, Laura Ernande, Frank A. Flachskampf, Elyse Foster, Steven A. Goldstein, Tatiana Kuznetsova, Patrizio Lancellotti, Denisa Muraru, Michael H. Picard, Ernst R. Rietzschel, Lawrence Rudski, Kirk T. Spencer, Wendy Tsang, and Jens-Uwe Voigt. 2015. "Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging." *Journal of the American Society of Echocardiography* 28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.

Legallois, Damien, Amir Hodzic, Paul Milliez, Alain Manrique, Charles Dolladille, Eric Saloux, and Farzin Beygui. 2022. "Left Atrial Strain Quantified after

Myocardial Infarction Is Associated with Early Left Ventricular Remodeling." *Echocardiography (Mount Kisco, N.Y.)* 39(12):1581–88. doi: 10.1111/echo.15492.

Machino-Ohtsuka, Tomoko, Yoshihiro Seo, Hiroshi Tada, Tomoko Ishizu, Takeshi Machino, Hiro Yamasaki, Miyako Igarashi, Dongzhu Xu, Yukio Sekiguchi, and Kazutaka Aonuma. 2011. "Left Atrial Stiffness Relates to Left Ventricular Diastolic Dysfunction and Recurrence after Pulmonary Vein Isolation for Atrial Fibrillation." *Journal of Cardiovascular Electrophysiology* 22(9):999–1006. doi: 10.1111/j.1540-8167.2011.02049.x.

Magnussen, Christina, Teemu J. Niiranen, Francisco M. Ojeda, Francesco Gianfagna, Stefan Blankenberg, Inger Njølstad, Erkki Vartiainen, Susana Sans, Gerard Pasterkamp, Maria Hughes, Simona Costanzo, Maria Benedetta Donati, Pekka Jousilahti, Allan Linneberg, Tarja Palosaari, Giovanni de Gaetano, Martin Bobak, Hester M. den Ruijter, Ellisiv Mathiesen, Torben Jørgensen, Stefan Söderberg, Kari Kuulasmaa, Tanja Zeller, Licia Iacoviello, Veikko Salomaa, Renate B. Schnabel, and BiomarCaRE Consortium. 2017. "Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe)." *Circulation* 136(17):1588–97. doi: 10.1161/CIRCULATIONAHA.117.028981.

Markman, Timothy M., Mirmilad Khoshknab, and Saman Nazarian. 2021. "Catheter Ablation of Atrial Fibrillation: Cardiac Imaging Guidance as an Adjunct to the Electrophysiological Guided Approach." *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 23(4):520–28. doi: 10.1093/europace/euaa249.

Marrouche, Nassir F., David Wilber, Gerhard Hindricks, Pierre Jais, Nazem Akoum, Francis Marchlinski, Eugene Kholmovski, Nathan Burgon, Nan Hu, Lluis Mont, Thomas Deneke, Mattias Duytschaever, Thomas Neumann, Moussa Mansour, Christian Mahnkopf, Bengt Herweg, Emile Daoud, Erik Wissner, Paul Bansmann, and Johannes Brachmann. 2014. "Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study." *JAMA* 311(5):498–506. doi: 10.1001/jama.2014.3.

Moon, Jeonggeun, Hye-Jeong Lee, Jongwook Yu, Hui-Nam Pak, Jong-Won Ha, Moon-Hyoung Lee, Young Jin Kim, and Boyoung Joung. 2017. "Prognostic Implication of Left Atrial Sphericity in Atrial Fibrillation Patients Undergoing Radiofrequency Catheter Ablation." *Pacing and Clinical Electrophysiology : PACE* 40(6):713–20. doi: 10.1111/pace.13088.

Mor-Avi, Victor, Chattanong Yodwut, Carly Jenkins, Harald Kühl, Hans-Joachim Nesser, Thomas H. Marwick, Andreas Franke, Lynn Weinert, Johannes Niel, Regina Steringer-Mascherbauer, Benjamin H. Freed, Lissa Sugeng, and Roberto M. Lang. 2012. "Real-Time 3D Echocardiographic Quantification of Left Atrial Volume: Multicenter Study for Validation with CMR." *JACC. Cardiovascular Imaging* 5(8):769–77. doi: 10.1016/j.jcmg.2012.05.011.

