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THE ROLE OF VOLTAGE MAPPING AND CARDIAC CT ANGIOGRAPHY IN PATIENTS UNDERGOING ABLATION FOR ATRIAL FIBRILLATION

PhD thesis

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TABLE OF CONTENT

DOI:10.14753/SE.2022.2731

DOI:10.14753/SE.2022.2731

DOI:10.14753/SE.2022.2731

List of Abbreviations

AAD	Antiarrhythmic Drug
AF	Atrial Fibrillation
BIFA	Box Isolation of the Fibrotic Area
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
BSA	Body Surface Area
CA	Catheter Ablation
CAC(S)	Coronary Artery Calcium (Score)
CAD	Coronary Artery Disease
CT(A)	Computed Tomography (Angiography)
CV	Cardiovascular
(DE)-MRI	(Delayed Enhancement) Magnetic Resonance Imaging
EAM	Electro-anatomical Map(ping)
EAMS	Electro-anatomical Mapping System
EP	Electrophysiology
FACM	Fibrotic Atrial Cardiomyopathy
HD	High-Density
HFrEF	Heart Failure with reduced Ejection Fraction
ICE	Intracardiac Echocardiography
LA	Left Atrium/Atrial
LAV(I)	Left Atrial Volume (Index)
LGE-MRI	Late Gadolinium Enhancement MRI
LVA	Low Voltage Area
LVEF	Left Ventricular Ejection Fraction
MRI	Cardiac Magnetic Resonance Imaging
NOAC	Non Vitamin K Antagonist Oral Anticoagulant
NT-proBNP	N-terminal Prohormone BNP
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QoL	Quality of Life
RA	Right Atrium/Atrial
RAV(I)	Right Atrial Volume (Index)
SR	Sinus Rhythm
TOE	Transoesophageal Echocardiography
VHA	Voltage Histogram Analysis
VKA	Vitamin K Antagonist

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1. INTRODUCTION

1.1. ATRIAL FIBRILLATION (AF)

1.1.1. *THE DEFINITION OF AF*

Atrial fibrillation (AF) is an irregular supraventricular tachycardia with ineffective atrial contraction due to uncoordinated atrial electrical activation. Diagnosis of AF is mianly made by a 12-lead electrocardiogram (ECG), which shows irregular R-R intervals (in case of no atrioventricular conduction impairment), absence of P waves, and irregular atrial activation ('f' waves). An episode of AF lasting ≥ 30 seconds is diagnostic for clinical AF. Symptoms of AF may range from none to disabling: including palpitation, shortness of breath, chest discomfort, and fatigue (1).

Traditionally the following patterns of AF are distinguished (1):

- first diagnosed: AF not known before
- paroxysmal: AF terminating spontaneously or by intervention within 7 days of onset
- persistent: sustained AF beyond 7 days of onset
- long-standing persistent: continuous AF of more than 12 months' duration with rhythm control strategy
- permanent: continuous AF with frequency control strategy

1.1.2. *SIGNIFICANCE OF AF*

AF is the most common cardiac arrhythmia in our population: the lifetime AF risk is estimated to be one out of three individuals of European ancestry at index age of 55 years, affecting globally 43.6 million people with a continuously rising prevalence (1-4). AF is associated with ischaemic stroke, heart failure, a decrease in cognitive function, lower quality of life (QoL), extended medical costs, as well as increased mortality (5). Therefore, risk stratification, primary and secondary prevention, and the development of effective treatments for AF are crucial (1).

1.1.3. *TREATMENT OF AF*

The treatment of AF requires an integrated management: the holistic 'ABC' pathway is suggested by the European Society of Cardiology's latest prevention guideline (6). Anticoagulation for avoiding stroke ('A'), better symptom management ('B'), and cardiovascular (CV) and comorbidity optimization ('C') (6).

In general, anticoagulation is recommended for AF patients with elevated thromboembolic risk score, estimated by CHA_2DS_2-VASc score (1). This score involves the following risk factors: Congestive heart failure, Hypertension, Age, Diabetes, Stroke/transient ischemic attack/thromboembolism, Vascular disease, and female Sex (7). The most commonly used oral anticoagulants are distinguished into two groups: K-vitamin antagonists (VKA, e.g. acenocoumarol, warfarin) and non-vitamin K antagonist oral anticoagulant (NOAC, e.g. rivaroxaban, apixaban, edoxaban, dabigatran) (8).

Better symptom control helps to improve AF-related symptoms with rate control and/or rhythm control therapy. Rate control therapy can be achieved with different medications (e.g. beta-blockers, digoxin, diltiazem and verapamil), targeting < 110 beats per minute and AF-related symptom release. Another definitive solution for rate control is pacemaker implantation and ablation of the atrioventricular node; mainly used for severely symptomatic patients with permanent AF. Rhythm control strategy refers to attempts to restore and maintain sinus rhythm, which could be used in combination. These treatments include electrical or pharmacological cardioversion, antiarrhythmic drug (AAD) administration (e.g. amiodarone, dronedarone, flecainide, propafenone, sotalol), catheter ablation, and surgical cure with maze procedure (1). Early rhythm control therapy for AF improves not just QoL, but also leads to the reduction of CV death, stroke, or hospitalization in symptomatic and asymptomatic AF patients (9).

The ‘C’ component of the pathway includes identification and management of concomitant diseases and cardiometabolic risk factors (e.g. hypertension, diabetes, obstructive sleep apnoea, heart failure, coronary artery disease, obesity), and unhealthy lifestyle factors (e.g. alcohol use, physical inactivity). Targeted therapy of underlying conditions and modification of risk factors may improve the success of rhythm control therapy (1).

1.1.4. *CATHETER ABLATION FOR AF*

Catheter ablation (CA) is a well-established rhythm control therapy for AF (5, 10). Its main benefit is the improvement of QoL with a long-term recurrence-free, asymptomatic period, significant reduction of CV hospitalizations, lowering antiarrhythmic drug utilization and prescription drug expenditures as well (11-14).

The aim of CA is to eliminate the arrhythmogenic substrate, most commonly found around the ostia of pulmonary veins (PV) in the left atrium (LA) (15). Pappone et al. developed the method of pulmonary vein isolation (PVI), where a persistent electrical disconnection is performed between the PVs and the LA (16). For isolation, radiofrequency or cryo energy-based ablation catheters are used, inserted percutaneously from the femoral vein, guided transseptal to the LA. The ablation catheter creates an electrically non-conducting, transmural myocardial scar establishing sinus rhythm (17).The radiofrequency-generated heat can be transmitted from an irrigated ablation catheter using point-by-point ablation technique or a multi-electrode circular ablation catheter using single-shot ablation technique. One of the most common used technique is the wide antral circumferential ablation (WACA) point-by point strategy, where wider continuous circumferential ablation lesions are created around the left and right PVs (Figure 1) (16). Upon the investigators' discretion, additional atrial substrates may be targeted, however, its additional benefit is still controversial, thus it is recommended rather in specific cases (18-22). On the other hand, the cryoballoon ablation system, being a single-shot ablation approach, creates electrical isolation around each pulmonary veins' ostia by freezing the targeted area (5). The non-inferiority of cryoballoon ablation compared to radiofrequency point by point CA was proved in the "FIRE AND ICE" multicentre randomized clinical trial (23).

Different imaging technologies help the investigator to precisely tailor the ablation strategy and give guidance during the procedure. A pre-procedural cardiac computed tomography angiography (CTA) or cardiac magnetic resonance imaging (MRI) gives detailed information about the anatomy of the LA and PVs. The integration of those images with the procedurally created electro-anatomical map (EAM) using multipolar catheters, creates a detailed and accurate 3D map of the targeted area. Catheter movement and ablation can be guided by fluoroscopy, transoesophageal echocardiography (TOE), intracardiac echocardiography (ICE), and the EAM System (EAMS) (5, 24).

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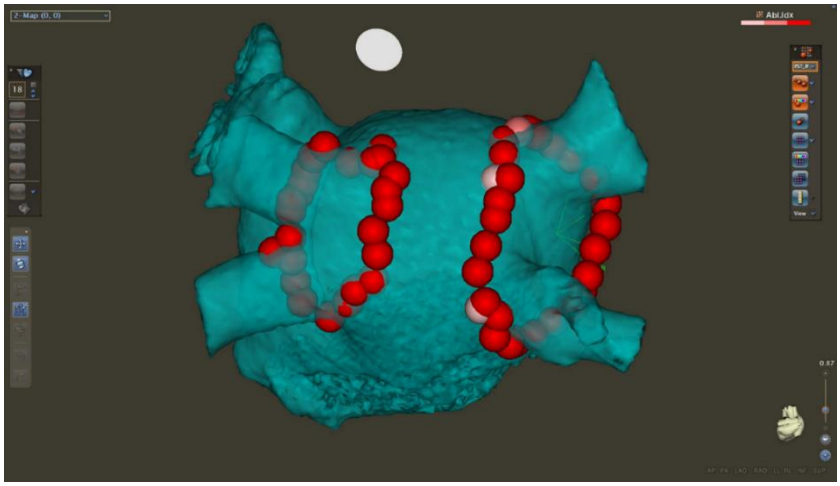

Figure 1. Pulmonary vein isolation projected on left atrial fast anatomic map (postero-anterior view, CARTO 3® platform) – ablation points are marked with red dots (Image of our working group)

CA might be a first-line therapy for AF patients with heart failure with reduced ejection fraction (HFrEF) (Class I indication), for symptomatic paroxysmal AF patients (Class IIa), and for symptomatic persistent AF patients without major risk factors for recurrence (Class IIb) (considering the patients' choice as well). In special conditions, CA could be considered a first-line therapy for patients with persistent AF and major risk factors for AF recurrence. Additionally, if the AAD therapy fails, CA should be considered as second-line for the paroxysmal, and persistent AF population (Class I), and for the individuals with HFrEF (Class IIa).

The alternative to CA for rhythm control is AAD therapy, which can be considered as first-line therapy for every AF patient based on their choice (1). Still, multiple studies proved longer arrhythmia-free rates and improvement in QoL after CA compared to the AAD approach (25-30). However, besides the improvement in symptoms and AF burden, no prospective and randomized trial have showed other benefits favouring CA vs AAD yet (1). In the most awaited CABANA trial, including more than two thousand patients, no significant reduction was presented in mortality, disabling stroke, serious bleeding, or cardiac arrest after CA compared to AAD therapy (30, 31). Based on the above, the current guideline recommends CA only for symptomatic AF patients (1). Nevertheless, the recent EAST-AFNET 4 trial involving over five thousand patients revealed that there was no significant difference in the effect of rhythm control therapy (including CA in about a quarter of the patients) in asymptomatic AF patients compared to symptomatic

ones. Thus, these findings suggest the favour of an early rhythm control therapy independent from AF symptoms (9). Hybrid AAD and CA are both accepted and often-used strategies, while AADs started or continued after CA may reduce AF recurrence (32-34).

1.1.5. *SUCCESS OF CATHETER ABLATION AND ITS RISK FACTORS*

The arrhythmia-free outcome of CA is superior to AADs, however, significant recurrence is still observed after the procedure. Early recurrence, defined as > 30 seconds of atrial tachyarrhythmia during the first 3 months after CA (blanking period), has been observed in 27-52% of the studied patients (5, 35-38). Early recurrence does not mean the failure of ablation therapy, but it is often considered as a predictor of long-term recurrence (36, 39, 40). Long-term recurrence is defined as > 30 seconds of atrial tachyarrhythmia after the 3 months long blanking period (5). The causes of recurrence could be in general microreentrant tachycardia due to the reconnection of PVs, non-PV dependent macroreentrant tachycardia (e.g. mitral isthmus dependent), or intrinsic/iatrogenic atrial scarring (5, 41). The single procedure one-year success rate has varied between 40-94 % (5, 42-45), the two-year success rate has been reported around 45-85% (11, 25, 46, 47), at 5 years it has been around 20-84% (5, 48-51), and some studies have observed 31-73% success rates after 10 years of follow-up (5, 52, 53). With multiple ablations, these numbers improve significantly to 52-80 % (47, 48, 51, 54, 55). However, the listed studies are hardly comparable due to different ablation techniques, types of AF, and comorbidities of the patients.

Nevertheless, the particularly variable success rates highlight the importance of different risk factors associated with AF recurrence. Additionally, they underline the relevance of wise patient selection, as well as the effective control of modifiable risk factors to maintain sinus rhythm after CA (1, 56, 57). The detailed introduction of these factors exceeds the scope of the current dissertation, therefore only the most common parameters are listed hereinafter. The expected success rates of CA for primary AF are lower with prolonged AF duration (persistent and long-standing persistent AF), increasing age, female sex, overweight, smoking, alcohol consumption, excessive exercise, hyperlipidaemia, obstructive sleep apnoea, hypertension, hyperglycaemia, impaired renal function, HFrEF, enlarged LA, diagnosis to ablation time, and early recurrence of AF after rhythm therapy (1, 48-50, 58, 59). Some of the risk factors were linked together to

create a risk stratification model for recurrence prediction, such as APPLE-, DR-FLASH-, and MB-LATER-scores (60). Growing literature confirms the role of atrial fibrosis as well, detailed in the next chapter.

