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ORIGINAL ARTICLE
Vascular and cardiac imaging

Predictive value of late gadolinium enhancement cardiovascular magnetic resonance in patients with persistent atrial fibrillation: dual-centre validation of a standardized method

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Aims With recurrence rates up to 50% after pulmonary vein isolation (PVI) in persistent atrial fibrillation (AF), predictive tools to improve patient selection are needed. Patient selection based on left atrial late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) has been proposed previously (UTAH-classification). However, this approach has not been widely established, in part owed to the lack of standardization of the LGE quantification method. We have recently established a standardized LGE-CMR method enabling reproducible LGE-quantification. Here, the ability of this method to predict outcome after PVI was evaluated.

Methods and results This dual-centre study ($n = 219$) consists of a prospective derivation cohort ($n = 37$, all persistent AF) and an external validation cohort ($n = 182$; 66 persistent, 116 paroxysmal AF). All patients received an LGE-CMR prior to first-time PVI-only ablation. LGE was quantified based on the signal-intensity-ratio relative to the blood pool, applying a uniform LGE-defining threshold of >1.2. In patients with persistent AF in the derivation cohort, left atrial LGE-extent above a cut-off value of 12% was found to best predict relevant low-voltage substrate (≥2 cm two with <0.5 mV during sinus rhythm) and arrhythmia-

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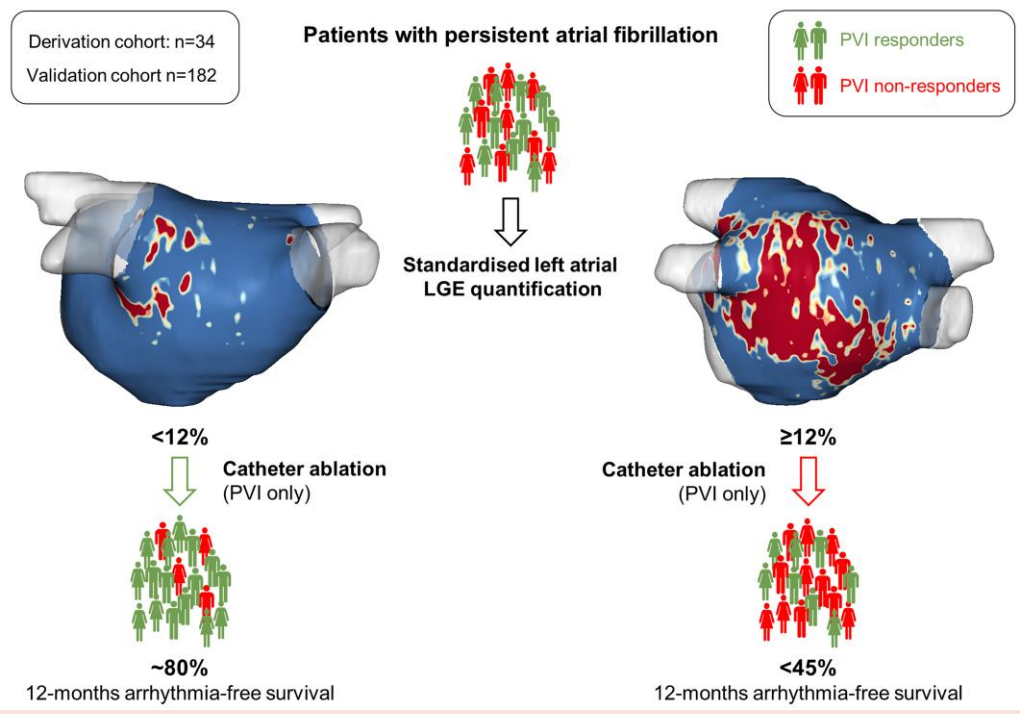
free survival 12 months post-PVI. When applied to the external validation cohort, this cut-off value was also predictive of arrhythmia-free survival for both, the total cohort and the subgroup with persistent AF (LGE < 12%: 80% and 76%; LGE > 12%: 55% and 44%; $P = 0.007$ and $P = 0.029$, respectively).

Conclusion This dual-centre study established and validated a standardized, reproducible LGE-CMR method discriminating PVI responders from non-responders, which may improve choice of therapeutic approach or ablation strategy for patients with persistent AF.

Graphical Abstract



Risk stratification of patients with persistent AF based on the individual extent of left atrial late gadolinium enhancement. In the derivation cohort (University Heart Center Freiburg, Germany), a cut-off value of 12% LA LGE was found to best discriminate between responders and non-responders to catheter ablation (PVI only). Application of this cut-off value to LGE-CMR performed in the validation cohort ($n = 182$, 36% paroxysmal AF, Hospital Clínic, University of Barcelona), confirmed its predictive value with equal discriminating power in patients with persistent AF. Shown are three-dimensional left atrial LGE-CMR reconstructions (postero-anterior view) with colour-coding based on LGE (blue: image intensity ratio ≤1.2; yellow: image intensity ratio >1.2; red: image intensity ratio ≤1.32). AF, atrial fibrillation; LA, left atrial; LGE, late gadolinium enhancement; PVI, pulmonary vein isolation; CMR, cardiac magnetic resonance.

