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A Novel Score using Left Atrial Volume Index, Gender, and Age to Predict the Presence of Left Atrial Low Voltage Zones in Patients with Atrial Fibrillation: the ZAQ score

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Alla mia famiglia

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Abstract

Background:

Pulmonary vein isolation (PVI) is the cornerstone of catheter ablation in patients with atrial fibrillation (AF). However, in presence of advanced left atrial structural changes, additional targeted catheter ablation of left atrial low voltage zones (LVZs) showed favorable results. Therefore, with the advent of single-shot techniques, it would be helpful to predict the presence of LVZs beforehand.

Objective:

This study hypothesized that computed tomography (CT) derived left atrial volume index (LAVI) in combination with objective parameters is able to predict the presence of LVZs.

Methods:

In a large cohort of patients undergoing first AF ablation, comprehensive echocardiographic evaluation and contrast-enhanced cardiac CT for pulmonary vein anatomy delineation, and LA volume quantification were performed. During an electrophysiology study, three-dimensional (3D) LA geometry and EAVM were

created. Zones with bipolar peak-to-peak voltage amplitudes <0.5 mV were defined as LVZs.

Results:

In the derivation cohort of 374 patients, predictors for the presence of LVZs were identified with regression analysis and used to build the ZAQ risk score (age≥65 years, female gender and LAVI≥57ml/m^2). The ZAQ score with a cut-off value of 2 points correctly identified the patients with and without LVZs (AUC 0.809; 95% CI 0.758-0.861; p<0.001). In the validation cohort of 103 patients, the predictive value of the ZAQ score was confirmed (AUC 0.786; 95% CI 0.700-0.827; p<0.001).

Conclusions:

The ZAQ score accurately identifies patients with or without LVZs and may be helpful to plan the ablation strategy ahead of time (i.e. single shot PVI vs 3D mapping-guided ablation).

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting around 1-2% of the adult population.[1] Incidence in recent years is increased due to changes in the underlying cardiovascular disease, and its prevalence is estimated to double in the next 50 years, in parallel with the increase in the average life expectancy of the population.[2-4]

Recent guidelines suggested a classification of AF based on the temporal pattern of the arrhythmia: Paroxysmal AF, that occurs sometimes and then stops by itself (up to 7 days). Persistent AF, that does not stop by itself and require medications or electrical cardioversion (longer than 7 days). Long Standing Persistent AF, that cannot be corrected with medications or electrical cardioversion (more than 1 year). For anticoagulated patients, this clinical classification has a purely practical utility, since the prognosis and the main complications of AF was similar across all AF patterns.[5]

The majority of patients experience symptoms like palpitations, dyspnea, chest pain, fatigue or dizziness, less frequent symptoms are lethargy, polyuria, asthenia and psychosocial stress.[6] AF is associated with increased mortality, morbidity and a deterioration in quality of life. Furthermore, AF is also associated with an increased hospitalization rates and other medical conditions such as cognitive

dysfunction (including vascular Dementia), coronary heart disease, and heart failure. In particular, the incidence of heart failure among AF patients is 3.3% per year, while the incidence of AF among heart failure patients is 5.4% per year,[7] and a study showed that 40% of patients with AF or heart failure will develop the other condition over the years.[8]

The increased prognostic risk of arrhythmia is predominantly due to an increased thromboembolic risk of stroke. It is estimated that patients with AF have a stroke risk about 5 times greater than the general population, and that 20% of all strokes have a cardioembolic origin related to the presence of AF. The cerebrovascular events related to this arrhythmia are often fatal or lead to greater disability more than other forms of stroke.[9]

Another important evidence is the correlation between AF and acute coronary syndromes. AF occurs in about 7.5% of patients admitted to the hospitals for acute coronary syndromes, a new onset was observed in 70% of cases and was associated with approximately double of in-hospital mortality compared to those who do not develop arrhythmias.[10-13]