1.2. ATRIAL FIBROSIS

1.2.1. *SIGNIFICANCE OF ATRIAL FIBROSIS*

Atrial fibrosis is a significant contributor to the complex pathomechanism of AF, thus, it is associated with AF recurrence after rhythm therapy (61). AF and atrial fibrosis together contribute to a vicious circle: while the arrhythmia itself can lead to "structural, architectural, contractile, or electrophysiological changes" in the atria; the fibrotic changes help in the manifestation of AF (62, 63). Fibroblast activation, inflammatory infiltration, and the development of atrial fibrosis cause local heterogeneity in the conduction system leading to a potential microreentrant arrhythmia (64, 65). The known risk factors of AF contribute to this atrial structural remodelling and consistent loss of atrial function (62, 66). Moreover, the increasing atrial pressure followed by atrial dilatation also plays an important role in the pathophysiology (67). Interestingly, those mechanisms are also observed in AF without any comorbidities. Kottkamp et al. suggested that the presence of fibrosis-driven atrial tissue damage cannot be solely explained by ageing, or underlying heart disease, or the AF burden itself, but AF is an element of the independent "arrhythmic manifestation" of the progressing fibrotic atrial cardiomyopathy (68). Histological examinations of atrial biopsy samples have proved that in severely remodelled atrial tissue and interstitial fibrosis are found both in persistent AF patients without concomitant diseases and in AF patients associated with underlying CV diseases. However, no interstitial fibrosis, minimal cardiomyocyte hypertrophy and myolitic damage was observed in controls (age-matched patients without known AF) (62, 69).

The nomenclature for atrial fibrosis also shows variability. Atrial fibrosis, atrial scar and atrial cardiomyopathy are often addressed as synonyms throughout the previously cited literature. Furthermore, depending on the imaging technology used to quantify fibrosis, it could be manifested as late gadolinium enhancement (LGE) or delayed enhancement (DE) by MRI, low voltage area by EAMS, and decreased atrial function, decreased compliance, or increased stiffness by echocardiography (70). All these conditions refer to the same remodelled, fibrotic atria.

In order to quantify atrial fibrosis, various methods have been developed to help the risk stratification of AF patients: cardiac imaging by DE-MRI, LA function by echocardiography, intracardiac electrogram analysis by electrophysiology procedure (EP) based on local conduction velocity, complex fractionated electrograms or voltage mapping (62). In the next chapter, I will present the role of DE-MRI and voltage mapping.

1.2.2. *QUANTIFICATION OF ATRIAL FIBROSIS*

1.2.2.1. MRI and atrial fibrosis

DE-MRI has become a well-validated technique for the diagnosis of LA fibrosis (70). During DE-MRI gadolinium contrast agent is administered, which accumulates for a longer time in the fibrotic tissue, causing delayed enhancement, and thereby the visualisation of the atrial fibrosis (71). It has been also validated by histological examinations based on surgical biopsy samples conducted by the research group of Marrouche (72). They presented the Utah classification in the DECAAF-study, where patients were divided into 4 stages regarding the percentage of fibrotic area of the total LA wall: stage 1 (< 10%); stage 2 (10%-20%); stage 3 (20%-30%); and stage 4 (≥ 30%). The degree of LA fibrosis has been independently associated with arrhythmia recurrence post-PVI ablation in other publications as well (72-75). The advantage of DE-MRI is the non-invasive approach and the automatic fibrotic area estimation. This method also strongly correlated with the low voltages on EAM and the decreased LA function assessed by echocardiographic speckle tracking (73, 76, 77).

However, the estimation of LA fibrosis by DE-MRI have not been widely used in routine clinical practice (70). Limitations of DE-MRI are the length of the procedure (about 45 minutes per patient), the financial burden and limited availability (78). Furthermore, the contraindication of contrast agent in severe renal dysfunction could cause a selection bias in the studies (78). Another downside of this method is the relatively poor spatial resolution in the thin LA wall, making it more difficult to perform good-quality images, leading to numerous exclusions due to tachyarrhythmia, irregular respiration, and high body mass index, generating also a potential selection bias (70, 72). Post-processing analysis is time-consuming (up to one hour per patient) and requires special training (79). Thus, the reproducibility of the results is difficult, causing several discussions on the overall validity of the method (70, 80-82).

1.2.2.2. Voltage mapping

Voltage mapping is an invasive method to assess the voltage of the myocardial surface with an EAMS during the EP procedure in order to detect low voltage area (LVA) associated with underlying fibrosis (62). The EAMS detect the location and orientation of the catheter's tip, as it moves real time in three dimensions around the endocardial tissue using magnetic field sensors and/or impedance ranging (83, 84). A mapping catheter can be a direct contact catheter collecting electrograms point-by-point, or a multi-electrode catheter. The mapping catheter collects multiple points simultaneously at each heart beat (QRS complex) with predefined beat acceptance criteria (e.g. cycle length stability and/or range, position/distance stability, QRS morphology/electrocardiogram stability, respiratory phase, speed of the catheter motion) (83, 85). The catheter's location and the simultaneously contact-based or noncontact-based collected local electrical data (electrogram, activation, timing, unipolar or bipolar voltage values) are stored by the EAMS (83, 84). Each point has location and electrical information associated with it. Bipolar endocardial voltage is calculated as a difference between two adjacent unipolar signals with the use of a differential amplifier or by post-processing (86). Afterwards, the EAMS do a surface reconstruction interpolating the collected data mostly between 3 points creating a color-coded voltage map. In general, LVAs are estimated based on the presence of ≥ 3 adjacent low-voltage points by rectified contact bipolar endocardial voltage measurement, that are < 3 mm apart from each other, and reported as a percentage area of the total mapped left atrium (85, 87-90). A high-density EAM (HD-EAM) presenting LVAs is shown in Figure 2.

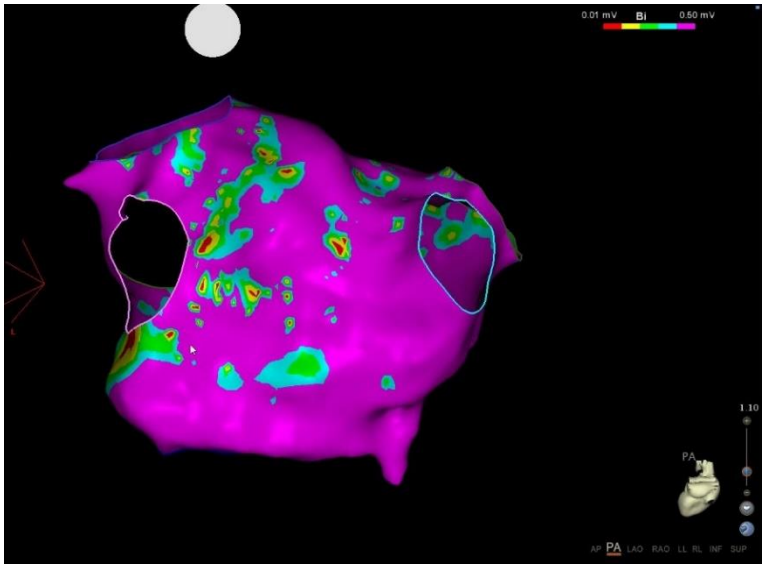

Figure 2. HD-electro-anatomical map (CARTO 3® platform with a CONFIDENSE™ module) displaying the low voltage areas of the left atrium (red, yellow, green and blue areas) and normal voltage areas (purple) – postero-anterior view (image of our working group).

The extent of LA low voltage area often is assessed by visual estimation only (87, 91), which has been shown to overestimate the amount of dense scar (< 0.2mV) and underestimate the extent of diseased atrial tissue (< 0.5mV) areas (92). However, with the reported novel EAM software it is possible to quantify the LVA burden exactly, automatically, online or offline, in a relatively short time (86, 92). The further advantage of LA fibrosis estimation with voltage mapping is its high resolution with a spatial resolution within millimetres.

The disadvantage of EAM is the invasive method of LA fibrosis assessment, which prolongs the EP procedures depending on the catheter used, challenging anatomy, cardiac rhythm, the number of points collected, software settings, and the experience of the investigator (86, 93, 94). In order to overcome these limitations, algorithms of EAMS are helping the investigator to improve good catheter contact (e.g. tissue proximity indication filter and respiratory gating in EAMS, contact force sensing catheters, catheter tip direction) and annotation of complex intracardiac signals (e.g. far field, spacing artefact, noise, catheter orientation), and to correctly interpret the EAM (e.g. setting thresholds, merging the created map with pre-ablation CT or MRI images) (83). Furthermore, there is a significant diversity in the cut-off values determining the burden of LA LVA, ranging from 0.1-1.5mV, with 0.5mV being most commonly used term (85, 92, 95). The above

presented, sometimes subjective and investigator-biased methods can raise concerns regarding the accuracy of LA voltage information. Regarding the definition of severity, the most simplistic approach of classification is based on the presence or absence of the LVAs, while others use four different stages (i.e. none, mild, moderate and severe), some adopt the burdens presented in the DECAAF-study detailed one chapter earlier (87, 89, 96-98). There is no consensus on the cut-offs for defining the groups of fibrosis severity, used in the prediction of CA outcomes (86-88, 96).

Although AF is known to cause biatrial fibrosis, the literature has focused on the LA. As a result, scarce evidence is available on the fibrosis of the right atrium (RA). Akutsu et al. reported that AF provides symmetrical structural and electric alterations in both atria, and the biatrial remodelling independently affects the outcome of AF ablation (99).

1.2.3. *LOW VOLTAGE AREA AS TARGET FOR ABLATION*

The indication to target non-PV areas during ablation is restricted to special individualized cases, as its clear benefit has been still an unresolved issue (18-22). Various techniques are used for voltage-guided substrate modification: box isolation of the fibrotic area (BIFA), scar homogenization, adding extra ablation lines on the posterior wall, or around the mitral isthmus (86).

There are multiple studies underlining the LVA-guided ablation strategy's positive effect on success rates. Rolf et al. presented the first case, where substrate modification was done right after PVI, in case of LVA < 0.5mV and inducible regular atrial tachycardia, resulting in a similar success rate compared to PVI-only group without LVA, and a better outcome compared to a historical PVI-only group with LVA (100). Kircher et al. reported a better outcome for patients undergoing LVA-targeted ablation (homogenization, linear lesion, or electrical isolation of LVA) vs PVI-only for paroxysmal and PVI plus box isolation (roof, posterior, and mitral isthmus line) for persistent AF (22). A review suggested a better outcome and a reduced occurrence of post-ablation atrial tachycardia for PVI plus LVA-targeted ablation compared to PVI plus conventional empirical wide ablation strategy. However, the definition of conventional empirical wide ablation was not well established (101). In the study of Yamaguchi et al., patients with LVA undergoing LVA-based substrate modification had fewer recurrence rates, than patients with LVA without additional ablation targets (102). Furthermore, Shreiber et al.

compared patients with no fibrotic atrial cardiomyopathy (FACM) (PVI-only ablation) to patients with and FACM stages I-IV (PVI with additional BIFA ablation strategy). According to their results, there was only a trend for better outcome in patients with no LVA. However, they also found that the extended total severe fibrosis area size (< 0.5mV) comes with an unfavourable impact on success rate (103).

1.3. THE PERI-ABLATION ROLE OF CARDIAC CT ANGIOGRAPHY

In 49%, pre-ablation cardiac CTA is used to tailor ablation, as a survey of the writing group members of HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of AF reported (5). Our EP Laboratory uses this imaging technique on a routine basis nearly for every AF patient, since among other findings, a variant left atrial anatomy may affect the ablation strategy. PV variants can be found in 29-62% leading to a high possibility of not being suitable for ablation with cryoballon or with multielectrode radiofrequency catheters (104, 105). Atrial dimensions and alterations, such as the left atrial appendage size, the orientation of right superior PV, the ostium area of left inferior PV, the abutting left atrial appendage and left superior vein, or the presence of posterior LA adipose tissue may also influence the success of PVI (105-109). On the other hand, Di Cori et al. reported, that pre-procedural cardiac CTA had no additional impact on success rates of ablation, but it increased statistically significant the cumulative radiological exposure (110), which is the main reason why pre-ablation cardiac CTA has still not been a mandatory workup before ablation (5). However, if cardiac CTA is well-timed, it can be also used for pre-ablation LA thrombus exclusion replacing the invasive TOE (5, 111).

Ling et al. reported for the first time that the image attenuation ratio derived from contrast-enhanced multidetector CT is associated with LA bipolar voltage. Based on their results, cardiac CT could be a useful alternative tool for LA fibrosis diagnosis (112).

An additional benefit of pre-ablation cardiac CTA could be the newly diagnosed incidental alterations, which would alter the patient's management and may also have a potential lifesaving effect (113). In a recent study of ours, 42% (820/1,952) of the patients had at least one incidental extracardiac finding, of which half of the cases were determined as clinically significant (114). The most common findings were pulmonary changes; lung nodules over 6 mm were detected in 3% (62/1,952) of the cases. Other

investigations reported 23-72% extracardiac findings and 16-33% clinically relevant cases (115-117).

If a more detailed analysis was performed during the pre-ablation cardiac CTA, the coronary artery status could be also revealed (coronary CTA). According to several publications, at least 10%, or in some cases even 70% of patients with AF had newly diagnosed coronary artery disease (CAD) (Figure 3.) (118-121). Since symptoms suggesting ischemic heart disease, such as chest pain could be observed in AF patients without CAD also, predicting CAD in AF patients is often challenging (122). An incidental obstructive CAD (≥ 50% luminal stenosis) or an advanced coronary artery calcium (CAC) require preventive treatment to decrease potential ischaemic events. It may also cause the reclassification of the most commonly used thrombotic risk stratification, the CHA_2DS_2-VASc score, which could alter the anticoagulant strategy of AF patients (120, 123). A subclinical CAD may affect the success of AF ablation (124), however, some publications reported no significant impact (125, 126).