Keywords Atrial fibrillation • Pulmonary vein isolation • Late gadolinium enhancement • Cardiovascular magnetic resonance • Patient selection

Introduction

Pulmonary vein isolation (PVI) through catheter ablation is an effective treatment for patients with paroxysmal atrial fibrillation (AF), but only of moderate efficacy in patients with persistent AF.[1–3] With heterogeneous recurrence rates around 50%, predictive tools that allow for an a priori discrimination of therapy responders and non-responders would be of utmost importance in persistent AF.[4] In fact, the 2019 EHRA White Paper on Knowledge Gaps in Arrhythmia Management and the 2020 ESC Atrial Fibrillation Guidelines explicitly name personalized therapy based on the improved assessment of the underlying phenotype as one of the major evidence gaps and unmet needs.[4,5]

Compared with paroxysmal AF, persistent AF is more dependent on an arrhythmogenic substrate, often related to an underlying atrial cardiomyopathy.[6] Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is a non-invasive method to assess atrial fibrotic substrate.[4] The seminal DECAAF trial found LGE-CMR to predict AF recurrence after PVI in a mixed cohort of patients with paroxysmal or persistent AF and proposed a risk stratification based on quantitative left atrial LGE-extent (UTAH-classification).[7] However, to date such an approach has not been widely established. This may in part be due to the lack of standardization of the quantification method and thus limited reproducibility of patient classification based on numeric values of quantitative left atrial LGE.[4]

Until now, there is no generally accepted, standardized method for LGE-CMR image acquisition, and the same applies to image post-processing and analysis.[8,9] Most importantly, as T1-weighted imaging is based on signal intensity contrast rather than directly measured absolute values, LGE quantification requires a consistent internal reference for normalization as well as validated signal intensity thresholds discriminating normal from abnormal tissue. The numeric value of LGE-extent and thus the individual risk stratification largely depends on the internal references and thresholds applied, which prohibits the application of the numeric UTAH-classification to other post-processing methods.[9] Moreover, the internal reference and the thresholds for LGE that the UTAH-classification is based on, are not uniform but individually chosen by the operator and thus not readily applicable across different centres in a standardized manner.[7,10]

Based on the signal intensity ratio method introduced by Khurram et al.,[11] in which the mean signal intensity of the blood pool serves as a reference for normalization, our group has recently established and validated standardized thresholds for LGE quantification that were derived from distinct cohorts of young healthy individuals and post-AF ablation patients.[12–16] In the study presented here, the predictive value of this method regarding low-voltage substrate and outcome after PVI-only catheter ablation in patients with persistent AF was assessed by two centres independently (University Heart Center Freiburg-Bad Krozingen, Germany and Hospital Clínic, University of Barcelona, Spain).

Methods

Study design and participants

This dual-centre study investigated the ability of pre-procedural LGE-CMR to detect relevant left atrial low-voltage and predict outcomes in patients with persistent AF undergoing first-time AF ablation using a PVI-only approach. The study consisted of a derivative cohort (to identify a predictive threshold of LGE-extent), prospectively investigated at University Heart Center Freiburg-Bad Krozingen, Germany and a validation cohort (to validate the LGE-threshold), retrospectively analysed at Hospital Clínic, University of Barcelona, Spain. Patients with long-standing (≥12 months) AF or contraindications for LGE-CMR were excluded. The primary outcome endpoint of arrhythmia recurrence was defined as any documented episode of AF, atypical atrial flutter or atrial tachycardia lasting >30 s after a 3-month blanking period.

Table 1 Patient characteristics derivation cohort

	n = 37
Age, years	66 ± 9
Female gender	6 (16)
Hypertension	27 (73)
Diabetes mellitus	3 (8)
BMI	27.4 ± 3.5
CHA_2DS_2-VASc score	2 (1–3)
LA diameter, mm	46.7 ± 6.3
LA diameter >45 mm	23 (62)
LVEF, %	56.7 ± 8.3
LVEF <45%	8 (22)
LA LGE-extent, %	16.5 (5.9–30.9)
LGE >12%	23 (62)

All values are *n*, (%), or mean ± SD (median and interquartile if not normally distributed). BMI, body mass index; LA, left atrial; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement.

Derivation cohort (Freiburg-Bad Krozingen, Germany)

Consecutive patients with symptomatic persistent AF scheduled for first-time AF ablation between February 2019 and July 2019 were prospectively included as described previously.[8] An LGE-CMR was performed within 24 h before PVI. In case of AF, electrical cardioversion was accomplished prior to LGE-CMR. Subsequently, high-density electroanatomical mapping and PVI using ablation index-guided radiofrequency ablation were performed as previously described.[8] For follow-up, ambulatory clinical visits including 12-lead-electrocardiogram (ECG) and 72-h Holter-ECG were scheduled 6 and 12 months after PVI. Patients in whom arrhythmic episodes were suspected based on symptoms, but not covered by 12-lead-ECG or holter-ECG, were provided a mobile event recorder (CARDIOCALL VS20, Reynolds Medical) and instructed to record symptomatic episodes.

The study was approved by the institutional ethics committee (University of Freiburg), registered at the German WHO primary registry DRKS (unique identifier: DRKS00014687), and all patients provided written informed consent prior to enrollment.

Validation cohort (Barcelona, Spain)

The validation cohort was based on a prospective ablation registry of patients with paroxysmal or persistent AF, conducted at the Arrhythmia Section of Hospital Clínic, University of Barcelona. Patients scheduled for first-time AF ablation are systematically included in this registry and receive an LGE-CMR within 4 days prior to ablation as well as a systematic follow-up including a 24-h Holter-ECG at 3, 6, and 12 months post-ablation. In this current study, all patients with PVI-only AF ablation between October 2015 and March 2021 and intraprocedural confirmation of complete PVI were analysed retrospectively, if the pre-procedural LGE-CMR was of sufficient quality. Although this article focuses on patients with persistent AF, data and analyses of patients with paroxysmal AF are also provided as a comparator.