Numerous studies have described a worst quality of life in patients with AF compared to the general population, in healthy controls, and in particular subgroups, such as patients with heart failure or coronary artery disease.[14] The main goals of AF therapy include symptom relief, reduction of arrhythmia recurrence, treatment of

concomitant cardiovascular disease and prevention of thrombo-embolic events. Compared to the rate control strategy, rhythm control is superior for quality of life, morbidity, mortality, bleeding and stroke rate.[13-16]

In recent years, due to the poor results of antiarrhythmic drug therapy alone and its associated side effects, the interventional methods have gained in importance. Catheter ablation is an effective method of maintaining sinus rhythm, preventing arrhythmias recurrences, progression to permanent forms of atrial fibrillation, and relieving symptoms.[17]

Pulmonary veins (PV) play an important role in the initiation of AF and represent one of the main targets for ablative treatment of this arrhythmia.[18] The anatomical, histological and electrical discontinuity in the area between the PV and the left atrium has provided the basis for several studies aimed to clarify the pathophysiological mechanisms responsible for triggering and maintaining AF. The anatomical discontinuity may favor the occurrence of focal triggers able to initiate AF, and possible cellular mechanisms may explain the electrical vulnerability of PV compared to the rest of the atrial tissue; i.e. the refractory periods of the atrial myocytes surrounding the pulmonary veins ostia are shorter than normal, and abnormal intracellular calcium (Ca2+) may be a key contributor to the electrical triggered activity.[19,20]

Although pulmonary vein isolation (PVI) is the cornerstone of ablation in patients with AF,[1] ablation results overall are still not satisfactory.[21] In addition to the occurrence of gaps in the ablation lines, due to difficulties in achieving contiguous and transmural lesions, the presence of potentially arrhythmogenic structural atrial changes outside the pulmonary veins may be the explanation for the relatively high recurrence rate.[22]

Studies using surgical ablation support the hypothesis that empiric linear ablation substrate modification is able to improves success rate especially in persistent AF.[23,24] There is renewed interest in substrate modification using catheter techniques, and additional targeted ablation of LVZs showed favorable results.[25,26] Although the ideal strategy is unclear, identification of LVZs would therefore be relevant for better patient selection.

There is only poor correlation between the temporal pattern of AF (i.e. paroxysmal vs. persistent) and the presence of atrial substrate.[26,27,28] Considering the more recent developments in catheter ablation technique (PVI is often performed using “single-shot” devices [e.g. cryoballoon]), it therefore would be important to assess the presence of structural changes before the ablation in order to decide the ablation strategy up-front.

Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR)[27,29] and electro-anatomic voltage mapping (EAVM)[30] have been used for substrate

characterization. The former is difficult to quantify using standard magnetic resonance imaging (MRI) software, the latter is performed during the electrophysiologic study and, therefore, does not allow to plan an ablation strategy beforehand.

Left atrial (LA) dimensions are related to the presence of atrial substrate, [26,28] and recently, a number of scores (i.e. DR-FLASH) using linear measurements obtained from 2D echocardiographic images have been proposed to predict the presence of LA substrate before the ablation procedure.[31]

We hypothesized that LA volume index (LAVI) is related to LA low voltage zones (LVZs) identified by electro-anatomic voltage mapping (EAVM) which may be an additional target for ablation. The aims of this study were to investigate whether continuous variables quantified by 3D CT-derived LA volume, following the current guidelines recommendation for LA assessment,[32] correlate better with the presence of LA LVZs than 2D echocardiography-derived LA diameters, and to develop a simple score based on objective parameters that reliably predicts the presence or absence of LVZs. This would allow to devise the ablation strategy (PVI alone vs. additional substrate modification) independent of AF temporal pattern before the electrophysiological study.

Methods

Study Design

The study includes the establishment of a score using simple and objective parameters identified with regression analysis in a derivation cohort and the validation of the score in a separate prospective cohort.