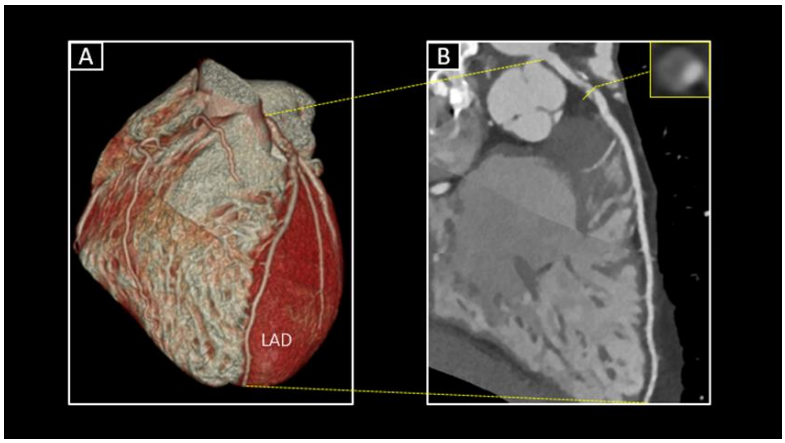

Figure 3. Obstructive coronary artery disease – significant stenosis on LAD (left anterior descending artery) diagnosed by coronary CTA (Image of our working group)

The complication rate of CA is approximately between 4-14%, of which 2-3% are potentially life-threatening (1, 127). CTA can also be a good tool to diagnose concealed complications, such as atrio-oesophageal fistula and pulmonary vein stenosis. It is also used to reveal post-ablation stroke, or could be a supplemental element to ultrasound for any vascular complications (1).

2. OBJECTIVES

2.1. ATRIAL LOW VOLTAGE AREA

We aimed to assess the LA LVA on HD-EAM by a novel software package which allows its automated quantification in our prospectively involved consecutive patients undergoing their first PVI for AF. We developed a graded classification system of the left atrial LVA using two different cut-offs: ≤ 0.2mV (equals Dense Left Atrial Scar), and ≤ 0.5mV (equals Diseased Left Atrial Tissue). We studied pre-procedural variables to set up risk factors for atrial fibrosis (128).

Our goal was also to assess the relationship between RA and LA LVA using HD-EAM in patients with AF. We used the previously determined LVA burden (Diseased Atrial Tissue) in both atria and we tried to identify the predisposing factors for higher RA Diseased Tissue burden (129).

Next we intended to analyse the predictive value of the Dublin Classification (Diseased LA Tissue burden) of recurrent AF in patients undergoing their first PVI (130).

2.2. CORONARY ARTERY DISEASE

We aimed was to assess the incidence of obstructive CAD by pre-ablation coronary CTA in consecutive patients with AF ablation. Our goal was also to study the relationship between traditional CV risk factors, the presence of chest pain and newly diagnosed obstructive CAD (Herczeg et al., 2022, under review).

3. METHODS

3.1. QUANTIFICATION AND RISK FACTORS OF ATRIAL LOW VOLTAGE AREA AND ITS RELATIONSHIP WITH THE SUCCESS RATE OF AF ABLATION

3.1.1. *STUDY POPULATION*

In our observational, prospective, single-centre study one hundred consecutive patients with either paroxysmal or persistent AF were included who underwent PVI in 2017 in the Mater Private Hospital, Dublin, Ireland. Exclusion criteria were: AF or atrial tachycardia during HD-EAM, and previous LA ablation (128). In a subset of the patient population, biatrial HD-EAM was obtained before PVI, which served as a basis for our second observational study, where we described the role of the RA. Patients with prior RA ablation or with persistent RA arrhythmia during mapping were excluded (129). In the follow-up study we extended our study population and included the follow-up data to analyse the factors associated with the recurrence of AF. Patients were excluded from the data analysis who received any additional non-PVI LA site ablation (130).

All the patients gave their prior written informed consent. The study protocols were reviewed and approved by the Clinical Research Ethics Committee of the Mater Misericordiae University Hospital and were in accordance with the declarations of Helsinki.

3.1.2. *ABLATION AND HD ELECTRO-ANATOMICAL MAPPING*

The procedures were performed under general anaesthesia in line with the up-to-date routine clinical AF ablation protocols (5). Briefly, a circular multipolar catheter with 20 electrodes (Lasso, Biosense Webster Inc., Irvine, California, USA; adjustable 15- to 25-mm circumference; 1–2mm inter-electrode spacing) was guided transseptal to the LA. Afterwards, an HD-EAM was performed in sinus rhythm (or in case of bradycardia with 600-ms cycle length coronary sinus pacing) by using the CARTO 3® platform with a CONFIDENSE™ module (Biosense Webster Inc., Irvine, California, USA) with filters enabled to ensure a good contact and catheter stability. Mapping was guided by electrogram characteristics, CARTO 3® imaging, tissue proximity indication filter, and fluoroscopy to map the whole atrium excluding noise and pacing spike artefacts. In case of anatomical challenges, the ablation catheter (ThermoCool SmartTouch™ 8Fr, Biosense Webster Inc., Irvine, California, USA) was also used for mapping to add more

details. The number of points created, the time of mapping and the volume of mapped LA were also recorded. After merging the created EAM with the pre-procedural cardiac CTA images, PVI with bilateral wide antral circumferential ablation method was performed with the ablation catheter. If typical atrial flutter was documented beforehand, an additional cavotricuspid isthmus line ablation was performed at the discretion of the investigator. LVAs were not a target during ablation. Moreover, if an additional LA non-PV site was ablated, those patients were excluded from the follow-up study, to maintain a homogenous group for data analysis (128).

In the study examining biatrial LVAs, the ablation method remained the same. However, the mapping strategy was extended to include the RA as well. Firstly, LA mapping and PVI were performed and then the circular multipolar mapping catheter was pulled back to the RA to acquire an HD-EAM (129).

3.1.3. *VOLTAGE MAP OFFLINE ANALYSIS*

In every case the LA appendage, the PVs, and the mitral annulus were manually excluded from the voltage map. Analyses of the HD-EAMs were made offline with a novel, automatic voltage histogram analysis (VHA) tool of the CARTO 3® platform. This tool uses the triangulated mesh of the created HD-EAM. It averages the voltages of the three closest points, to calculate the voltage of the created small triangular area. After setting the voltage ranges to ≤ 0.2 mV and ≤ 0.5 mV (as they are the most often used cut-off values), we calculated the percentage surface area of LA LVAs falling within the pre-set ranges. Areas with voltage ≤ 0.2 mV were defined as “Dense LA Scar”, while areas with voltage ≤ 0.5 mV as “Diseased LA Tissue”. Next, quartiles were calculated to categorize patients by the extent (percentage) of Dense LA Scar (≤ 0.2 mV) and Diseased LA Tissue (≤ 0.5 mV) as well. The lowest percentage surface area quartile was categorized as “Class I”, while the highest percentage surface area quartile was categorized as “Class IV” (128). In our third study we named the classification by Diseased LA Tissue, as “Dublin Classification”, using the same burden as set in our first study, thus, inventing a novel classification for LVAs (130).

During the offline RA voltage map analysis, inferior and superior vena cava and the tricuspid annulus were excluded from the RA map. In our second study, the quartiles for Diseased LA Tissue (≤ 0.5 mV) and RA Tissue (≤ 0.5 mV) were created for each atrium:

Q1 as the lowest quartile, while Q4 as the highest quartile of Diseased LA/RA Tissue (129).

3.1.4. *MEASUREMENT OF ATRIAL DIMENSIONS*

Atrial volumes were determined by the CARTO 3® platform, based on the created fast anatomical maps during ablation.

In our second and third studies we extended the data of atrial dimensions with the measurements based on pre-ablation cardiac CTA. On cardiac CTA images the shortest longitudinal atrial diameter (L), atrial area on two- (A1) and four-chamber (A2) views were measured in end-systole using Carestream version 11 Software (Phillips Healthcare, Amsterdam, The Netherlands). LA volume and RA volume (LAV/RAV ml) were calculated afterwards, based on the area-length method equation ($8/3\pi$ x[(A1) x (A2)/L]) (131-133). Indexed LAV (LAVI) and indexed RAV (RAVI) (ml/m^2) were also reported as indexed to body surface area (BSA) (129).

3.1.5. *FOLLOW-UP*

Follow-up data were collected for our third publication. Patients with no complications were discharged a day after the procedure. All patients were given a proton pump inhibitor medication for 6 weeks and continued anticoagulation therapy for at least 6 weeks. Patients were scheduled for follow-up visits at 6 weeks, and 3, 6, and 12 months after the ablation. In case of any symptoms, an unscheduled visit was organised, otherwise, after 12 months, an annual visit was recommended. At every visit a 12 lead ECG and 24 hour Holter-ECG were obtained. Recurrence was defined as a documented episode of AF, LA tachycardia or LA flutter lasting for more than 30 seconds. Ablation was regarded as successful, if no recurrence has happened after the three months long blanking period.

AAD therapy was terminated after 3 months. At the discretion of the investigator, in some cases, regular AAD was continued, restarted or used as a *pill in the pocket* therapy. Therefore, two separate success-analyses defining different primary endpoints (success definitions) were presented on the same studied population. Firstly, in patients without AADs (*OFF AAD*), the documented recurrence or AAD administration after the blanking period (even without any documented arrhythmia) were the primary endpoints. The second analysis (*ON AAD*) determined the primary endpoint only in case of documented recurrence irrespective of AAD usage.

3.2. OBSTRUCTIVE CORONARY ARTERY DISEASE IN PATIENTS WITH AF

3.2.1. *STUDY POPULATION*

This was a retrospective, observational study. Inclusion criteria were: patients with a history of AF and ≥ 18 years old in whom coronary CTA was performed before AF ablation between 2013 and 2020 at the Heart and Vascular Centre of Semmelweis University, Budapest, Hungary. We excluded patients if a previous CAD was known (history of acute myocardial infarction and coronary revascularization, known CAD treated conservatively), or the coronary CTA image was non-diagnostic to assess the coronary artery luminal stenosis. If multiple coronary CTA examinations were performed for one patient, the first good-quality image was included in the study. Demographics, medical history, and symptoms were collected pre-procedurally from questionnaires and medical documentation. Two groups were identified based on whether the patients had reported any type of chest pain or had no chest pain. Afterwards, we analysed the relationship between the collected data and novel obstructive CAD diagnosed by coronary CTA.

All the patients gave their prior written informed consent. The study protocol was reviewed and approved by the Local Research Ethics Committee of the Semmelweis University (SE RKEB: 142/2019) and was in accordance with the Declarations of Helsinki.

3.2.2. *CORONARY CT ANGIOGRAPHY AND IMAGE ANALYSIS*

Coronary CTA examinations were performed on a 256-slice scanner (Brilliance iCT 256, Philips Healthcare, Best, The Netherlands) with a prospective ECG-triggered axial acquisition mode. Metoprolol was administered for heart rate control if needed. In case of a heart rate < 80/min, mid-diastolic triggering was applied with 3-5% padding (73-83% of the R-R interval), if the heart rate was ≥80/min, systolic triggering was chosen (35-45% of the R-R interval). CAC was also measured. Non-contrast datasets were remodelled with a slice thickness and increment of 2.5 mm, while coronary CTA datasets were remodelled with 0.8 mm slice thickness and increment of 0.4 mm.

Cardiologist experts and radiologist experts evaluated the cardiac CTA images. Coronary artery status was analysed with a semi-automated software (HeartBeat-CS, Philips IntelliSpace Portal, Philips Healthcare, Best, The Netherlands). Coronary artery stenosis

was classified into seven groups according to the percentage of the measured most severe luminal stenosis: normal (absence of stenosis), minimal (1-25% stenosis), mild (25-49% stenosis), moderate (50-69% stenosis), severe (70-99% stenosis), and occluded (100% stenosis). We defined obstructive CAD as a lesion with ≥50% luminal stenosis (134). Additionally, the total CAC score (CACS) was presented as well.

3.3. STATISTICAL ANALYSIS

Categorical variables are reported as numbers and percentages and analysed with the Fisher's exact test, the Chi-square test, and/or the Chi-square test for trend, as appropriate. Continuous variables showed a non-Gaussian distribution by using the Shapiro-Wilk normality test, thus, they were presented as median with interquartile ranges. At some parts, continuous data were split into two groups by using the median value (e.g. LAV, LAVI, RAVI), or by clinically used burdens (e.g. age, body mass index (BMI), BSA, CHA_2DS_2-VASc score, left ventricular ejection fraction (LVEF)), afterwards calculations for categorical data were performed. Otherwise, non-parametric variables were compared by the Mann-Whitney U-test.

Correlation between continuous parameters was analysed by the Spearman's correlation. For multiple comparisons, the Kruskal-Wallis test was used. The success rate of ablation was analysed by the Kaplan-Meier survival test, and compared by the log-rank test. To define the predictors of recurrence, we used the univariate Cox regression analysis. Uni- and multivariate analyses were performed by binary logistic regression using the entry method to study the association between Diseased LA Tissue Classes, obstructive CAD, traditional CV risk factors, and chest pain.

Statistical analysis was conducted with Prism (Version 6.01, GraphPad Software Inc., La Jolla, California, USA), and IBM SPSS Statistics (Version 25, IBM Corp., Armonk, New York, USA) software. A two-tailed $p<0.05$ was considered statistically significant in every case.