The protocol was reviewed and approved by the local research ethics committee, and written informed consent was obtained from each patient.

Electroanatomical mapping

High-definition left atrial endocardial voltage and activation maps were acquired in sinus rhythm prior to catheter ablation using multipolar mapping catheters—either a 20-polar LassoNav or a PentaRay (both with an electrode size of 1 mm and 2–6–2 mm spacing, Biosense Webster, CA) in combination with the endocardial mapping system CARTO-3 as described previously.[8,17] Left atrial areas with bipolar voltage <0.5 mV in sinus rhythm were considered as low-voltage substrate. Relevant low-voltage substrate was defined as a cumulative left atrial low-voltage substrate extent of >2 cm^2 as described previously.[8,17]

LGE-CMR image acquisition

LGE-CMR was performed as previously described.[8,13] In brief, CMR studies were performed in sinus rhythm using one of three different 3-Tesla scanners (see below), all with 32-channel phase array cardiovascular coils. Inversion recovery prepared T1-weighted gradient echo sequences were acquired in axial orientation using ECG gating and a free-breathing three-dimensional navigator.

Sequence parameters for Somatom Skyra scanner, Siemens Healthineers (University Heart Center Freiburg)

Acquisition 15–20 min after intravenous contrast injection (ProHance®, Bracco) at a dose of 0.1 mmol/kg; repetition time 3.1 ms; echo time 1.4 ms; flip angle 14°, acquired voxel size 1.25 × 1.25 × 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm).

Sequence parameters for Magnetom Prisma scanner, Siemens Healthineers (Hospital Clínic, University of Barcelona):