Naruse, Yoshihisa, Hiroshi Tada, Makoto Satoh, Mariko Yanagihara, Hidekazu Tsuneoka, Yumi Hirata, Yoko Ito, Kenji Kuroki, Takeshi Machino, Hiro Yamasaki, Miyako Igarashi, Yukio Sekiguchi, Akira Sato, and Kazutaka Aonuma. 2013. "Concomitant Obstructive Sleep Apnea Increases the

Recurrence of Atrial Fibrillation Following Radiofrequency Catheter Ablation of Atrial Fibrillation: Clinical Impact of Continuous Positive Airway Pressure Therapy." *Heart Rhythm* 10(3):331–37. doi: 10.1016/j.hrthm.2012.11.015.

Nattel, Stanley, Brett Burstein, and Dobromir Dobrev. 2008. "Atrial Remodeling and Atrial Fibrillation: Mechanisms and Implications." *Circulation. Arrhythmia and Electrophysiology* 1(1):62–73. doi: 10.1161/CIRCEP.107.754564.

Nattel, Stanley, and Dobromir Dobrev. 2012. "The Multidimensional Role of Calcium in Atrial Fibrillation Pathophysiology: Mechanistic Insights and Therapeutic Opportunities." *European Heart Journal* 33(15):1870–77. doi: 10.1093/eurheartj/ehs079.

Neilan, Tomas G., Ravi V Shah, Siddique A. Abbasi, Hoshang Farhad, John D. Groarke, John A. Dodson, Otavio Coelho-Filho, Ciaran J. McMullan, Bobak Heydari, Gregory F. Michaud, Roy M. John, Rob van der Geest, Michael L. Steigner, Ron Blankstein, Michael Jerosch-Herold, and Raymond Y. Kwong. 2013. "The Incidence, Pattern, and Prognostic Value of Left Ventricular Myocardial Scar by Late Gadolinium Enhancement in Patients with Atrial Fibrillation ." *Journal of the American College of Cardiology* 62(23):2205–14. doi: 10.1016/j.jacc.2013.07.067.

Nguyen, Thao P., Zhilin Qu, and James N. Weiss. 2014. "Cardiac Fibrosis and Arrhythmogenesis: The Road to Repair Is Paved with Perils." *Journal of Molecular and Cellular Cardiology* 70:83–91. doi: 10.1016/j.yjmcc.2013.10.018.

Njoku, Augustine, Munish Kannabhiran, Rishi Arora, Pratap Reddy, Rakesh Gopinathannair, Dhanunjaya Lakkireddy, and Paari Dominic. 2018. "Left Atrial Volume Predicts Atrial Fibrillation Recurrence after Radiofrequency Ablation: A Meta-Analysis." *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 20(1):33–42. doi: 10.1093/europace/eux013.

Onishi, Naoaki, Kazuaki Kaitani, Masashi Amano, Sari Imamura, Jiro Sakamoto, Yodo Tamaki, Soichiro Enomoto, Makoto Miyake, Toshihiro Tamura, Hirokazu Kondo, Chisato Izumi, and Yoshihisa Nakagawa. 2018. "Relationship between Left Ventricular Diastolic Dysfunction and Very Late Recurrences after Multiple Procedures for Atrial Fibrillation Ablation." *Heart and Vessels* 33(1):41–48. doi: 10.1007/s00380-017-1027-y.

Parwani, Abdul Shokor, Daniel-Armando Morris, Florian Blaschke, Martin Huemer, Burkert Pieske, Wilhelm Haverkamp, and Leif-Hendrik Boldt. 2017. "Left Atrial Strain Predicts Recurrence of Atrial Arrhythmias after Catheter Ablation of Persistent Atrial Fibrillation." *Open Heart* 4(1):e000572. doi: 10.1136/openhrt-2016-000572.

Platonov, Pyotr G., Lubov B. Mitrofanova, Victoria Orshanskaya, and Siew Yen Ho. 2011. "Structural Abnormalities in Atrial Walls Are Associated with Presence and Persistency of Atrial Fibrillation but Not with Age." *Journal of the American College of Cardiology* 58(21):2225–32. doi: 10.1016/j.jacc.2011.05.061.