4. RESULTS

4.1. QUANTIFICATION AND RISK FACTORS OF ATRIAL LOW VOLTAGE AREA AND ITS RELATIONSHIP WITH THE SUCCESS RATE OF AF ABLATION

4.1.1. *QUANTITATIVE ASSESSMENT OF LEFT ATRIAL LOW VOLTAGE AREA*

4.1.1.1. Patient demographics and distribution of left atrial low voltage area

One hundred patients were involved in our study, 27/100 (27%) were female, the median age was 64 [56-72] years. Persistent AF was present in 39/100 (39%) of the cases. Hypertension being the most common comorbidity was reported in 43/100 (43%) of the population. There were 45/100 (45%) patients scoring ≥2 CHA_2DS_2-VASc points. Median LAV was 144 [123-175] ml. A median of 1,049 [690-1,405] points were taken per voltage map in a median of 10 [8-15] minutes. A detailed description is shown in Table 1.

Table 1. Baseline patient characteristics (128).

Baseline and procedural characteristics (n=100)		
Female sex	27	(27%)
Age (years)	64	[56-72]
Persistent AF	39	(39%)
CHA_2DS_2-VASc score ≥2	45	(45%)
Congestive Heart Failure	9	(9%)
Hypertension	43	(43%)
Diabetes	1	(1%)
Prior Stroke or TIA	5	(5%)
Vascular Disease	16	(16%)
Coronary Artery Disease	9	(9%)
Underlying Heart Disease	16	(16%)
Prior CTI Ablation	8	(8%)
Left Atrial Volume (ml)	144	[123-175]
Number of Mapped Points	1049	[690-1,405]
Time spent creating HD-EAM (min)	10	[8-15]
Dense LA Scar (%)	3.5	[0.8-7.8]
Diseased LA Tissue (%)	17.8	[8.9-30.5]

(AF = atrial fibrillation, TIA = transient ischemic attack, CTI = cavotricuspid isthmus, HD-EAM = high-density electro-anatomical map, LA = left atrium)

We created quartiles for Dense LA Scar (≤ 0.2mV) and Diseased LA Tissue (≤ 0.5mV), as shown in Table 2. Figure 4. presents examples of HD-EAM from each class of Diseased LA Tissue.

Table 2. Thresholds for quartiles I-IV for classification of Dense Left Atrial (LA) Scar and Diseased LA Tissue. (128)

Classification by the extent of Dense LA Scar (≤ 0.2mV)		Classification by the extent of Diseased LA Tissue (≤ 0.5mV) (later named Dublin Classification)	
Class I	< 1%	Class I	< 9%
Class II	1-3%	Class II	9-18%
Class III	3.1-8%	Class III	18.1-31%
Class IV	> 8%	Class IV	> 31%

(LA = left atrium)

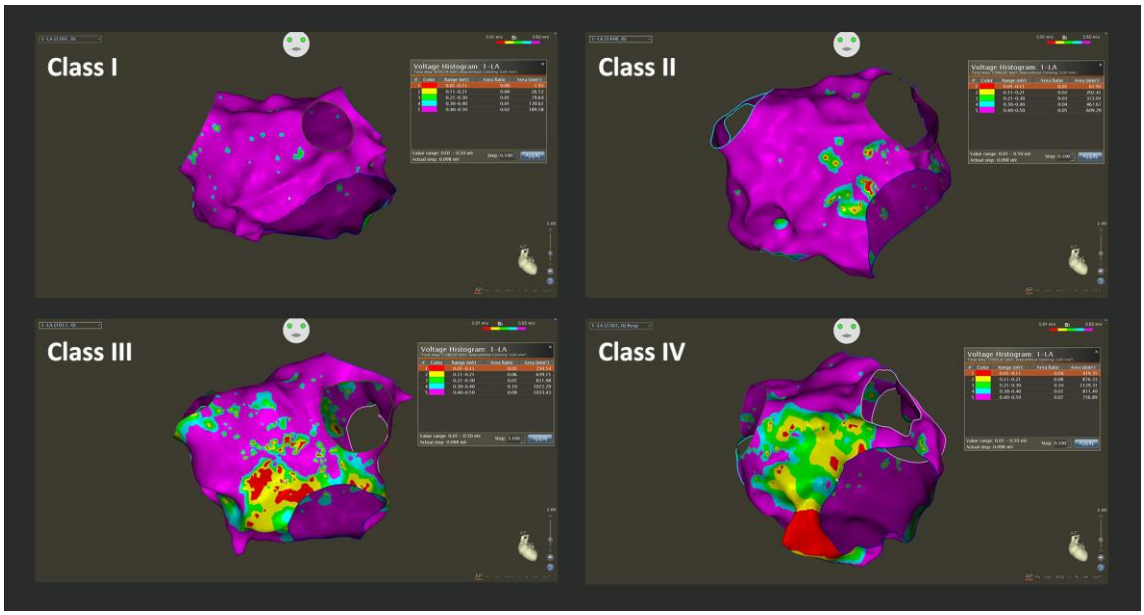

Figure 4. Anteroposterior view and Voltage Histogram Analysis of left atrial voltage maps: Class I-IV of Diseased Left Atrial Tissue burden (128).

4.1.1.2. Relationship of Diseased LA Tissue burden and patient characteristics

Trend analysis showed that the prevalence rate of female sex (p=0.003), age ≥65 years (p<0.0001), persistent AF (p=0.004), and CHA_2DS_2-VASc score ≥2 (p<0.0001) increased with every increment in Diseased LA Tissue from Class I to IV (Figure 5.)

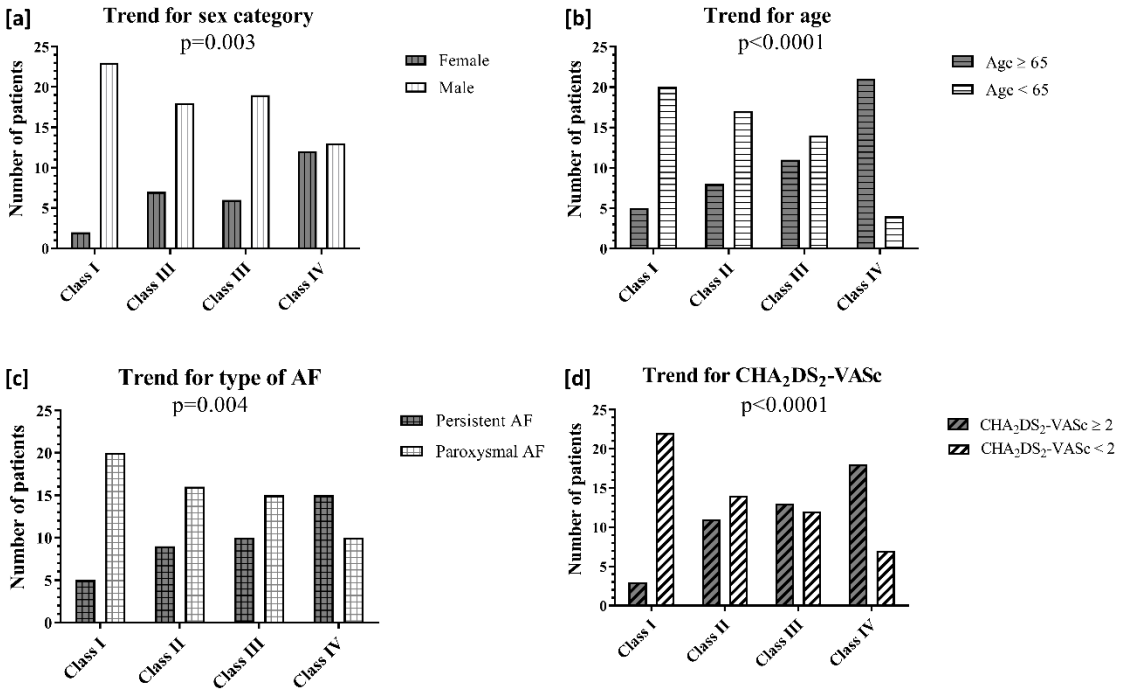

Figure 5. Relationship between Diseased LA Tissue Classes and [a] sex category, [b] age, [c] type of AF and [d] CHA_2DS_2-VASc score (Chi-square test for trend) (128).

Similar results were reported with the Mann-Whitney U-test, where a significantly higher median Diseased LA Tissue burden was found in patients who were female (28% vs 16%, p=0.001), ≥65 years old (30% vs 13%, p<0.0001), had persistent AF (24% vs 14%, p=0.002), and those with a CHA_2DS_2-VASc ≥2 (26% vs 13%, p<0.0001) (Table 3.).

Table 3. Relationship between baseline characteristics and median percentage of Diseased LA Tissue burden assessed by the Mann-Whitney U-test (128).

	Parameter present		Parameter absent		p
	Number of patients	Diseased LA Tissue burden median %	Number of patients	Diseased LA Tissue burden median %	
Female sex	27	29	73	16	0.001
Age ≥ 65 years	45	30	55	13	< 0.0001
Persistent AF	39	24	61	14	0.002
CHA_2DS_2-VASc ≥ 2	45	26	55	13	< 0.0001
Congestive Heart Failure	9	28	91	17	0.42
Hypertension	43	21	57	15	0.11
Diabetes	1	14	99	18	N/A
Previous TIA / Stroke	5	26	95	17	0.20
Vascular Disease	16	20	84	18	0.67
Coronary Artery Disease	9	23	91	18	0.52
Underlying Heart Disease	16	21	84	17	0.81
Prior CTI ablation	8	32	92	17	0.21
LAV ≥ 144ml	50	19	50	16	0.53

(AF = atrial fibrillation, TIA = transient ischemic attack, CTI = cavotricuspid isthmus, LA = left atrium, LAV = left atrial volume)

Furthermore, Diseased LA Tissue Classes I-III and Diseased LA Tissue Class IV were compared (Table 4). Patients with Diseased LA Tissue Class IV were more likely observed among patients ≥ 65 years old (OR=11.16, CI 95%: 3.45-36.11, p<0.0001), female (OR=3.69, CI 95%: 1.40-9.72, p=0.009), ones with persistent AF (OR=3.19, CI 95%: 1.12-8.13, p=0.01), and among patients having CHA_2DS_2-VASc score ≥ 2 (OR=4.57, CI 95%: 1.69-12.33, p=0.002) compared to Diseased LA Tissue Classes I-III. Multivariate analysis proved that only age ≥ 65 years (OR=4.70, CI 95%: 1.50-14.71, p=0.008) and persistent AF (OR=10.50, CI 95%: 2.93-37.63, p<0.0001) were independent risk factors for the Diseased LA Tissue Class IV.

Table 4. Comparison of Diseased LA Tissue Class IV vs Diseased LA Tissue Classes I-III regarding baseline characteristics by Fisher's exact test (128).

	Class IV (n=25)	Class I-III (n=75)	p	OR	CI 95% of OR
Female sex	12	15	0.009	3.69	1.40-9.72
Age ≥ 65 years	21	24	<0.0001	11.16	3.45-36.11
Persistent AF	15	24	0.01	3.19	1.25-8.13
CHA_2DS_2-VASc ≥ 2	18	27	0.002	4.57	1.69-12.33
Congestive Heart Failure	2	7	1.00	0.84	0.16-4.36
Hypertension	12	31	0.64	0.76	0.31-1.99
Diabetes	0	1	N/A	N/A	N/A
Prior Stroke / TIA	2	3	0.59	0.48	0.08-3.05
Vascular Disease	3	13	0.75	1.54	0.40-5.91
Coronary Artery Disease	1	8	0.44	2.87	0.34-24.13
Underlying Heart Disease	2	14	0.34	2.64	0.56-12.53
Prior CTI ablation	4	4	0.10	0.30	0.07-1.29
LAV ≥ 144ml	16	34	0.16	2.12	0.77-6.20

(AF = atrial fibrillation, TIA = transient ischemic attack, CTI = cavotricuspid isthmus, LA = left atrium, LAV = left atrial volume)

4.1.2. *Right Atrial Diseased Tissue burden in the prediction of Left Atrial Diseased Tissue burden*

4.1.2.1. Patient and procedure characteristics

A total of 36 patients were included in this study with a median age of 69 [58-75] years, who were mainly male (27/36, (75%)), and had persistent AF in 21/36 (58%) of the cases (Table 5). The studied population had a CHA_2DS_2-VASc score of two or higher in 23/36 (64%), hypertension in 15/36 (42%) and coronary artery disease in 8/36 (22%). Nine patients had structural heart disease (7 with ischemic heart disease, 1 with non-ischemic dilated cardiomyopathy and 1 with prior aortic valve replacement and coronary bypass graft surgery). The median of the LVEF was within the normal range (56% [52-61%]). Left atrial and right atrial indexed volumes were mildly elevated based on the CTA images (59 [50-78] ml/m^2, and 53 [37-66] ml/m^2, respectively).

During the procedure, nearly one thousand homogenous points (987 [680-1,165] LA; 897 [658-1,153] RA]) were collected for LA and RA in 8 [6-9] and 7 [6-8] minutes of procedure times, respectively (Table 5). The median Diseased Tissue burden (≤ 0.5 mV) assessed by the VHA tool was 19% [13-53%] for LA and 24% [14-34%] for RA.

Table 5. Baseline patient characteristics (129).