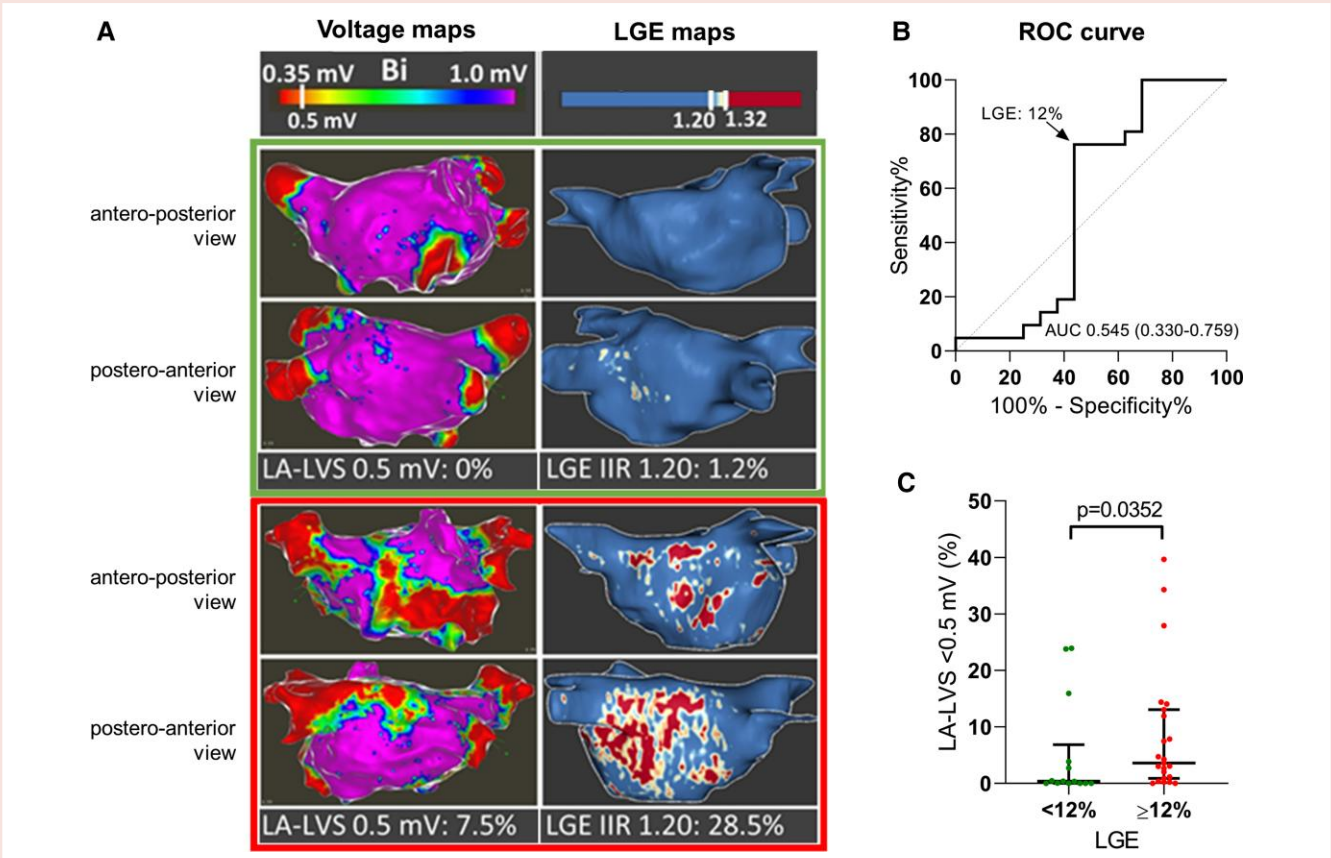


Figure 1 Predictive value of LGE with respect to relevant low-voltage substrate. (A) Representative examples of a patient without (upper panel, green frame) and with relevant left atrial low-voltage substrate (lower panel, red frame). Relevant low-voltage substrate was defined as ≥2 cm^2 of the left atrium with <0.5 mV signal amplitude during sinus rhythm. Shown are left atrial bipolar voltage maps applying the indicated voltage thresholds and LGE-maps (three-dimensional reconstruction of left atria with colour-coding based on signal intensity ratios applying thresholds of ≥1.2 and >1.32 using ADAS 3D software (Adas3D Medical Barcelona, Spain)) of the same patients head-to-head. The upper case illustrates an example for a good match and the lower case an example for a suboptimal agreement regarding both the regional distribution and extent of diseased areas between left atrial low-voltage substrate and LGE. (*B*) Receiver-operating characteristic (ROC) analysis identified the best trade-off between sensitivity and specificity for an LGE-threshold of 12% as a predictor of relevant left atrial low-voltage substrate. (*C*) Application of the determined cut-off value of 12% left atrial LGE-extent allows for differentiation of patients with significant variability of left atrial low-voltage extent. Whisker plots depict median with 25% and 75% interquartile range. LA-LVS, left atrial low-voltage substrate; LGE, late gadolinium enhancement.

Acquisition 15–20 min after intravenous contrast injection (Gadobutrol®, Gadovist, Bayer) at a dose of 0.2 mmol/kg; repetition time 2.3 ms, echo time 1.4 ms, flip angle 11°, acquired voxel size 1.25 × 1.25 × 2.5 mm.

Sequence parameters for Signa Architect scanner, General Electric (Hospital Clínic, University of Barcelona):

Acquisition 15–20 min after intravenous contrast injection (Gadobutrol®, Gadovist, Bayer) at a dose of 0.2 mmol/kg; repetition time 6.4 ms; echo time 2.2 ms; flip angle 20°; acquired voxel size 1.25 × 1.25 × 2.4 mm.

Independent of scanner and study site, TI scout sequences were used in order to determine the optimal TI that nullified the left ventricular myocardial signal (typically 280–380 ms).

LGE-CMR post-processing

LGE quantification was performed independently at each of the two study sites, but using identical methods and software (ADAS 3D software, Adas3D Medical SL). LGE-CMR post-processing was performed by highly experienced experts (derivation cohort, Freiburg: R.F.; validation cohort, Barcelona: E.F., P.G.), blinded to data from invasive mapping. For semi-automatic three-dimensional reconstruction of left atria and PVs, the atrial wall was manually traced on each axial-plane slice and automatically adjusted to build a three-dimensional shell.

LGE was quantified in a standardized manner based on voxel signal intensities relative to the mean blood pool signal intensity, applying a previously validated signal intensity ratio threshold of ≥1.2 to define LGE indicative of fibrotic tissue.[13] After manual exclusion of pulmonary veins, left atrial appendage, and the mitral valve, LGE-extent was automatically calculated as the absolute LGE area relative to the total left atrial surface area based on the reconstructed left atrial three-dimensional shell.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 24 (IBM, NY, USA), Graphpad Prism 8 (Graphpad Software, San Diego, CA, USA), an MedCalc Statistical Software 20.009 (MedCalc Software bv, Ostend, Belgium). Dichotomous variables were compared using Fisher's exact test. Normality was assessed by the Shapiro–Wilk test. Normally distributed data are given as mean ± SD and skewed distributed data as median with interquartile range (IQR, 1st and 3rd quartiles). A receiver-operating characteristic (ROC) analysis was performed to select the LGE-threshold with the optimum trade-off between sensitivity and specificity for prediction of

relevant LA low-voltage substrate within the derivation cohort. Kaplan–Meier curves were used to illustrate arrhythmia-free survival among patients with persistent AF in both cohorts and compared using the log-rank test. Impact of clinical covariates on arrhythmia recurrence was analysed using logistic regression models. All variables with a *P*-value <0.1 in univariate regression analyses were included in multivariate regression analysis. Inter-rater reliability of LGE in terms of agreement with left atrial low-voltage substrate was assessed by calculating Cohen's kappa coefficient (κ). A two-tailed $P < 0.05$ was considered significant.

Table 2 Logistic regression—odds ratios for arrhythmia recurrence in the derivation cohort (persistent AF, *n* = 37)

Predictor	Unadjusted		
	Odds ratio	95% CI	*P*
≥12% LGE	7.20	1.29–40.05	0.024
LA diameter	1.05	0.95–1.17	0.352
LA diameter >45 mm	2.00	0.51–7.80	0.318
LVEF	1.02	0.94–1.11	0.582
Age	1.03	0.95–1.11	0.497
Female sex	1.58	0.27–9.17	0.608
Hypertension	1.87	0.40–8.80	0.430
Diabetes	3.23	0.27–39.29	0.358
BMI	1.02	0.78–1.15	0.95
BMI >30	0.44	0.09–2.93	0.291
CHA_2DS_2-VASc score	1.22	0.80–1.86	0.362

Odds ratios, 95% CIs, and probability values for predictors of arrhythmia recurrence. LGE, late gadolinium enhancement; LA, left atrial; LVEF, left ventricular ejection fraction; BMI, body mass index.