Study Populations

All consecutive patients who underwent their first catheter ablation for symptomatic, drug-refractory paroxysmal and persistent AF at our institution between October 2014 and July 2018 were retrospectively included in the derivation cohort. AF was defined according to current recommendations.[1] Exclusion criteria were age <18 years, previous PVI procedure or any cardiac surgery during the prior 3 months, presence of an intracavitary thrombus, severe mitral regurgitation, the inability to obtain sinus rhythm after electrical cardioversion on antiarrhythmic drugs or missing pre-procedural cardiac CT. In order to validate the newly developed score, all consecutive patients who underwent their first catheter ablation for symptomatic, drug-refractory paroxysmal and persistent AF at our institution between July 2018 and June 2019 were prospectively analyzed and included in the validation cohort. All patients provided written informed consent for data being used for research purposes.

Left Atrium size quantification

An echocardiographic evaluation was performed before the procedure with the patient in the left lateral decubitus position. Commercially available echocardiographic system (Vivid 7, GE Healthcare, Horten, Norway) with a phased array sector transducer (1.5-4 MHz) at a depth of 16 cm were used, all images were digitally recorded and analyzed offline by a single investigator blinded to all patient outcomes. Left ventricular ejection fraction (EF) was computed using the biplane method of disks summation (modified Simpson's rule), and LA diameter was measured from the parasternal long axis, orthogonal to the aortic root, at the level of the sinus of Valsalva using the leading edge-to-leading edge convention as suggested by the American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations.[32]

Additionally, each patient underwent contrast-enhanced CT scanning using a 64-slice scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany) at inspiratory breath hold after intravenous and weight-dependent injection of 65-80 ml of nonionic, iodine-based contrast agent (Ultravist, Bayer Heathcare, Berlin, Germany). Beta-blockers were administrated if the baseline heart rate was > 65 beats per minute.

The CT scan was ECG-triggered, with a collimation of 64 x 0.6 mm and a reconstruction thickness of 0.75 mm. The Quantitative assessment of the LA was

performed offline using a dedicated workstation (Syngo Workplace, Siemens AG, Munich, Germany). LA volume measurement was performed automatically or semi-automatically on the basis of the 3D threshold method.

The anatomy of the LA and Pulmonary veins (PV) were identified for all cases. The PV were cut at the ostia and the left atrial appendage was not excluded. The LAVI was calculated by dividing the LA volume by body surface area using the DuBois formula. CT images were evaluated by two investigators, and any inconsistencies was resolved by a senior investigator.

Left Atrium voltage mapping and definition of Low Voltage Zones

All patients were studied under deep sedation with propofol, non-invasive monitoring of arterial blood pressure, oxygen saturation and capnography. Non-fluoroscopic 3D navigation was performed with EnSite NavX (Abbott Medical, St Paul, USA) or CARTO 3 (Biosense Webster, Diamond Bar, CA).

After two transseptal punctures, commercially available mapping catheters (Abbott Medical, St Paul, USA or Biosense Webster, Diamond Bar, USA) were introduced into the LA using an SL0™ and an Agilis™ sheath (Abbott Medical, St Paul, USA). 3D geometry acquisition and initial voltage mapping of the LA were performed

in sinus rhythm with commercially available 10-pole circular mapping catheter (Abbott Medical, St Paul, USA or Biosense Webster, Diamond Bar, USA), and the presence of LVZs in the PV antrum was not considered. Subsequently, an open-irrigated 3,5-mm tip electrode catheter (Tacticath™, Abbott Medical, St Paul, USA or Thermocool Smarttouch®, Biosense Webster, Diamond Bar, CA) was used to create the high-density map of LA LVZs using contact force (CF) technology (starting from a CF of 2 grams).

If patients were in AF, external biphasic DC cardioversion with 250 J was performed before or right after PVI in order to collect the high-density voltage map in sinus rhythm. Signals were filtered at 30–300 Hz, and the interpolation threshold for surface color projection was set to 10 mm.

The map points density (at least 200 points for each map) and the automatic measurements were manually reviewed. Zones with bipolar peak-to-peak voltage amplitudes <0.5 mV in more than 3 adjacent points were defined as LVZs.[33,34]

Statistical analysis

Continuous variables are represented as median and Interquartile Range [IQR]. Categorical variables are presented as counts and percentages. Statistical comparisons for variables were performed with the Mann Whitney U test and the Fisher exact test, as appropriate.