Baseline characteristics (n=36)		
Female sex	9	(25%)
Median age (years)	69	[58-75]
BMI (kg/m^2)	27	[26-29]
BSA (m^2)	2.0	[1.8-2.1]
Persistent AF	21	(58%)
CHA_2DS_2-VASc ≥2	23	(64%)
LVEF (%)	56	[52-61]
Hypertension	15	(42%)
Diabetes	4	(11%)
Prior Stroke / TIA	3	(8%)
Vascular Disease	5	(14%)
Coronary Artery Disease	8	(22%)
Structural Heart Disease	9	(25%)
LAVI $_{(CTA)}$ (ml/m^2)	59	[50-78]
RAVI $_{(CTA)}$ (ml/m^2)	53	[37-66]
Number of LA points	987	[680-1,165]
Number of RA points	897	[658-1,153]
LA mapping time (min)	8	[6-9]
RA mapping time (min)	7	[6-8]
Diseased LA Tissue (%)	19	[13-53]
Diseased RA Tissue (%)	24	[14-34]
LAVI $_{(HD-EAM)}$ (ml/m^2)	78	[60-84]
RAVI $_{(HD-EAM)}$ (ml/m^2)	87	[71-100]

(BMI = body mass index, BSA = body surface area, AF = atrial fibrillation, LVEF = left ventricular ejection fraction, TIA = transient ischemic attack, LAVI/RAVI = left/right atrial volume index, CTA = CT-angiogram, HD-EAM = high-density electro-anatomical map)

4.1.2.2. Relationship of Diseased RA Tissue and baseline characteristics

We determined the relationship between the baseline characteristics and the percentage of diseased RA tissue burden. Patients with a CHA_2DS_2-VASc score ≥ 2 (p=0.03), larger LAVI measured on CTA (p=0.02) and on 3D EAM (p=0.006), larger RAVI measured on 3D EAM (p=0.002) had significantly higher RA Diseased Tissue burden (Table 6.).

Table 6. Relationship between baseline characteristics and percentage of Diseased RA Tissue burden calculated by Mann-Whitney U Test (4).

	Parameter present		Parameter absent		
	Number of patients	Diseased RA Tissue burden median %	Number of patients	Diseased RA Tissue burden median %	p
Female sex	9	30	27	21	0.17
Age ≥ 65 years	20	30	16	20	0.12
BMI ≥ 30 kg/m^2	6	27	30	23	0.78
BSA ≥ 2 m^2	16	22	20	24	0.70
Persistent AF	21	28	15	19	0.07
CHA_2DS_2-VASc ≥ 2	23	30	13	15	0.03
LVEF < 50%	4	26	32	24	0.98
Hypertension	15	21	21	28	0.96
Diabetes	4	27	32	21	0.29
Previous stroke / TIA	3	24	33	24	0.74
Vascular Disease	5	30	31	21	0.34
Coronary Artery Disease	8	27	28	23	0.53
LAVI $_{(CTA)}$ ≥ 59 ml/m^2	17	30	18	15	0.02
RAVI $_{(CTA)}$ ≥ 53 ml/m^2	17	30	18	20	0.10
LAVI $_{(HD\text{-}EAM)}$ ≥ 78 ml/m^2	18	31	18	16	0.006
RAVI $_{(HD\text{-}EAM)}$ ≥ 87 ml/m^2	18	31	18	15	0.002
LA-Q4	9	38	27	19	0.0007

(BMI = body mass index, BSA = body surface area, AF = atrial fibrillation, LVEF = left ventricular ejection fraction, TIA = transient ischemic attack, LA/RA = left/right atrium, LAVI/RAVI = left/right atrial volume index, CTA = CT-angiography, HD-EAM = high-density electro-anatomical map)

4.1.2.3. Correlation between Diseased RA and LA Tissue

We examined the correlation of LA and RA low voltage area percentages, and found a statistically significant correlation (≤0.1mV: $p<0.0001$, $R=0.5760$; ≤0.2mV: $p<0.0001$, $R=0.6250$; ≤0.3mV: $p<0.0001$, $R=0.6120$; ≤0.4mV: $p<0.0001$, $R=0.6660$; ≤0.5mV: $p<0.0001$, $R=0.6461$, Spearman's correlation).

We also determined the relationship of the extent of Diseased RA Tissue and Diseased LA Tissue. Patients with higher Diseased LA Tissue quartiles had higher percentage of Diseased RA Tissue ($p=0.003$), while patients with higher Diseased RA Tissue quartiles had a higher percentage of Diseased LA Tissue area percentage ($p=0.001$) according to Kruskal-Wallis test, as presented in Figure 6. Also, patients in RA-Q4 more frequently belonged to LA-Q4 (OR=7.1, CI 95%: 1.3-38.9, $p=0.01$, Chi-square test).

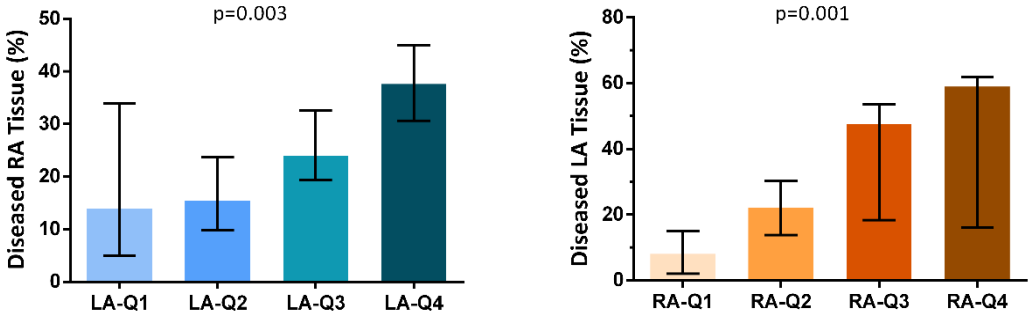

Figure 6. Comparison of Diseased Left Atrial (LA) and Right Atrial (RA) Tissue burden (Kruskal-Wallis test, error bars – median with interquartile ranges; Q – quartiles) (129)

4.1.3. *PREDICTIVE VALUE OF LEFT ATRIAL LOW VOLTAGE AREA FOR THE OUTCOME OF ABLATION*

4.1.3.1. Patient and procedure characteristics

In our third study, 109 dominantly male (83/109 (76%)) patients were included with a median age of 62 [55-70] years (Table 6.). Almost one third (34/109 (31%)) of the patients had persistent AF. Hypertension (39/109, 36%), vascular disease (16/109, 15%) and underlying heart disease (16/109, 15%) were the most frequent comorbidities. Seven per cent (8/109) of the patients had LVEF < 50%.

Table 6. Baseline and procedural characteristics (130).

Parameters (n=109)		
Female sex	26	(24%)
Median age (years)	62	[55-70]
Median BMI (kg/m^2)	28	[26-31]
Persistent AF	34	(31%)
CHA_2DS_2-VASc score ≥ 2	41	(38%)
LVEF < 50%	8	(7%)
Hypertension	39	(36%)
Diabetes	0	(0%)
Prior stroke / TIA	5	(5%)
Vascular Disease	16	(15%)
Coronary Artery Disease	10	(9%)
Underlying Heart Disease	16	(15%)
Prior CTI ablation	8	(7%)
Median LAV (CTA) (ml)	142	[124-169]
Median No. of Mapped LA points	958	[658-1,257]
Mapping time (min)	10	[8-14]
Dense LA Scar (≤ 0.2mV) (%)	2.49	[0.54-7.17]
Diseased LA Tissue (≤ 0.5mV) (%)	15.85	[6.94-28.41]

(AF – atrial fibrillation, BMI – body mass index, CTA – CT angiography, CTI – cavotricuspid isthmus, LA(V) – left atrium (volume), LVEF – left ventricular ejection fraction, TIA – transient ischaemic attack)

During the procedure, median 958 [658-1,257] points were collected while mapping the LA in the median of 10 [8-14] minutes. All patients were classified: (1) by the extent of Dense LA Scar (≤ 0.2mV) and (2) by the extent of Diseased LA Tissue (≤ 0.5mV) defined as Dublin Classes I-IV (Table 7.), based on the classification range set in our previous publication (Table 2.) (128).

Table 7. Distribution of the study population in the Dense LA Scar and Dublin Classes (130).

Classification by the extent of Dense LA Scar (≤ 0.2mV)		No. patients (n=109)	Classification by the extent of Diseased LA Tissue (≤ 0.5mV) (Dublin Classification)		No. patients (n=109)
Class I	< 1%	36 (33%)	Dublin Class I	< 9%	36 (33%)
Class II	1-3%	21 (19%)	Dublin Class II	9-18%	25 (29%)
Class III	3.1-8%	29 (27%)	Dublin Class III	18.1-31%	27 (25%)
Class IV	> 8%	23 (21%)	Dublin Class IV	> 31%	21 (19%)

(LA – left atrium)

The acute success of the PVI, demonstrated by the entrance block to the veins, was achieved in all cases. Five (5/109, 5%) major complications were recorded (3 pericardial effusion requiring pericardial drainage, 1 severe pericarditis, and 1 right phrenic nerve palsy) all being un-related to the mapping process and the VHA, and resolved without sequel.

4.1.3.2. Follow-up results and overall success rates

The median duration of the follow-up period was 632 [469-760] days. 30/109 (28%) patients had palpitations during the blanking period with or without ECG documentation. After the blanking period 23/109 (21%) patients had taken AADs. We detected 33/109 (30%) recurrences with ON AAD analysis, and 35/109 (32%) with OFF AAD analysis. Out of the 25/75 (33%) patients with paroxysmal AF who had a recurrence, 18/25 (72%) patients continued to have paroxysmal AF and 5/25 (20%) progressed to a persistent stage. Two out of twenty-five (8%) patients experienced no recurrence, however they stayed on AADs up to 4 months after PVI, thus, had reached the set endpoint of the OFF AAD analysis. Out of the 10/34 (29%) patients who had persistent AF before ablation and experienced a recurrence, 8/10 (80%) developed persistent AF and in 2/10 cases (20%) we observed an improvement to a paroxysmal type of AF post-ablation. Altogether 12/109 (11%) patients underwent electrical cardioversion and 24/109 (22%) patients

underwent repeated ablation. The overall success rate was 78% and 67% ON AAD, and 74% and 67% OFF AAD at 1- and 2-years follow-up, respectively (Figure 7.).

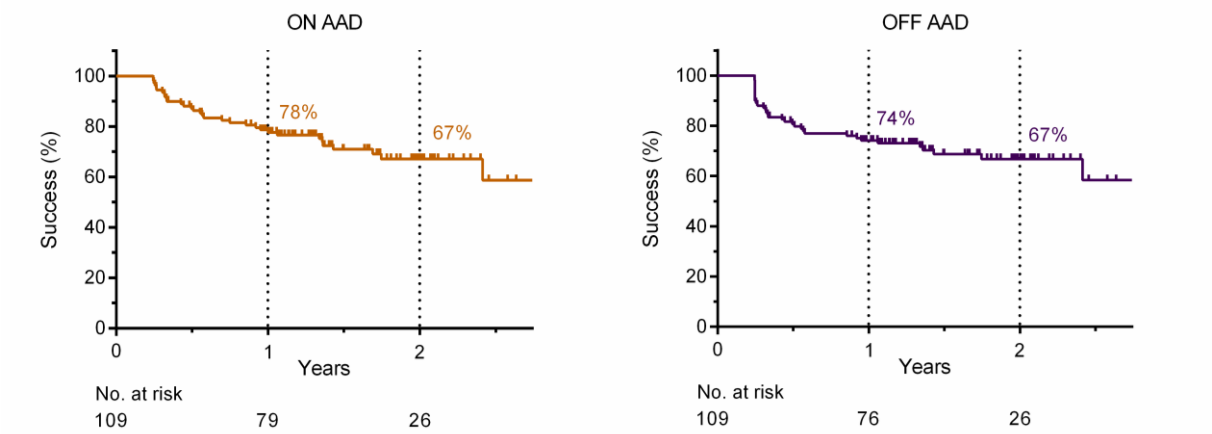

Figure 7. The overall success of first pulmonary vein isolation for atrial fibrillation, ON AAD (left) and OFF AAD (right) analysis, Kaplan-Meier curve (130).

Firstly, the success rates of CA in the different Dense LA Scar Classes (I-IV) were compared, but no statistically significant difference was found (p=0.20 ON AAD; p=0.38 OFF AAD; log-rank test). However, the separation of the survival curves showed a tendency to lower success rates in Class IV. Therefore, Classes I-III were grouped together and compared with Class IV. Although, there was a tendency, we did not find a significant difference in the success rates between Dense LA Scar Classes I-III vs Class IV patients (p=0.07 ON AAD; p=0.12 OFF AAD; log-rank test, Figure 8.).