De Potter, Tom, Antonio Berruezo, Lluis Mont, Maria Matiello, David Tamborero, Claudio Santibañez, Begoña Benito, Nibaldo Zamorano, and Josep Brugada. 2010. "Left Ventricular Systolic Dysfunction by Itself Does Not Influence Outcome of Atrial Fibrillation Ablation." *Europace : European Pacing,*

Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology 12(1):24–29. doi: 10.1093/europace/eup309.

Rodevan, O., R. Bjornerheim, M. Ljosland, J. Maehle, H. J. Smith, and H. Ihlen. 1999. "Left Atrial Volumes Assessed by Three- and Two-Dimensional Echocardiography Compared to MRI Estimates." *International Journal of Cardiac Imaging* 15(5):397–410. doi: 10.1023/a:1006276513186.

Sarvari, Sebastian I., Kristina H. Haugaa, Thomas M. Stokke, Hamza Z. Ansari, Ida S. Leren, Finn Hegbom, Otto A. Smiseth, and Thor Edvardsen. 2016. "Strain Echocardiographic Assessment of Left Atrial Function Predicts Recurrence of Atrial Fibrillation." *European Heart Journal. Cardiovascular Imaging* 17(6):660–67. doi: 10.1093/ehjci/jev185.

Shin, Sung-Hee, Mi-Young Park, Woong-Jin Oh, Soon-Jun Hong, Hui-Nam Pak, Woo-Hyuk Song, Do-Sun Lim, Young-Hoon Kim, and Wan-Joo Shim. 2008. "Left Atrial Volume Is a Predictor of Atrial Fibrillation Recurrence after Catheter Ablation." *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography* 21(6):697–702. doi: 10.1016/j.echo.2007.10.022.

Suksaranjit, Promporn, Nazem Akoum, Eugene G. Kholmovski, Gregory J. Stoddard, Lowell Chang, Kavitha Damal, Krishna Velagapudi, Allen Rassa, Erik Bieging, Shridhar Challa, Imran Haider, Nassir F. Marrouche, Christopher J. McGann, and Brent D. Wilson. 2015. "Incidental LV LGE on CMR Imaging in Atrial Fibrillation Predicts Recurrence After Ablation Therapy." *JACC. Cardiovascular Imaging* 8(7):793–800. doi: 10.1016/j.jcmg.2015.03.008.

Thomas, Liza, and Walter P. Abhayaratna. 2017. "Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and Clinical Significance." *JACC. Cardiovascular Imaging* 10(1):65–77. doi: 10.1016/j.jcmg.2016.11.003.

Thomas, Liza, Thomas H. Marwick, Bogdan A. Popescu, Erwan Donal, and Luigi P. Badano. 2019. "Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC State-of-the-Art Review." *Journal of the American College of Cardiology* 73(15):1961–77. doi: 10.1016/j.jacc.2019.01.059.

Thomas, Liza, Denisa Muraru, Bogdan A. Popescu, Marta Sitges, Monica Rosca, Gianni Pedrizzetti, Michael Y. Henein, Erwan Donal, and Luigi P. Badano. 2020. "Evaluation of Left Atrial Size and Function: Relevance for Clinical Practice." *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography* 33(8):934–52. doi: 10.1016/j.echo.2020.03.021.

Triposkiadis, F., K. Tentolouris, A. Androulakis, A. Trikas, K. Toutouzas, M. Kyriakidis, J. Gialafos, and P. Toutouzas. 1995. "Left Atrial Mechanical Function in the Healthy Elderly: New Insights from a Combined Assessment of Changes in Atrial Volume and Transmitral Flow Velocity." *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography* 8(6):801–9. doi: 10.1016/s0894-7317(05)80004-5.

Verheule, Sander, and Ulrich Schotten. 2021. "Electrophysiological Consequences of Cardiac Fibrosis." *Cells* 10(11). doi: 10.3390/cells10113220.

Verma, Atul, David E. Haines, Lucas V Boersma, Nitesh Sood, Andrea Natale, Francis E. Marchlinski, Hugh Calkins, Prashanthan Sanders, Douglas L. Packer, Karl-Heinz Kuck, Gerhard Hindricks, Birce Onal, Jeffrey Cerkvenik, Hiroshi

Tada, David B. DeLurgio, and PULSED AF Investigators. 2023. “Pulsed Field Ablation for the Treatment of Atrial Fibrillation: PULSED AF Pivotal Trial.” *Circulation* 147(19):1422–32. doi: 10.1161/CIRCULATIONAHA.123.063988.