Receiver operator characteristic curve (ROC) analysis was performed to determine the optimal cut-off value for the strongest independent predictor of the presence of LVZs, based on the highest combined sensitivity and specificity. Area under the ROC curve was used to evaluate the prognostic value of the score for predicting LVZs. To calculate odds ratios (OR), a logistic regression model was used.

The test-retest reliability was calculated using the intraclass correlation coefficient (ICC). Statistical analyses were performed with SPSS (version 24.0, IBM Corporation, Armonk, NY, USA). A 2-sided p-value < 0.05 was considered statistically significant.

Results

From October 2014 to July 2018, a total of 374 patients (149 [40%] female, median age 63 [56-70] years) with symptomatic paroxysmal or persistent AF undergoing catheter ablation were included in this study. The demographic, clinical characteristics of the study cohort are presented in Table 1.

The comparison of the demographic data and clinical parameters between patients with and without low voltage zones are presented in Table 2. The calculated ICC for CT derived LA volume was 0.989 (95% CI 0.981-0.994, p<0.001), indicating excellent reliability.

AUC for predicting LVZs by Age was 0.747 (95% CI 0.688-0.807, p<0.001) with an optimal cut-off threshold of 65 years. AUC for LAVI was 0.733 (95% CI 0.671-0.795, p<0.001) with an optimal cut-off threshold of 57 ml/m^2 (Figure 1). LAVI <40 ml/m^2 was associated with no LVZs and LAVI of >73 ml/m^2 with LVZs in 90% of cases.

Using the independent predictors for presence of LVZs identified by logistic regression analysis (Table 3), the new **Zentralklinik Bad Berka and University of L'Aquila (ZAQ) score** was developed by assigning 1 point each for: age ≥65 years, female gender, and LAVI ≥57 ml/m^2.

AUC of the ZAQ score (Figure 2A) in the derivation cohort was 0.809 (95% CI 0.758-0.861, p<0.001), with an optimal cut-off threshold of 2 points. In the validation study cohort, the AUC of the ZAQ score (Figure 2B) was 0.786 (95% CI 0.700-0.827, p<0.001), with an optimal cut-off threshold of 2 points. In our study population, the ZAQ score was more accurate than the DR-FLASH score for predicting LVZs both in derivation (AUC 0.749; CI 0.688-0.810; p<0.001) and validation group (AUC 0.777; CI 0.730-0.823; p<0.001).

Discussion

This is the first study showing that LAVI is a more accurate reflection of the presence of LA structural changes (remodeling) than 2D echocardiography-derived LA diameters, and the combination of 3 simple parameters (age, female gender and LAVI) is able to discriminate patients with and without LVZs in the LA. These patients without evidence of substrate may be successfully treated with single shot PVI (e.g. cryoballoon) even in the presence of non-paroxysmal AF.

LA diameter obtained from 2D echocardiographic images is a predictor of AF recurrence after cardioversion or catheter ablation,[35,36] and it is used in a number of scores to predict the presence of atrial substrate.[31] In particular, the DR-FLASH Score[37] (based on LA diameter >45 mm, age >65 years, female gender, persistent AF, diabetes mellitus, renal dysfunction and hypertension) showed a good capability to predict the presence of LVZs. However, despite the larger number of clinical parameters used, it was less accurate than the ZAQ score in our study population.

LAVI allows more accurate assessment of LA remodeling and is independently associated with AF recurrence after cardioversion or catheter ablation.[38,39,40] In healthy subjects, LAVI is not influenced by age,[41] is closely related to diastolic dysfunction, and is a powerful predictor of AF as well as other cardiovascular events.[42]

In the absence of LVZs, patients with persistent AF undergoing (only) PVI have clinical outcomes comparable to those with paroxysmal AF,[43] and in a recent study,

the efficacy of cryoballoon ablation in paroxysmal and persistent AF was equivalent when LAVI was <61 ml/m^2.[44] Interestingly, LVZs detected by EAVM and the fibrotic content detected by LGE MRI were associated with larger LA volume and able to predict AF recurrence in paroxysmal as well as persistent AF.[43,45] Moreover, two other studies demonstrated the presence of LVZs in a significant number of patients both with paroxysmal and persistent AF, and in both studies a LVZs-targeted ablation approach was used resulting in improved outcomes independent of AF type.[26,46]