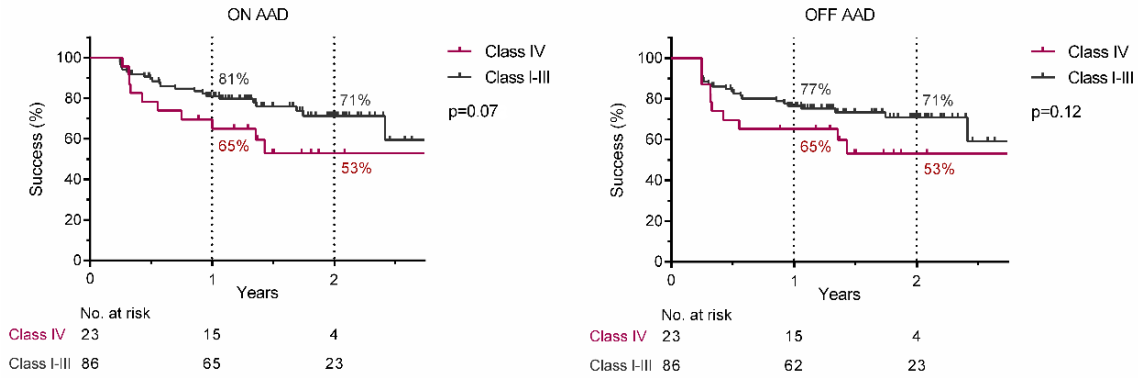

Figure 8. Success rates of patients with Class IV vs Classes I-III Dense LA Scar, ON AAD (left) and OFF AAD (right) analysis, log-rank test (130).

In the Diseased LA Tissue burden analysis, there was a statistically significant separation of the four survival curves; and the Dublin Class IV showed the lowest success rate (p=0.01 ON AAD; p=0.03 OFF AAD; log-rank test). Similarly, Dublin Classes I-III were grouped together and compared with Dublin Class IV. Patients with Dublin Class IV had a significantly lower success rate, than patients with Dublin Class I-III, irrespective of AAD use (p=0.004, ON AAD; p=0.008, OFF AAD; log-rank test; Figure 9.).

Figure 9. Success rates of patients with Dublin Class IV vs Dublin Classes I-III, ON AAD (left) and OFF AAD (right) analysis, log-rank test (130).

4.1.3.3. Predictors of recurrence

Next, we determined the predictors of recurrence with both ON AAD and OFF AAD analyses (Table 8.). Among the various clinical and procedural parameters, only two significant predictors were found with univariate Cox-regression analysis: the presence of arrhythmia in the blanking period (OR=3.14, CI 95%: 1.55-6.36, p=0.001 for ON AAD; OR=3.28, CI 95%: 1.65-6.52, p=0.001 for OFF AAD) and Dublin Class IV (OR=2.51, CI 95%: 1.22-5.14, p=0.01 for ON AAD; OR=2.27, CI 95%: 1.12-4.61, p=0.02 for OFF AAD, Table 8.).

Table 8. Univariate Cox-regression test for predictors of recurrence (separate ON AAD and OFF AAD analyses) (130).

Parameters	n (%)	ON AAD Analysis			OFF AAD Analysis		
		p	OR	CI (95%)	p	OR	CI (95%)
Female sex	26 (24%)	0.87	0.94	0.43-2.03	0.96	1.01	0.47-2.17
BMI > 30 kg/m^2	25 (23%)	0.73	1.15	0.51-2.55	0.35	1.41	0.67-2.98
Age ≥ 65 years	41 (38%)	0.28	1.45	0.73-2.90	0.47	1.27	0.65-2.50
Persistent AF	34 (31%)	0.90	0.95	0.45-2.01	0.62	0.83	0.39-1.74
CHA_2DS_2-VASc ≥2	41 (38%)	0.32	1.40	0.70-2.80	0.53	1.23	0.63-2.41
LVEF < 50%	8 (7%)	0.12	2.28	0.79-6.57	0.25	1.84	0.64-5.27
Hypertension	39 (36%)	0.97	1.01	0.50-2.04	0.81	0.92	0.46-1.83
Diabetes	0 (0%)	-	-	-	-	-	-
Prior Stroke / TIA	5 (5%)	0.11	2.63	0.79-8.69	0.12	2.52	0.76-8.30
Vascular Disease	16 (15%)	0.22	0.47	0.14-1.59	0.17	0.43	0.13-1.45
Coronary Artery Disease	10 (9%)	0.74	0.81	0.23-2.79	0.61	0.73	0.32-2.48
Underlying Heart Disease	16 (15%)	0.70	1.19	0.48-2.94	0.92	1.04	0.42-2.55
LAV > 142 ml (CTA)	56 (51%)	0.27	1.49	0.73-3.05	0.27	1.47	0.73-2.93
Arrhythmia in blanking period	30 (28%)	0.001	3.14	1.55-6.36	0.001	3.28	1.65-6.52
Class IV	23 (21%)	0.10	1.81	0.87-3.77	0.17	1.64	0.80-3.37
Dublin Class IV	21 (19%)	0.01	2.51	1.22-5.14	0.02	2.27	1.12-4.61

(AAD – antiarrhythmic drug, AF – atrial fibrillation, BMI – body mass index, CTA – computed tomography angiography, LAV – left atrial volume, LVEF – left ventricular ejection fraction, TIA – transient ischaemic attack)

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4.2. OBSTRUCTIVE CORONARY ARTERY DISEASE IN PATIENTS WITH AF

4.2.1. *PATIENT CHARACTERISTICS*

A total of 3,335 pre-ablation coronary CTA examinations have met inclusion criteria. Of those, 570 cases were excluded due to non-diagnostic images, and 169 patients due to previously known CAD. Additionally, 274 images were excluded, because of multiple coronary CTAs being performed. In those cases, only the first good-quality image was involved. Finally, 2,321 patients with paroxysmal and persistent AF were included in our study population (Figure 10.).

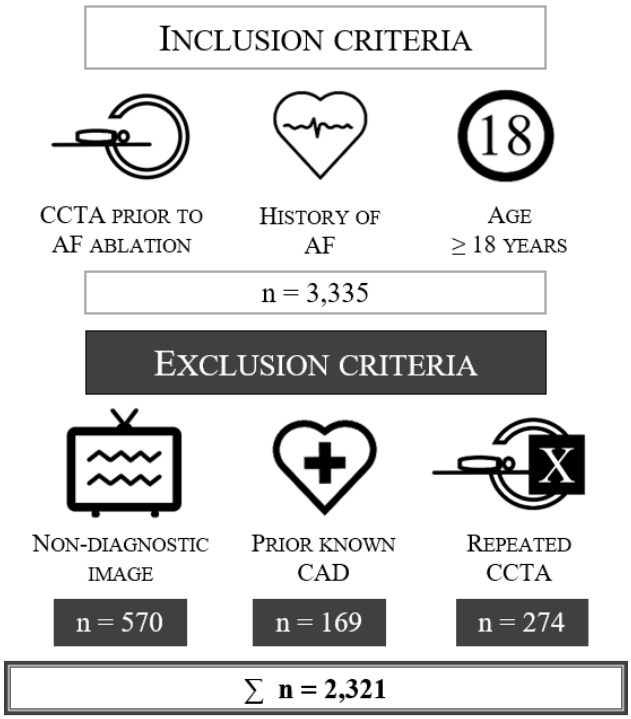

Figure 10. Illustration of our study population (CCTA – coronary CT angiography, CAD – coronary artery disease, Image of our working group).

The median age of the involved patients was 63 [54-69] years. The main characteristics are shown in Table 9. The population was rather overweight: the median body mass index was 29 [26-32] kg/m^2. Hypertension was present in 68% (1,580/2,321) of the patients, 35% (803/2,321) had dyslipidaemia, and 31% (724/2,321) had a history of smoking. 17% (401/2,321) of the patients reported having a positive family history of CV diseases. There were 404/2,321 (17%) patients who mentioned any chest pain before the coronary CTA without any known CAD.

Table 9. Characteristics of the studied population.

Parameters	n=2,321
Age (years)	63 [54-69]
Female sex	1,052 (45%)
BMI (kg/m^2)	29 [26-32]
Hypertension	1,580 (68%)
Diabetes	313 (14%)
Dyslipidaemia	803 (35%)
History of smoking	724 (31%)
Positive family history of CV disease	401 (17%)
Peripheral vascular disease	108 (5%)
Prior stroke / TIA	126 (5%)
Any chest pain	404 (17%)

(BMI – body mass index, CV – cardiovascular, TIA – transient ischaemic attack)

4.2.2. *Comparison of patients with and without any chest pain*

Patients with and without any chest pain were compared (Table 10.) Patients with any chest pain were statistically significant older (65 [58-70] vs 63 [54-69] years, p<0.001), rather female (59% (238/404) vs 43% (814/1,917), p<0.001), presenting with hypertension (72% (292/404) vs 67% (1,288/1,917), p=0.04), peripheral vascular disease (8% (31/404) vs 4% (77/1,917), p<0.001), and reporting positive family history of CV disease (24% (98/404) vs 16% (303/1,917), p<0.001). Obstructive CAD (≥ 50% luminal stenosis revealed by the current coronary CTA) was in equal distribution in both groups (23% (91/404) vs 21% (397/1,917), p=0.41), respectively.

Table 10. Comparison of traditional CV risk factors of patients with and without any chest pain, Mann-Whitney U-test and Chi-square test.

Parameters	Any chest pain (n= 404)	Without chest pain (n=1,917)	p
Age (years)[#]	65 [58-70]	63 [54-69]	< 0.001
Female sex[¤]	238 (59%)	814 (43%)	< 0.001
BMI (kg/m^2)[#]	29 [26-32]	29 [26-32]	0.67
Hypertension[¤]	292 (72%)	1288 (67%)	0.04
Diabetes mellitus[¤]	53 (13%)	260 (14%)	0.80
Dyslipidaemia[¤]	145 (36%)	658 (34%)	0.53
History of smoking[¤]	127 (32%)	597 (31%)	0.88
Positive family history for CV disease[¤]	98 (24%)	303 (16%)	< 0.001
Peripheral vascular disease[¤]	31 (8%)	77 (4%)	0.001
Prior stroke / TIA[¤]	25 (6%)	101 (5%)	0.46
Obstructive CAD[¤]	91 (23%)	397 (21%)	0.41

([¤] Chi-square test; [#]Mann-Whitney U-test; BMI – body mass index, CV – cardiovascular, TIA – transient ischaemic attack, CAD – coronary artery disease)

Multivariable analysis was performed too; factors associated with any chest pain were age > 65 years (OR=1.30, 95% CI: 1.03-1.64, p=0.02) female sex (OR=1.84, 95% CI: 1.47-2.30, p<0.001), positive CV family history (OR=1.70, 95% CI: 1.30-2.22, p<0.001), and peripheral vascular disease (OR=1.74, 95% CI: 1.11-2.75, p=0.01). Obstructive CAD was not associated with symptoms of chest pain (OR=1.06, 95% CI: 0.80-1.39, p=0.69).

4.2.3. *CORONARY ARTERY STATUS OF THE STUDIED POPULATION*

The severity of stenosis was determined on all coronary artery segments. In 577/2,321 (25%) no stenosis, 573/2,321 (25%) minimal, 683/2,321 (30%) mild stenosis was found. Moderate stenosis was observed in 311/2,321 (13%) of the patients, and severe ones in 151/2,321 (7%). Occluded coronary arteries were diagnosed only in 1 per cent (26/2,321). In total, 488/2,321 (21%) patients were diagnosed with novel obstructive CAD (≥ 50% luminal stenosis). The total median CACS was 17.8 [0.0-168.6].

We determined different factors associated with prevalent obstructive CAD with uni- and multivariable tests (Table 11.). In multivariable analysis age > 65 years (OR=2.51, 95% CI: 2.02-3.13, p<0.001), male sex (OR=1.59, 95% CI: 1.28-1.98, p<0.001), hypertension (OR=1.40, 95% CI: 1.08-1.81, p=0.01), diabetes (OR=1.50, 95% CI: 1.13-1.99, p=0.006), dyslipidaemia (OR=1.33, 95% CI: 1.07-1.66, p=0.01), and history of smoking (OR=1.34, 95% CI: 1.07-1.68, p=0.01) were identified as statistically significant associated factors for obstructive CAD. Any chest pain reported was not associated statistically significant with obstructive CAD (OR=1.06, 95% CI: 0.81-1.40, p=0.67).

Table 11. Factors associated with prevalent obstructive CAD as determined by uni- and multivariable analysis, using logistic regression.

Parameters	Univariate OR (95% CI)	p	Multivariable OR (95% CI)	p
Age > 65 years	2.68 (2.19-3.30)	<0.001	2.51 (2.02-3.13)	<0.001
Female sex	0.78 (0.64-0.96)	0.01	0.63 (0.50-0.78)	<0.001
BMI >25 kg/m^2	1.14 (0.88-1.48)	0.32	1.00 (0.75-1.32)	0.99
Hypertension	1.97 (1.56-2.50)	<0.001	1.40 (1.08-1.81)	0.01
Diabetes	2.07 (1.59-2.68)	<0.001	1.50 (1.13-1.99)	0.00
Dyslipidaemia	1.67 (1.36-2.04)	<0.001	1.33 (1.07-1.66)	0.01
History of smoking	1.23 (1.00-1.52)	0.05	1.34 (1.07-1.68)	0.01
Positive family history for CV disease	1.11 (0.85-1.43)	0.44	1.10 (0.83-1.45)	0.51
Peripheral vascular disease	2.04 (1.34-3.05)	<0.001	1.40 (0.90-2.18)	0.13
Prior stroke / TIA	1.67 (1.12-2.46)	0.01	1.39 (0.92-2.12)	0.12
Any chest pain	1.11 (0.86-1.44)	0.41	1.06 (0.81-1.40)	0.67

(BMI – body mass index, CV – cardiovascular, TIA – transient ischaemic attack)

5. DISCUSSION

5.1. VOLTAGE MAPPING AND ITS ROLE IN PATIENTS WITH AF

5.1.1. *TECHNICAL VARIANCES OF VOLTAGE MAPPING*

The technique of voltage mapping has still not been a standardized method among AF patients undergoing CA (86). Multiple studies have reported results of maps created in AF and/or in sinus rhythm (SR) (86, 135, 136). It has been already known that during AF atrial voltages are lower and more variable than during SR, which makes difficult to compare the results with each other (137, 138). Since the majority of the centres perform the procedure in SR, we also created the HD-EAMs in stable SR, or – in case of bradycardia – under pacing from the coronary sinus catheter.