Results

Baseline characteristics (derivation cohort)

In the derivation cohort (University Heart Center Freiburg-Bad Krozingen), 37 consecutive patients with persistent AF were included between February 2019 and July 2019. All patients received an LGE-MRI during sinus rhythm, followed by PVI-only ablation procedure including high-density left atrial mapping (mean 2129 ± 484 mapped sites) prior to radiofrequency energy application. Patient characteristics are summarized in *Table 1*.

Left atrial LGE

According to the pre-ablation CMR, patients displayed LGE indicative of fibrotic tissue that accounted for a median of 16.5 (5.9–30.9) per cent of the total left atrial surface area. Subsequent high-density electroanatomical mapping revealed a median low-voltage extent (bipolar voltage <0.5 mV) of 2.7 (0.2–12.5) per cent of the total left atrial surface area, with 21 patients (57%) meeting the criteria of relevant left atrial low-voltage substrate (≥2 cm^2 with bipolar voltage <0.5 mV during sinus rhythm). The voltage maps and the corresponding LGE-maps of two representative patients without and with relevant left atrial low-voltage substrate are illustrated in *Figure 1A*.

Predictive value of left atrial LGE with regard to left atrial low-voltage substrate

To assess the predictive value of LGE with respect to relevant LA-LVS and atrial cardiomyopathy, respectively, a ROC analysis was performed (*Figure 1B*). According to the ROC analysis, a cut-off value of 12% left atrial LGE-extent yielded the optimum trade-off between sensitivity (76.2%) and specificity (56.2%) for the presence of left atrial low-voltage substrate. This cut-off discriminated well between patients without and with low-voltage substrate (*Figure 1C*). Moreover, applying

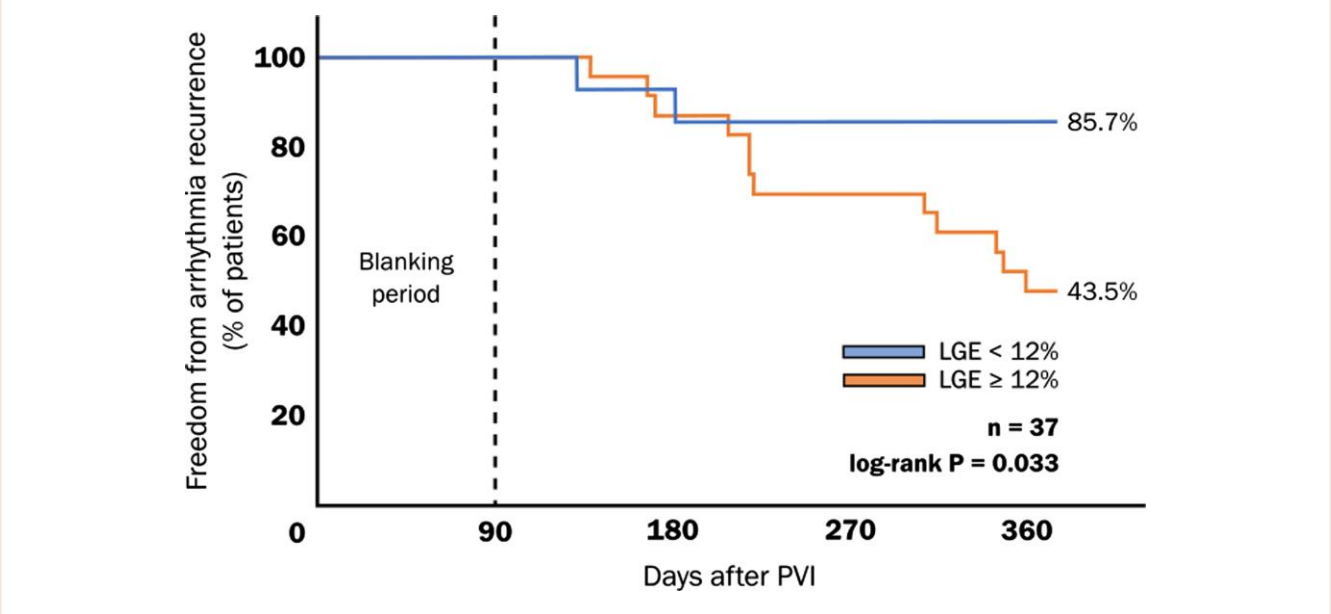


Figure 2 Freedom from arrhythmia recurrence according to left atrial LGE (derivation cohort). Kaplan–Meier curves for freedom from arrhythmia recurrence in patients with LGE <12% vs. ≥12% of left atrial surface area. Statistical significance (*P*-value) based on log-rank test. LGE, late gadolinium enhancement.

Table 3 Patient characteristics validation cohort

	full cohort n = 182	persistent AF n = 66	paroxysmal AF n = 116
Age, years	59.4 ± 10.6	59.6 ± 10.9	59.3 ± 10.5
Female gender	52 (29)	16 (24)	36 (31)
Hypertension	82 (45)	32 (48)	50 (43)
Diabetes mellitus	21 (12)	8 (12)	13 (11)
BMI	27.9 ± 4.5	28.7 ± 4.6	27.4 ± 4.4
CHA_2DS_2-VASc score	1 (0–2)	1 (0–2)	1 (0–2)
LA diameter, mm	41.9 ± 6.5	43.2 ± 6.1	40.9 ± 6.2
LA diameter ≥45mm	21 (12)	10 (15)	11 (9)
LVEF, %	57.4 ± 6.3	55.7 ± 7.4	58.4 ± 5.4
LVEF <45%	7 (4)	4 (6)	8 (7)
LA LGE-extent (%)	5.4 (2.5–9.8)	6.1 (3.1–10.9)	4.8 (2.1–8.2)
LGE >12%	33 (18)	16 (24)	19 (16)

All values are *n*, (%), or mean ± SD (median and interquartile if not normally distributed). BMI, body mass index; LA, left atrial; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement.