Although patients with paroxysmal AF in general have smaller atria and better ablation outcomes compared to those with persistent AF, in a large prospective study, CT-derived LAVI was the strongest predictor of AF recurrence after PVI, followed by female gender, AF type and age.[47] Furthermore, other groups showed that female gender, age and left atrial dimensions (2D Echo derived LA area or EAVM derived surface area) were able to predict the presence of LVZs and associated with a significantly lower bipolar amplitude of the LA compared with patients without LVZs.[48,49]

In summary, consistent with previous findings, the presence of LVZs (one potential explanation of AF recurrence) is closely associated with LAVI, which should, therefore, be the preferred method to assess the LA in clinical practice. The ZAQ score is able to improve patient selection for ablation and offers an easy and objective method to identify patients with or without LVZs who may require either single shot

PVI (e.g. cryoballoon) or 3D mapping-guided ablation with the option of additional substrate modification (Figure 3).

Whether 3D echocardiography (which is not recommended in current guidelines for this purpose due to the lack of a standardized methodology and limited normative data) will be an alternative to CT-derived measurements in the future remains to be determined.[32]

Limitations

LA LVZs were used in this study as the "gold standard" for the presence of LA substrate. Although there is a good correlation between LVZs and the presence of fibrosis,[50] changes in tissue architecture and cell coupling as well as early stages of fibrosis may initially manifest in delay of atrial activation rather than electrogram amplitude changes.[22] Therefore, all present markers of substrate may actually identify more advanced stages of fibrosis, and the earlier phase may be missed. However, next to ablation of extra-PV triggers,[51] LVZs are currently the only clinically used target for additional ablation.[26,46,52]

Both the derivation and the validation cohort are from a single center. Although the results are very consistent and biologically plausible, they require confirmation in validation cohorts with larger patient numbers.

There were different patient characteristics and in particular a higher incidence of LVZs in the validation cohort. Although this could be seen as a limitation, it also supports the clinical value of the new score in a patient group with more advanced structural changes.

Conclusions

LAVI correlates well with presence or absence of LVZs. The ZAQ score accurately predicts the presence of LVZs and may be helpful to plan the ablation strategy ahead of time (single shot PVI vs 3D mapping-guided ablation).

The hypothesis that tailored additional substrate modification ablation, if LVZs are present, results in better outcome is based on pathophysiologic considerations,[22] catheter ablation studies,[26,46,52] and surgical ablation data,[23,24] but requires further confirmation in future randomized studies.

Tables

Table 1. Demographic data and clinical parameters of patients included in the study.

(CT) Computed Tomography, (LA) Left Atrium, (LAVI) Left Atrial Volume Index.

Patient Characteristics	**Derivation cohort (n = 374)**	**Validation cohort (n = 103)**	**p value**
Age (years), median [IQR]	63 [56-70]	68 [63-73]	<0.001
Female Gender, n (%)	149 (40)	42 (41)	0.910
Hypertension, n (%)	275 (73)	91 (88)	0.001
Diabetes mellitus, n (%)	59 (16)	26 (25)	0.030
Dyslipidemia, n (%)	225 (60)	79 (77)	0.002
CAD, n (%)	60 (16)	23 (22)	0.187
Previous TIA/Stroke, n (%)	22 (6)	7 (7)	0.816
Persistent AF, n (%)	152 (41)	71 (69)	<0.001
Duration of AF (months), median [IQR]	21 [6-69]	24 [6-56]	0.773
CHA_2DS_2-VASc Score, median [IQR]	2 [1-3]	3 [2-4]	<0.001
Ejection Fraction (%), median [IQR]	60 [55-60]	55 [50-55]	<0.001
Echo LA diameter (mm), median [IQR]	40 [37-43]	42 [39-45]	0.001
CT LA Volume (ml), median [IQR]	115 [95-138]	138 [113-157]	<0.001
CT LAVI (ml/m^2), median [IQR]	57 [48-68]	69 [57-80]	<0.001
Antiarrhythmic Drugs			<0.001
Amiodarone, n (%)	119 (32)	37 (36)	
Dronedarone, n (%)	86 (23)	8 (8)	
Others, n (%)	46 (12)	10 (10)	

Table 2. Comparison of the demographic data and clinical parameters between patients with and without low voltage zones (LVZs). (CT) Computed Tomography, (LA) Left Atrium, (LAVI) Left Atrial Volume Index.