Further difficulties arise from the interpretation of the LVAs, the choice and proper usage of various tools (ablation catheters and/or multielectrode mapping catheters) for mapping, and the numbers of mapped points (mean 100-1024) (86). Few studies have suggested that multipolar catheters overestimate the voltage values as compared to the points created by point-by-point ablation catheters (93, 95). However, the number of points collected with the ablation catheters were minimal in those studies (229±96, and 252±184, respectively), which makes the reported results questionable. Since more voltage points collected imply a more detailed and reproducible maps (139), we created HD-EAMs by multipolar mapping catheters with a higher number of collected points (median 1049 [IQR 690-1405]), as compared to what was documented in previous studies (86, 88, 128, 140). Those studies included between 41-201 patients according to the review of Sim et al., thus our patient group's size was comparable with those (86).

Since the often used visual estimation overestimates the amount of dense scar and underestimates the extent of diseased atrial tissue areas, novel EAM software is needed to estimate the LA fibrosis more accurately (86, 92). We presented in our publications a novel user-friendly tool, which creates automated, rapid, detailed, and potentially reproducible measurements to accurately assess the per cent of LA fibrosis based on the percentage of surface area fulfilling the pre-set criteria. With a quick change of the voltage burden, physicians can report any voltage range of interest and calculate the surface area percentage of the left atrium falling within that range offline, or even in an online setting (128, 130).

There is no consensus on the voltage threshold for defining left atrial fibrosis/scar, which has varied between ≤ 0.05mV and ≤ 0.5mV in studies published (95, 112, 141, 142). Some investigators have used a higher threshold varying between 0.5-1.5mV, which is probably not a true dense scar (103, 112). We chose to apply the most frequently used ≤ 0.5mV threshold to be able to set quartiles for the Dublin Classification, as Diseased LA Tissue is a more likely substrate for the perpetuation of AF than the dense very low voltage (≤ 0.2mV) scars (103, 141). Our outcome results confirmed this burden since Diseased LA Tissue (≤ 0.5mV) was associated with the success rate of the PVI, while the classes of Dense LA Scar (≤ 0.2mV) showed no significant separation regarding the success rates (130).

Reporting the severity of LA fibrosis has also not been well established. Clinicians can assess it based on the presence or absence of the LVAs, some use visually estimated different stages (i.e. none, mild, moderate and severe), others apply the thresholds reported in the DECAAF-study adopting the burdens from MRI measurements (87, 89, 96-98). We used a purely mathematical approach by defining the quartiles based on the first one hundred patients' analysis. Based on our observation, we created a new classification for Diseased LA Tissue, the Dublin Classification. There was a statistically significant separation of the four survival curves of Dublin Classes, and Dublin Class IV showed the lowest success rate. We presented that Dublin Class IV predicts the outcome of PVI (130).

5.1.2. *RISK FACTORS OF LOW VOLTAGE AREA*

Several studies have been searching for factors associated with the presence of LA LVA; demographic parameters, female sex, and advanced age were the most frequently reported ones (88, 89, 143-145). The presence of low voltage zones was also higher in patients with chronic kidney disease, diabetes, hypertension, and obstructive sleep apnoea syndrome (62, 146-149). Echocardiographic data, such as enlarged LA, diastolic dysfunction and reduced LVEF were also related to lower LA voltage rates (62, 89, 143-145, 150). LVA was also more frequently observed in patients with persistent AF as compared to paroxysmal ones (138, 144). Additionally, CACS was significantly higher in the group with the presence of LVA compared to the non-fibrotic LA group (147). The CAAP-AF and CHA_2DS_2-VASc scores, which include CAD, were also associated with low voltage zones (151).

Based on the previous findings, few scores were created or framed in order to predict LA fibrosis. D'Ambrosio et al. invented the ZAQ score to predict the presence and extent of LVA including the following factors: age, female sex, and LAVI measured by CT (152). Another score, the SPEED score was presented by Matsuda et al., as a useful tool to predict the prevalence of LVAs involving factors such as female sex, persistent type of AF, serum B-type natriuretic peptide (BNP) level, serum N-terminal prohormone BNP (NT-proBNP) level and diabetes (153). The APPLE-score (age, persistent AF, impaired renal function, enlarged LA diameter, LVEF < 50%) was originally used for PVI outcome prognosis, but it turned to be a good marker for LVA prediction before AF ablation as well (154). Furthermore, the CHA_2DS_2-VASc score designed for thromboembolic risk stratification showed a good correlation with LVAs (88). The DR-FLASH score developed to estimate AF recurrence after CA. It performs well for LVA prediction and includes similar factors as described previously: diabetes, renal dysfunction, persistent AF, prolonged LA diameter, age, female sex, and hypertension (155). In a recent publication by Kiedrowicz et al., several risk factors were analysed for LVA prediction in long-standing persistent AF patients, where CAAP-AF ≥ 7, DR-FLASH ≥ 4, and CHA_2DS_2-VASc score ≥ 3 predicted the presence of LVA (151). CAAP-AF score incorporates CAD, LA diameter, age, persistent AF, number of failed AADs, and female sex (156). The most recently published AF-SCORE (age ≥ 60 years, female sex, persistent AF) showed also a good correlation with the presence of fibrotic atrial cardiomyopathy (> $5cm^2$, < 0.5mV) (157).

Moreover, some lifestyle parameters, such as the regular moderate alcohol consumption and obesity were also factors associated with lower LA voltage (143, 158, 159).

Our results were in line to that of the cited publications. Higher median Diseased LA Tissue burden was found in patients who were female (28% vs 16%, p=0.001), ≥ 65 years old (30% vs 13%, p<0.0001), had persistent AF (24% vs 14%, p=0.002) and those with a CHA_2DS_2-VASc score ≥ 2 (26% vs 13%, p<0.0001). According to the multivariate analysis, only age ≥ 65 years (OR=4.70, CI 95%: 1.50-14.71, p=0.008) and persistent AF (OR=10.50, CI 95%: 2.93-37.63, p<0.0001) were independent factors associated with Dublin Class IV (128).

5.1.3. *PREDICTIVE ROLE OF LOW VOLTAGE AREA*

One of the most important reasons to study LA LVA is its potential predictive role in determining PVI outcomes. A detailed voltage map allows physicians to have a more thorough discussion with the patient after the CA with regards to the degree of atrial cardiomyopathy present and the long-term likelihood of AF cure by ablation (128).

There have already been multiple studies showing the predictive capacity of LA LVA presence and/or burden. Wang et al. created LA LVA (< 0.5mV) map by a contact-force sensing ablation catheter (150-200 points collected) in 150 patients. The percentage of LVA of the total LA surface was calculated by Carto® software and categorized into four groups: none (0%), mild (<10%), moderate (10-20%) and severe (>20%). Patients with >10% LVA had a significantly higher risk for AF recurrence (89). Next, Vlachos et al. involved 80 patients with a higher resolution of the maps (median 2485 points) and used the DECAAF-study's four categories. According to their results, >10% of < 0.4mV LVA was the only predictor for AF recurrence (85). Furthermore, Begg et al. revealed that a high proportion (> 30%) of LVA (< 0.5mV, multipolar mapping catheter, at least 864 points) mapped in SR or AF also predicts the outcome of PVI (160). Moteleb et al. used 5% of LVA (< 0.5 mV, multipolar mapping catheter, ≥ 100 points) as a burden to estimate the success of CA after 6 months long follow-up: LVA and AF burden were the only significant predictors of ablation success (161). On the other hand, there have been a few publications suggesting opposite opinions. In a recent study by Takahashi et al. involving 448 patients, no correlation was found between > 5% of LVA (< 0.5mV, multipolar catheters, SR, mean 1,271 points) and CA success rates. However, they performed LVA targeted ablation additionally, which makes these results slightly comparable to that of the previously reported mainly PVI-only ablation strategies not targeting LVAs (146).

According to our findings, there is a clear association between the extent of Diseased LA Tissue (Dublin Classification) and the success of PVI. Patients in Dublin Class IV (> 31% of ≤ 0.5mV) have a significantly higher chance of recurrence. No such observation was made with the Dense LA Scar classification (≤ 0.2mV) in our cohort. Arrhythmia in the blanking period was also a risk factor for AF recurrence. No other conventional baseline clinical parameters predicted the success of AF ablation (130).

We decided to present outcomes based on OFF AAD and ON AAD; for the results to be more comparable to what physicians experience in a clinical setting. In our studied population, the one- and two-year success rates were 57% and 45% for Dublin Class IV vs 78% and 73% for Dublin Classes I-III OFF AAD, while 57% and 45% for Dublin Class IV vs 83% and 73% for Dublin Classes I-III with the ON AAD analysis, respectively. These results indicate that the use of AAD did not relevantly affect the PVI outcome at 2 years. Parallel the literature data, our results on PVI success were within the previously reported ranges: 72-93% at one year with low, and 28-75% at one year with high LVA burden (85, 87-89, 96).

Our results may help to manage AF patients after ablation in a more personalized way. During a discussion about the degree of atrial cardiomyopathy and the long-term likelihood of AF cure, we could manage the patient's expectations too. In case of a high LVA burden an increased frequency of follow-up visits might be reasonable, or additional rhythm control therapies such as prolonged anti-arrhythmic therapy, or even further catheter ablation using different non-PV targets might be needed. On the other hand, a severe atrial fibrosis predicting an unsuccessful long-term rhythm control strategy, may facilitate a reduction in reablation procedures, resulting in a more conservative management with early frequency control strategy. However, further studies should confirm the clinical benefits of LA fibrosis imaging.

5.1.4. *BIATRIAL LOW VOLTAGE AREA*

The majority of publications have focused on LA fibrosis and only a few have demonstrated that RA is also affected in AF patients. Histological and molecular studies have suggested that the fibrotic changes at a cellular and subcellular level do happen in both atria and they are not limited to the LA (162, 163). Moteleb et al. measured the voltage of LA and RA as well. They reported fibrosis (> 5%, < 0.5mV) in 6/29 (21%) cases in the LA, and only in 1/29 (4%) cases in the RA. The only patient with the RA LVA had a recurrence, however, of course, no further assumptions can be made based on this single case (161). Prabhu et al. performed biatrial mapping in 40 persistent AF patients with ablation catheters collecting a few hundreds of points. To determine the percentage of low voltage, they directly calculated the number of low voltage points related to the number of the total collected points, but not to the actual surface. They found that the LA and RA bipolar voltage showed a good correlation, and there was no

significant difference between their global voltage (LA 1.89 ± 0.77mV vs RA 1.77 ± 0.57mV, p = 0.57) (164).

In our study we recorded biatrial voltages with multipolar catheters, creating HD-EAMs with a high number of collected points (LA median 987, RA median 897 points). Next, the previously described automated VHA tool allowed us the rapid LVA quantification in both atria. The presence of a high percentage of low voltage areas in the RA predicted the same in the LA and the percentage of Diseased Tissue burden correlated statistically significant between the two atria. The most important potential value of the automated RA LVA is that it can be used as a surrogate marker for the LA fibrosis, without the need for transseptal catheterization, for example in AF patients undergoing an EP study or RA ablation. Thus, the extent of the Diseased RA Tissue burden might provide useful information on the severity of AF, which would be an important clinical implication. However, further studies are still needed to confirm the predictive value of the automated RA LVA analysis on the success of AF ablation (129).

5.2. THE ROLE OF PRE-ABLATION CORONARY CT ANGIOGRAPHY IN AF PATIENTS

5.2.1. *RELATIONSHIP OF CHEST PAIN AND CORONARY ARTERY DISEASE IN AF PATIENTS*

There has been still a lot of uncertainties regarding the relationship between chest pain and AF. Rottlander et al. suggest that there might be only a weak association between AF patients hospitalized due to chest pain and relevant CAD (165). Furthermore, Brown et al. showed among 140 AF patients with chest pain syndromes that the patients had no increased risk for acute coronary syndrome as compared to a matched control group (11.4% vs 10.8%) (166). On the other hand, Graf et al. studied 79 patients reporting only typical chest pain (with no data available on cardiac rhythm) who had no stenosis on coronary arteries, but 65% had reduced coronary flow reserve (167). They suggested that clinical cardiac risk factor analysis may help the prediction of the individual probability of microvascular dysfunction (167).

In our study, chest pain was not associated with obstructive CAD. The incidence of obstructive CAD was similar in patients with and without any chest pain (23% vs 21%). Elderly, female patients, or patients suffering from peripheral vascular disease or hypertension, and subjects with positive family history for CV disease were more likely

to report chest pain. The difference between the associated factors for chest pain and obstructive CAD suggests that the reported chest pains are rather non-cardiac of origin or are related to AF. These findings underline the importance of coronary artery diagnostics in patients undergoing pre-ablation cardiac CTA, while patients without any symptoms could have hidden CAD as well.

5.2.2. *TECHNICAL VARIANCES OF CORONARY ARTERY DISEASE DIAGNOSTICS WITH CT*

In our practice, nearly every AF patient awaiting PVI undergoes pre-ablation cardiac CTA or MRI examination to gather information on atrial anatomy, possible cardiac thrombus or any accidental finding affecting the management of the patient.