Table 4 Logistic regression—unadjusted and adjusted odds ratios for arrhythmia recurrence in the validation cohort (full cohort, *n* = 182)

Predictor	Unadjusted			Adjusted		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
LGE ≥12%	2.92	1.32–6.49	0.008	3.82	1.47–9.89	0.006
Persistent AF (vs. paroxysmal)	1.89	0.95–3.76	0.071	1.20	0.50–2.86	0.688
LA diameter	1.05	0.99–1.11	0.118			
LA diameter >45 mm	2.91	1.10–7.69	0.032	2.41	0.82–7.10	0.109
LVEF	0.94	0.88–0.99	0.020	0.94	0.88–1.00	0.038
Age	1.03	0.99–1.06	0.137			
Female sex	1.09	0.51–2.32	0.827			
Hypertension	1.26	0.64–2.49	0.502			
Diabetes	0.73	0.23–2.30	0.591			
BMI	1.02	0.94–1.11	0.615			
BMI >30	1.69	0.79–3.64	0.177			
CHA_2DS_2-VASc score	0.98	0.74–1.31	0.906			

Odds ratios, 95% CIs, and probability values for predictors of arrhythmia recurrence. Columns 2 through 4 present results from the unadjusted model; columns 5 through 7 show results from the adjusted model. LGE, late gadolinium enhancement; AF, atrial fibrillation; LA, left atrial; LVEF, left ventricular ejection fraction; BMI, body mass index.

this cut-off value, LGE was found to be an independent predictor of relevant left atrial low-voltage substrate (odds ratio 4.11, CI: 1.01–16.83, $P = 0.049$), although the quantitative agreement between LGE >12% and relevant left atrial low-voltage substrate was rather weak (kappa 0.33, $P = 0.044$).

Predictive value of left atrial LGE with regard to AF recurrence after PVI

Most importantly, however, this LGE cut-off value of 12% proved to be an independent predictor of arrhythmia recurrence after PVI-only AF ablation (*Table 2*). Kaplan–Meier curves indicate a good capacity of the 12% LGE-threshold to discriminate PVI responders from non-responders, with freedom from any arrhythmia being significantly higher in patients with LGE <12% compared with patients with LGE ≥12% of the left atrial surface area (85.7% vs. 43.5%, $P = 0.033$) (*Figure 2*).

External validation

In the external validation cohort (Hospital Clínic, University of Barcelona), 182 consecutive patients (66 persistent AF, 116 paroxysmal AF) with PVI-only AF ablation and pre-procedural LGE-CMR between October 2015 and March 2021 were retrospectively analysed. Patient characteristics for the full cohort and the subgroups of persistent vs. paroxysmal AF are summarized in *Table 3*.

Applying the 12% LGE cut-off, identified in the derivation cohort, binary LGE was predictive of arrhythmia-free survival, both in the full

cohort of 182 AF patients (*Table 4*) as well as in the subgroup of 66 patients with persistent AF (*Table 5*). While LGE ≥12% was the only variable with the significant predictive value among patients with persistent AF, logistic regression analyses of the full cohort (paroxysmal and persistent AF) also found left atrial diameter >45 mm and left ventricular ejection fraction to be statistically significant predictors of arrhythmia recurrence. However, in the adjusted regression model including all covariates with a *P*-value <0.1, LGE ≥12% remained the only independent predictor of arrhythmia recurrence. Of note, the inclusion of AF type (paroxysmal vs. persistent AF) as a covariate did not improve the predictive model for the full cohort (*Table 4*).

Finally, Kaplan–Meier curves indicate a good capacity of the 12% LGE-threshold to discriminate PVI responders from non-responders among patients with persistent AF, also in the validation cohort (*Figure 3*): patients with persistent AF and left atrial LGE <12% had an arrhythmia-free survival rate in the range of that in patients with paroxysmal AF, whereas patients with LGE ≥12% had a poor outcome with an arrhythmia-free survival of only 43.9% (*Figure 4*).

Table 5 Logistic regression—odds ratios for arrhythmia recurrence in the validation cohort (only patients with persistent AF, *n* = 66)

Predictor	Unadjusted		
	Odds ratio	95% CI	*P*
LGE ≥12%	4.00	1.17–13.70	0.027
LA diameter	1.00	0.91–1.09	0.939
LA diameter >45 mm	0.98	0.26–3.74	0.981
LVEF	0.96	0.90–1.04	0.324
Age	1.01	0.96–1.06	0.640
Female sex	0.50	0.16–1.60	0.243
Hypertension	0.41	0.14–0.19	0.101
Diabetes	0.49	0.09–2.52	0.391
BMI	0.91	0.80–1.03	0.144
BMI >30	0.88	0.29–2.65	0.813
CHA_2DS_2-VASc score	0.85	0.57–1.28	0.440

Odds ratios, 95% CIs, and probability values for predictors of arrhythmia recurrence. LGE, late gadolinium enhancement; LA, left atrial; LVEF, left ventricular ejection fraction; BMI, body mass index.

Discussion

This dual-centre study established and validated the predictive value of left atrial LGE as determined by a standardized method of CMR acquisition and post-processing, which is readily reproducible across different centres.