Wen, Song-Nan, Nian Liu, Rong Bai, Ri-Bo Tang, Rong-Hui Yu, De-Yong Long, Cai-Hua Sang, Chen-Xi Jiang, Song-Nan Li, Jia-Hui Wu, Yan-Fei Ruan, Rong Hu, Xin Du, Xiao-Hui Liu, Jian-Zeng Dong, and Chang-Sheng Ma. 2017. “Right Atrial Diameter and Outcome of Catheter Ablation of Atrial Fibrillation.” *Journal of Interventional Cardiac Electrophysiology : An International Journal of Arrhythmias and Pacing* 49(2):157–64. doi: 10.1007/s10840-017-0258-2.

Wijesurendra, Rohan S., and Barbara Casadei. 2019. “Mechanisms of Atrial Fibrillation.” *Heart (British Cardiac Society)* 105(24):1860–67. doi: 10.1136/heartjnl-2018-314267.

Wu, Xiao-Yan, Song-Nan Li, Song-Nan Wen, Jun-Gang Nie, Wen-Ning Deng, Rong Bai, Nian Liu, Ri-Bo Tang, Ting Zhang, Xin Du, Jian-Zeng Dong, and Chang-Sheng Ma. 2015. “Plasma Galectin-3 Predicts Clinical Outcomes after Catheter Ablation in Persistent Atrial Fibrillation Patients without Structural Heart Disease.” *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology* 17(10):1541–47. doi: 10.1093/europace/euv045.

Wylie, John V, Dana C. Peters, Vidal Essebag, Warren J. Manning, Mark E. Josephson, and Thomas H. Hauser. 2008. “Left Atrial Function and Scar after Catheter Ablation of Atrial Fibrillation.” *Heart Rhythm* 5(5):656–62. doi: 10.1016/j.hrthm.2008.02.008.

Yuda, Satoshi, Atsuko Muranaka, and Tetsuji Miura. 2016. “Clinical Implications of Left Atrial Function Assessed by Speckle Tracking Echocardiography.” *Journal of Echocardiography* 14(3):104–12. doi: 10.1007/s12574-016-0283-7.

9.List of abbreviations

Abbreviation	Full name
AF	atrial fibrillation
PVI	pulmonary vein isolation
RA	right atrium
LA	left atrium
CMR	cardiac magnetic resonance
CCT	cardiac computed tomography
TTE	transthoracic echocardiography
TEE	transesophageal echocardiography
LV	left ventricle
LA	left atrium
LAA	left atrial appendage
2D	two dimensional
3D	three dimensional
PLAX	parasternal long axis
LAVi	LA volume index
LAVmax	maximum LA volume
LAVmin	minimal LA volume
LAEF	left atrial emptying fraction
LVEF	left ventricular emptying fraction
LVDD	left ventricular diastolic dysfunction
LAD	left atrial diameter
TDI	tissue Doppler imaging
STE	speckle tracking echocardiography
2D-STE	two-dimensional speckle tracking echocardiography
3D-STE	three-dimensional speckle tracking echocardiography
ROI	region of interest
LAAFV	LAA flow velocity
LASI	LA stiffness index
LGE	late gadolinium enhancement

AMD	atrial mechanical dispersion
ECG	electrocardiogram
SD-TPS	standard deviation of the time to peak positive strain
BMI	body mass index
BSA	body surface area
CHA2DS2-VASc	C Congestive heart failure
	H Hypertension
	A2 Age ≥75 years
	D Diabetes Mellitus
	S2 Prior Stroke or TIA or Thromboembolism
	V Vascular disease
	A Age 65–74 years
	Sc Sex category
HR	hazard ratios
CI	confidence intervals
ROC	Receiver Operating Characteristic
PAF	paroxysmal atrial fibrillation
PersAF	persistent atrial fibrillation
IQR	interquartile range
ANP	atrial natriuretic peptide
BNP	B-type natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
Gal-3	galectin-3
IL-6	interleukin-6
CRP	C-reactive protein

10. Acknowledgment

Entfällt aus datenschutzrechtlichen Gründen.

11. Curriculum Vitae

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12. Eidesstattliche Erklärung

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