Patient Characteristics	LVZs No (n = 299)	LVZs Yes (n = 75)	p value
Age (years), median [IQR]	62 [54-68]	71 [65-74]	<0.001
Female Gender, n (%)	97 (32)	52 (69)	<0.001
Hypertension, n (%)	215 (72)	60 (80)	0.188
Diabetes mellitus, n (%)	45 (15)	14 (19)	0.479
Dyslipidemia, n (%)	175 (59)	50 (67)	0.235
CAD, n (%)	46 (15)	14 (19)	0.599
Previous TIA/Stroke, n (%)	17 (6)	5 (7)	0.784
Ejection Fraction (%), median [IQR]	60 [55-60]	60 [55-60]	0.042
Echo LA diameter (mm), median [IQR]	40 [37-43]	40 [37-43]	0.634
CT LA Volume (ml), median [IQR]	110 [93-134]	130 [114-147]	<0.001
CT LAVI (ml/m2), median [IQR]	54 [46-64]	69 [58-74]	<0.001
Persistent AF, n (%)	109 (37)	43 (57)	0.001
Duration of AF (months), median [IQR]	21 [6-69]	19 [7-76]	0.845
CHA2DS2-VASc, median [IQR]	2 [1-3]	3 [2-4]	<0.001
Antiarrhythmic drugs			0.906
Amiodarone, n (%)	89 (45)	30 (48)	
Dronedarone, n (%)	64 (32)	22 (35)	
Others, n (%)	37 (19)	9 (14)	

Table 3. Logistic regression analysis for predictors of LVZs. (LAVI) Left Atrium Volume Index, (CAD) Coronary artery disease.

Clinical parameters	p value	ODD Ratio	95% C.I.	
Female Gender	<0.001	4.713	2.516	8.827
Age ≥65 years	<0.001	3.226	1.679	6.199
LAVI ≥57 ml/m^2	<0.001	5.478	2.732	10.982
Hypertension	0.612	0.824	0.391	1.738
Diabetes	0.822	1.094	0.500	2.397
Dyslipidemia	0.743	1.110	0.595	2.072
CAD	0.611	1.135	0.697	1.847
Previous TIA/Stroke	0.758	1.215	0.352	4.191

Figures

Figure 1.

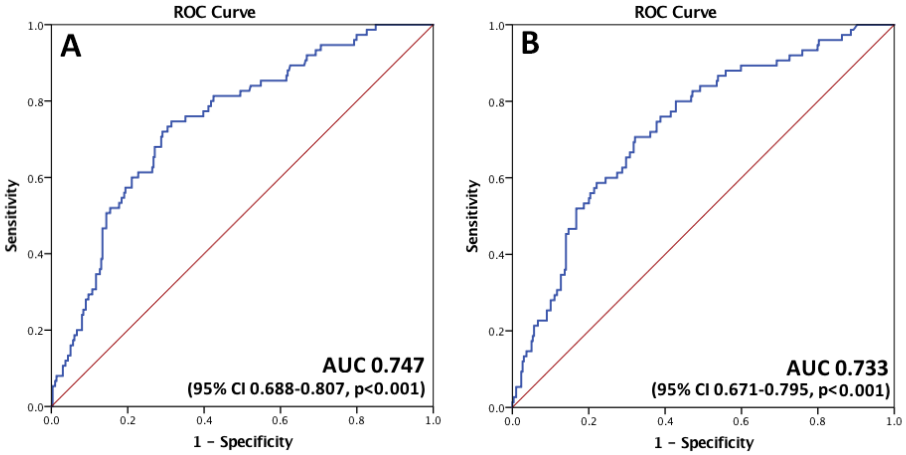

Figure 1. Receiver operating characteristic curves for (A) Age and (B) CT-derived LA volume index for prediction of left atrial low voltage zones.