Improved choice of therapeutic approach or ablation strategy in persistent AF

With recurrence rates as high as 50% and above, there is an urgent need of predictive tools or models to improve patient selection for catheter ablation or repeat ablation, particularly in persistent AF. Here, we found an LGE-extent above a threshold of 12% of the left atrial surface area to predict not only relevant left atrial low-voltage substrate, but also arrhythmia recurrence after PVI-only AF ablation in patients with persistent AF.

Validation in an independent external cohort confirmed this predictive value both for the group of patients with persistent AF (*n* = 66) as well as the full cohort including 182 patients with paroxysmal or persistent AF. Of note, those analyses revealed a higher predictive value of LGE ≥12% than that of established predictors like AF type or left atrial size. Most importantly, the LGE-threshold of 12% was able to a priori discriminate responders from non-responders among patients with persistent AF to a clinically relevant extent in both, the derivation cohort and the validation cohort. Patients with persistent AF and left atrial

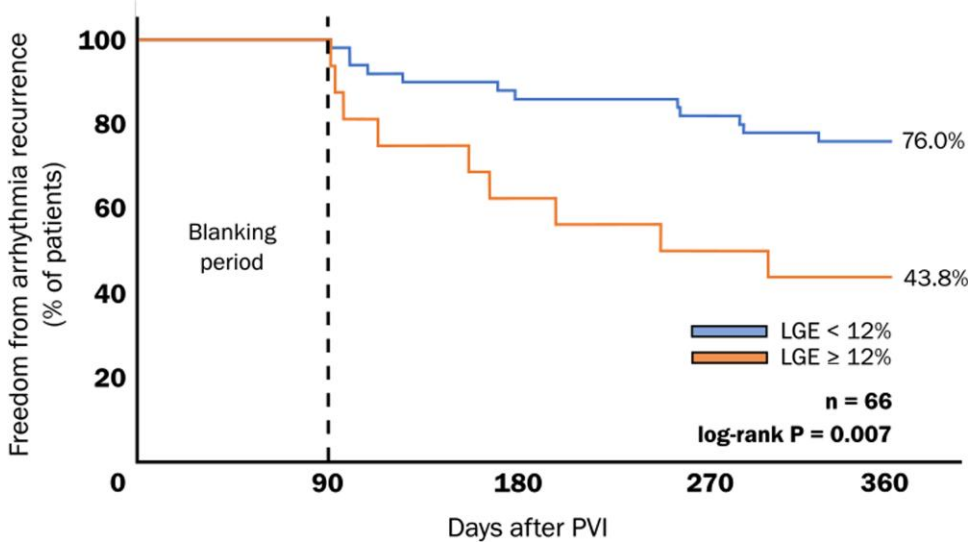


Figure 3 Freedom from arrhythmia recurrence according to left atrial LGE (validation cohort, persistent AF patients). Kaplan–Meier curves for freedom from arrhythmia recurrence in patients with LGE <12% vs. ≥12% of left atrial surface area. Statistical significance (*P*-value) based on log-rank test. LGE, late gadolinium enhancement.