Technical differences and variable definition of CAD make the comparison of literature data more complicated. Some use CACS detected on cardiac CT images without angiography. CAC was visually detected at a very high level, 70% among the 638 patients with AF in Dunleavy et al.'s investigation. They performed the examinations on low-resolution, 64-slice CT scanners (168). Visual CACS estimation was also used in the study of Hillerson et al., where 60-64% CAC was found on 278 non-gated CT scans retrospectively (169). Cardiac CTA was performed by Kornej et al., where ≥ 75% luminal reduction was defined as clinically relevant stenosis. Out of the 238 AF patients studied, 28% had such stenosis observed (170). In most of the studies, ≥ 50% luminal coronary artery stenosis was identified as CAD: Weijs et al. found underlying CAD in 49% of paroxysmal AF cohort of 390 patients (121), while Nucifora et al. reported similar, 41% obstructive CAD cases among 150 patients with AF using 16- and 64-slice scanners (171). In a recent study involving 94 patients, only 26% had obstructive CAD on a 128-slice CT (120).

In our study, we applied the most widely used definition of CAD (≥ 50% luminal stenosis). A very high resolution, 256-slice CT-scanner was used, which allows an accurate diagnosis. We observed a relatively high incidence (21%) of coronary artery luminal stenosis in patients a high number of patients without any suspect of CAD (Herczeg et al., 2022, under review).

5.2.3. *RISK FACTORS OF CORONARY ARTERY DISEASE*

There has been a significant literature available on the risk factors for CAD in the AF population. The most often described associated factors are age and male sex (118, 172). Weijs et al. compared 115 paroxysmal AF patients with subjects with constant sinus rhythm. According to their results, besides the above demographic risk factors, the history of AF and prolonged LA diameter are also predictors for luminal stenosis (121). The CADAF-CT trial identified independent risk factors of myocardial ischemia in 757 AF patients: male sex, high number of co-existing coronary risk factors (hypertension, diabetes, dyslipidaemia, family history of CV disease, history of smoking, BMI >25kg/m^2), elevated BNP levels, enlarged LAV, and elevated CACS (118, 172). In the retrospective study of Rottlander et al. including 566 paroxysmal or newly diagnosed AF patients, diabetes, Framingham score, and CHA_2DS_2-VASc score were also predictors for CAD (165). In contrast, in the report of Chen et al., CACS was seen in patients without any conventional CV risk factors (123).

In our investigation, obstructive CAD was threefold more likely to be present among patients > 65 years old, and nearly twofold more likely to be present in male and in patients with diabetes. Hypertension, dyslipidaemia, and history of smoking were also significant variables anticipating obstructive CAD, similar to the previously presented publications. Surprisingly, positive CV family history and obesity did not show a statistically significant correlation with CAD (Herczeg et al., 2022, under review).

5.2.4. *CLINICAL IMPACT OF PRE-ABLATION CORONARY CT ANGIOGRAPHY*

Our study underlines the importance of coronary artery status characteristics in AF patients. The defined associated factors and relatively high number of novel obstructive CAD suggest that it is beneficial extending the routine pre-ablation left atrial CT examination with characterization for coronary artery stenosis even in case of patients with no chest pain. For AF treatment, the holistic ‘ABC’ pathway is suggested by the European Society of Cardiology’s new prevention guideline (6). The identification and management of concomitant diseases and cardiometabolic risk factors (‘C’) play an equal role as the anticoagulation (‘A’) and better symptom (‘B’) management (6). Since a newly diagnosed obstructive CAD could raise the ischaemic risk of the AF patients, these patients would need a re-evaluation of preventive medical treatment (e.g. statins, antithrombotic therapy), lifestyle changes (e.g. weight loss, the secession of smoking),

reduction of modifiable risk factors (e.g. hypertension, hyperglycaemia), or even further investigations (e.g. stress echocardiography, coronarography) based on other individual risk factors and chronic diseases (6).

Besides, a newly discovered obstructive CAD could make it necessary to recalculate the CHA_2DS_2-VASc score, elevating the risk for thromboembolic events. The change in the score would potentially also modify the anticoagulation strategy in patients with AF. Moreover, a review confirmed that AF patients with obstructive CAD had a higher incidence of thromboembolic events (ischemic stroke and systemic thromboembolism) as compared to subjects adjusted for CHA_2DS_2-VASc score components and relevant variables (173). CHA_2DS_2-VASc reclassification was indicated in 20-50% of AF patients after cardiac CTA examination (120, 123, 174). Anticoagulation treatment was modified in 20% of the cohort according to Wang et al. (174).

6. LIMITATIONS

The main limitation of our first three prospective studies is its single-centre setting with a relatively low number of patients included. However, the overall number of the population was comparable to those reported in the literature. While great effort was taken to minimise this (by re-mapping areas of low voltage with the mapping catheter using the tissue proximity indicator algorithm, and with the ablation catheter using contact force), it is impossible to completely exclude a potential underestimation of the measured voltage through poor contact. Manual registration of each point's voltage and subsequent low voltage area quantification was not part of our protocol, which could be considered as a limitation. The manual exclusion of appendages, pulmonary veins, mitral annulus, vena cava from maps introduces a potential for operator bias or error, and may affect overall accuracy to a limited degree. The potential effect of measuring left atrial voltage during coronary sinus pacing or immediately post AF cardioversion was not taken into consideration. The new VHA Tool had not been released in the commercially available CARTO3® EAMS, thus, the use of the software was limited at the time of our publication. Our third study was not designed to evaluate the right atrial low voltage area as a risk factor of AF recurrence post-ablation; a larger scale study would be required to show its clinical impact in that regard.

The most important limitation of our fourth study is its retrospective nature. Unfortunately, there was a significant lack of follow-up of the patients regarding the consequence of the results of the coronary CTA image. Therefore, we could not demonstrate our investigation's ultimate clinical impact. Moreover, some patients were excluded from our study, due to the poor quality caused by tachyarrhythmias, which could be a selection bias.

7. CONCLUSIONS

We analysed LVA in patients with AF with a novel, automated voltage histogram analysis tool, which allowed rapid, detailed, systematic and accurate assessment of Diseased LA Tissue burden (≤ 0.5mV) and Dense LA Scar (≤ 0.2mV) in patients undergoing PVI by creating high-density bipolar voltage maps.

We found that the highest quartile of Diseased LA Tissue burden (Dublin Class IV) predicted the two-year outcome of PVI, while Dense LA Scar showed no predictive value. The usage of AAD did not affect the success rates. Furthermore, arrhythmias in the blanking period do predict the success of ablation in our patient population, but no other baseline clinical parameter does. The application of the Dublin Classification may be a useful clinical tool in predicting recurrent AF post PVI. This finding may help to develop more personalized management for patients after PVI.

We could also determine the LVA in the RA with the help of the VHA tool. We found that the Diseased RA Tissue burden has a strong correlation with the Diseased LA Tissue burden. Our study confirmed previous observations suggesting that the RA is a window of the LA, thus, biatrial remodelling and fibrosis are present in patients with AF.

According to pre-ablation coronary CTA images, we observed a high (21%) incidence of obstructive CAD (≥ 50% luminal stenosis) among patients awaiting ablation due to AF in our Clinic. Chest pain was not associated with the incidence of obstructive CAD. Our findings suggest that it is beneficial extending the routine pre-ablation cardiac CT with characterization for coronary artery stenosis even for patients experiencing no chest pain, since a newly diagnosed obstructive CAD could raise the ischaemic and thromboembolic risk and alter medical treatment strategies.

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To summarize, the most important implications of our study are the following:

1. Dublin Class IV (patients with >31% of Diseased Left Atrial Tissue (≤ 0.5mV)) predicts the success rate of pulmonary vein isolation in patients with atrial fibrillation. Dense Left Atrial Scar (≤ 0.2 mV) revealed no such predictive value.

2. Diseased Right Atrial Tissue burden has a good correlation with the Diseased Left Atrial Tissue burden.

3. Pre-ablation coronary CT angiography is a useful tool to detect novel obstructive coronary artery disease even in patients without chest pain.

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8. SUMMARY

Atrial fibrillation (AF), being the most common cardiac arrhythmia, affects a significant proportion of our population. Due to the complex pathophysiology of AF, the management of these patients, requires a holistic and personalised approach, like the 'ABC' pathway suggested by the European Society of Cardiology's new prevention guideline (6). This recommendation underlines the importance of ('A') anticoagulation, ('B') better symptom management, and ('C') cardiovascular risk factor and comorbidity optimisation.

During my PhD work, I focused on part 'B', studying patients undergoing catheter ablation treatment for AF. The quantitative definition of low voltage areas by the novel, automated voltage histogram analysis tool helped us to characterize patients with Dense Left Atrial Scar (≤ 0.2mV) and Diseased Left Atrial Tissue (≤ 0.5mV). Diseased Left Atrial Tissue burden gave us a better understanding of left atrial cardiomyopathy. Also, the percentage of Diseased Left Atrial Tissue correlated with the percentage of Diseased Right Atrial Tissue. Additionally, the Dublin Classification was created by our group for quantifying the Diseased Left Atrial Tissue burden, after a clear association was found between its extent and the success of catheter ablation regardless of antiarrhythmic drug therapy. Patients in Dublin Class IV (> 31% of ≤ 0.5mV) had a significantly higher chance of recurrence. According to our results, the prediction of success of catheter ablation based on the Dublin Classification, should play an important part in the patients' management, as a more diseased atrial tissue could affect the long-term likelihood of AF cure.

Next, I targeted part 'C' of the 'ABC pathway', and investigated the role of pre-ablation coronary CT angiography. Analysing more than two-thousand patients' images, a high incidence (21%) of obstructive coronary artery disease (CAD) was found in AF patients without previously known CAD regardless of reported chest pain. This high incidence confirms that coronary artery diagnostics added important information to the generally used left atrial CT only. Therefore, it could alter the ischemic and thromboembolic risk stratification, and possibly change the holistic management of patients with AF.

In conclusion, defining the factors associated with AF and predictors of success of catheter ablation guides us towards a more personalized and holistic treatment for AF.

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9. ÖSSZEFOGLALÁS

A pitvarfibrilláció (PF), mint leggyakoribb szívritmuszavar a populációnk jelentős részét érinti. A ritmuszavar komplex patomechanizmusa végett, a PF menedzsmentje egy holisztikus és személyre szabott megközelítést igényel. Egy ilyen PF kezelési stratégia az „ABC" stratégia, mely az antikoagulációt („A"), a tüneti kezelést („B"), valamint a szív-érrendszeri rizikó faktorok és társbetegségek optimalizálását („C") emeli ki (6).

A PhD munkám során a „B" részre fókuszálva, a PF ritmuskontroll terápiájaként ismert katéteres abláció vonatkozásait kutattam. Egy új, feszültség térkép alapú, automatizált szoftver által kvantifikáltunk alacsony feszültségű területeket, melyek a pitvar hegesedésének mértékét mutatták. A 0,5 mV alatti feszültségű terület, ún. *Diseased Tissue,* jobban magyarázta a bal pitvari cardiomyopathia jelenségét a 0,2mV határértékű *Dense Scar* csoportosításhoz képest. Továbbá, jó korrelációt mutattunk ki a bal és jobb pitvari hegesedés között. Miután egyértelmű összefüggést mutattunk ki a bal pitvari *Diseased Tissue* kiterjedése és a PF katéteres ablációjának antiaritmikumoktól független sikeressége között, megalkottuk a bal pitvari heges területek új osztályzását, a Dublin Klasszifikációt. A Dublin IV. osztályába tartozó betegeknél (> 31%, ≤ 0,5mV) szignifikánsan magasabb volt a PF rekurrencia valószínűsége. Eredményeink alapján a katéteres abláció sikerességének Dublin Klasszifikáción alapuló előrejelzését célszerű lenne a beteg kezelésének részévé tenni, mivel a kiterjedt bal pitvari hegesedés (*Diseased Tissue*) befolyásolhatja a PF hosszú-távú sikeres terápiájának valószínűségét.

Ezt követően az „ABC" stratégia „C" részére összpontosítva a PF ablációt megelőző koronária CT angiographia szerepét vizsgáltam. Kétezer feletti beteg képanyagát elemezve, a betegeknél mellkasi fájdalomtól függetlenül, nagy arányban (21%-ban) találtunk obstruktív koronária betegséget, mely korábban nem volt ismert. Ez a magas előfordulás megerősíti azt a feltételezést, hogy az ablációt megelőző bal pitvari CT angiographia vizsgálatokat érdemes kiegészíteni a koronáriákra kiterjesztett felvételekkel. Hiszen egy újonnan felfelfedezett koronária betegség megváltoztathatja az iszkémiás és tromboembolikus rizikó stratifikációt, valamint a betegutat is.

Összefoglalva, a pitvarfibrilláció asszociálta faktorok, illetve a katéteres abláció sikerességi prediktorainak meghatározása, a pitvarfibrilláció személyre szabottabb, holisztikus ellátását alapozza meg.

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11. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATION

11.1. BIBLIOGRAPHY RELATED TO THE PRESENT THESIS

1. Herczeg S, Keaney JJ, Keelan E, Howard C, Walsh K, Geller L, Szeplaki G, Galvin J. (2021) Classification of Left Atrial Diseased Tissue Burden Determined by Automated Voltage Analysis Predicts Outcomes after Ablation for Atrial Fibrillation. Dis Markers, 2021: 5511267.
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