Figure 2.

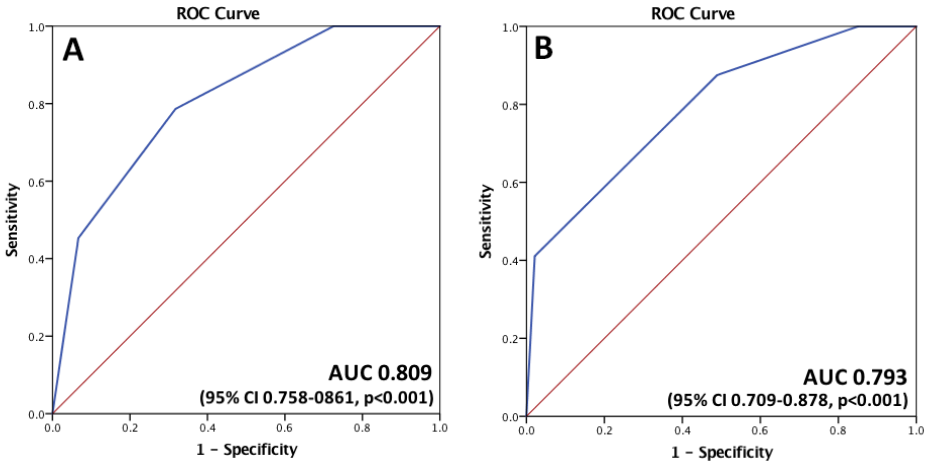

Figure 2. Receiver operating characteristic curves for ZAQ score for prediction of left atrial low voltage zones in (A) derivation and (B) validation cohort. ZAQ score based on age≥65 years, female gender and LAVI≥57ml/m^2.

Figure 3.

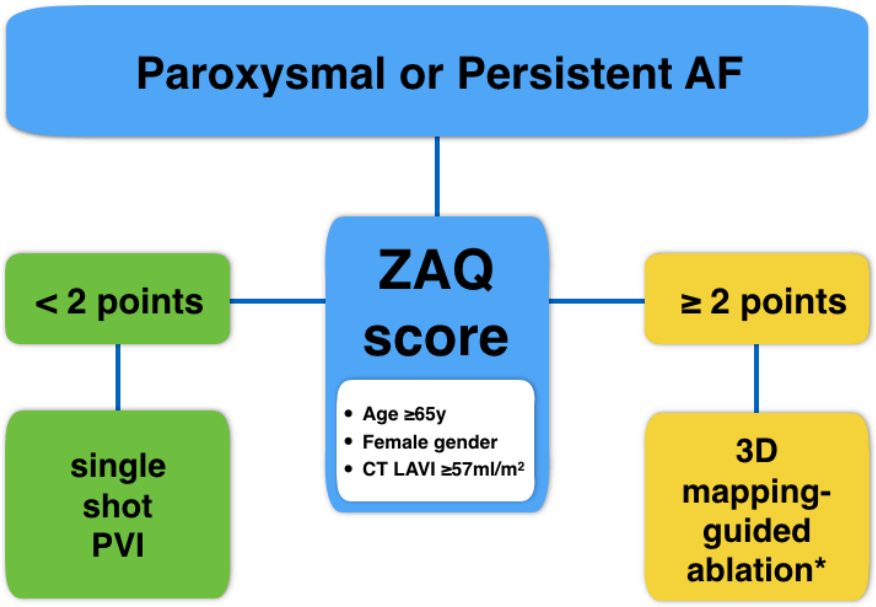

Figure 3. Proposed AF ablation workflow independent of the temporal pattern of AF (ie. Paroxysmal vs. persistent). (CT) Computed Tomography, (LAVI) Left Atrial Volume Index, (PVI) Pulmonary vein isolation. *Low voltage zones, if present, could be targeted with add

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