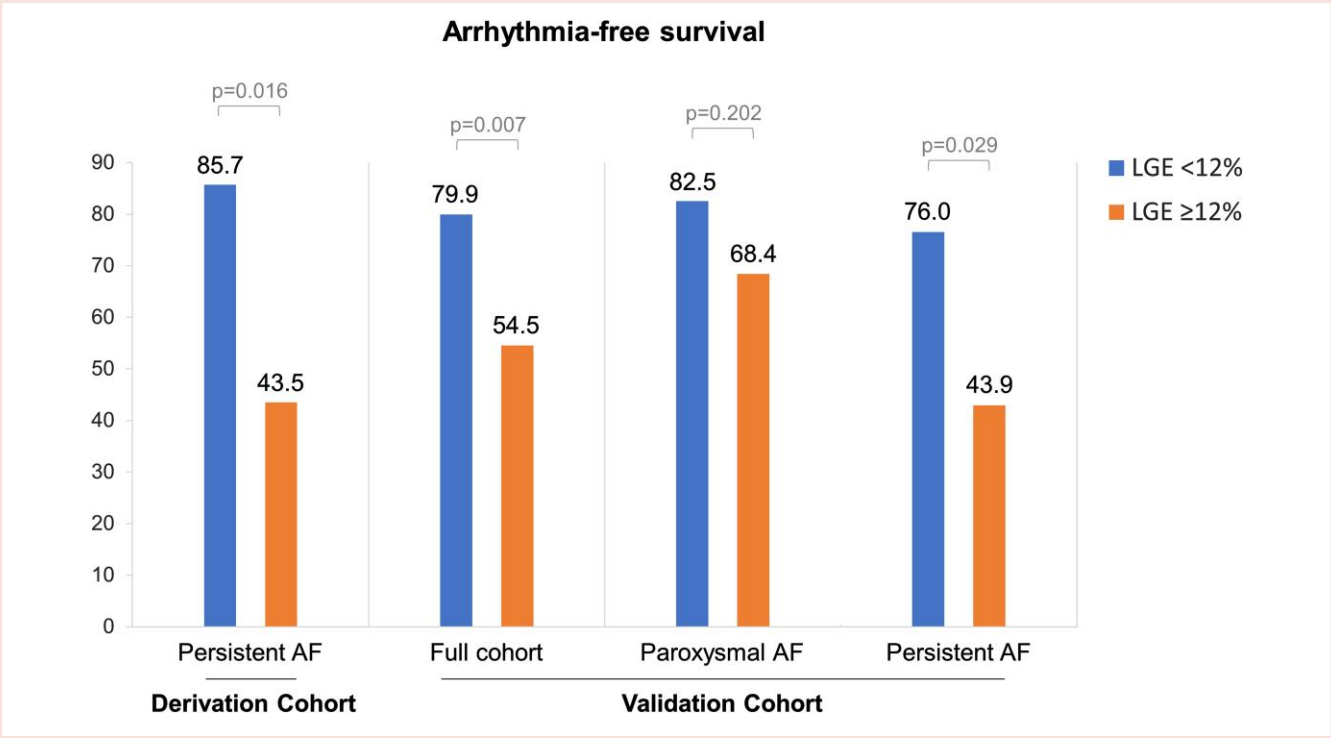


Figure 4 Arrhythmia-free survival rates according to LGE-extent and AF type. 12-month arrhythmia-free survival rates in per cent in patients with LGE <12% vs. ≥12% of left atrial surface area. Statistical significance (*P*-values) based on Fisher exact test. AF, atrial fibrillation; LGE, late gadolinium enhancement.

LGE <12% had an arrhythmia recurrence rate in the range of that in patients with paroxysmal AF (arrhythmia-free survival rates around 80%), whereas patients with LGE ≥12% had a poor outcome with arrhythmia-free survival rates below 45%. While the presence of left atrial LGE ≥12% does not mean that these patients should be excluded from catheter ablation therapy, the indication, particularly in case of repeat procedures, should be reconsidered more carefully and maybe more restrictively. It is tempting to speculate that those patients may benefit from additional ablation strategies beyond PVI-only.

Standardized quantification of left atrial LGE

A risk stratification based on left atrial LGE has been proposed previously (UTAH-classification), but to date this approach has not been widely established. This may partly be due to the fact that the underlying definition of LGE and its quantification are not standardized and may thus yield different numeric values of quantitative LGE-extent for a given patient, depending on the investigator or centre.[7] As outlined above, T1-weighted imaging is based on signal intensity contrast rather than directly measured absolute values. For quantification, LGE must therefore be defined by a signal intensity threshold relative to an internal reference. Obviously, different internal references and/or thresholds applied to the same images will inevitably yield different numerical values of LGE-extent.[8,9] Thus, for universal applicability of a numeric risk stratification, uniform thresholds and internal references defining LGE are required.

LGE quantification in the dual-centre study reported here is based on a previously validated, standardized method with uniform definitions of signal intensity threshold and internal reference, rendering it universally applicable independent of the investigator, allowing for a widespread clinical use across different centres. This assumption is corroborated by our study, where the proposed LGE cut-off was equally predictive at both centres (Freiburg-Bad Krozingen, Germany and Barcelona, Spain), despite the fact that image acquisition post-processing and LGE quantification were performed independently at the two study sites.

It shall be emphasized that various other methods using distinct internal references and thresholds have been reported ,[10,11,18,19] some of which fulfill the pre-requisite of standardized, reproducible thresholds, and internal references for LGE quantification, as outlined above. However, predictors based on quantitative LGE only apply to the specific quantification method they have been established with. Thus, quantitative predictors have to be established and validated separately and specifically for each quantification method.

Applicability across different patient populations

The fact that the proposed LGE cut-off of ≥12% was predictive of arrhythmia-free survival in two rather distinct cohorts of patients with persistent AF suggests a general applicability across different patient populations. In fact, the derivative cohort seems to represent an older population with more advanced disease and more comorbidities, as reflected by a larger LA size and higher CHA2DS2-VASc score as well as a larger proportion of patients with hypertension, diabetes, or LVEF <45%. Consistent with a more advanced disease stage and comorbidities, LGE-CMR detected a higher extent of left atrial LGE in the derivative cohort compared with patients with persistent AF in the validation cohort.

Limited agreement between LGE and low-voltage substrate

In line with previous studies, the agreement of left atrial LGE and low-voltage substrate was rather weak, which may reflect a partial failure of LGE to detect fibrotic tissue.[8] However, it also highlights the fact that neither LGE nor endocardial low-voltage is specific for atrial fibrosis, but should rather be considered as surrogates that may not detect identical histological entities. Of note, histological validation of both, LGE and left atrial low-voltage substrate, in a larger series of patients is lacking. Taken together, while there are certainly limitations accuracy of LGE-CMR to detect fibrosis, electroanatomical voltage mapping cannot be considered a definite reference either. However, both surrogates have proven predictive of AF recurrences in this and other studies.[7,20–22]

Conclusion

In this dual-centre study, we established and validated a predictive LGE-threshold that can a priori discriminate PVI responders from non-responders among patients with persistent AF and may therefore guide selection of suitable candidates for PVI and those that are unlikely to benefit from PVI or re-PVI only. This predictor is based on a standardized, investigator-independent LGE quantification method, that may allow for universal applicability across different centres.

Lead author biography

Dr Althoff was Head of Cardiac Electrophysiology at the Department of Cardiology and Angiology, Charité University Medicine Berlin, until he joined the Arrhythmia Section of Hospital Clínic, University of Barcelona as a senior electrophysiologist in 2020. His clinical and scientific work focuses on the personalized treatment of complex atrial and ventricular arrhythmias making use of novel imaging and non-invasive electroanatomical mapping techniques. He is also directing a translational research lab within the German Center for Cardiovascular Research (DZHK).

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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