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CLINICAL RESEARCH

Effect of fibrosis regionality on atrial fibrillation recurrence: insights from DECAAF II

Ala Assaf [1], Mario Mekhael [1], Charbel Noujaim [1], Nour Chouman [1], Hadi Younes [1], Han Feng [1], Abdelhadi ElHajjar [2], Botao Shan [1], Peter Kistler [3], Omar Kreidieh [1], Nassir Marrouche [1], and Eoin Donnellan [1]*

[1]Tulane Research Innovation for Arrhythmia Discovery (TRIAD), Tulane University School of Medicine, 1324 Tulane Avenue, Suite A128, New Orleans, LA 70112, USA; [2]Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, USA; and [3]Clinical Electrophysiology Research Laboratory, Baker Heart and Diabetes Research Institute, Melbourne, Australia

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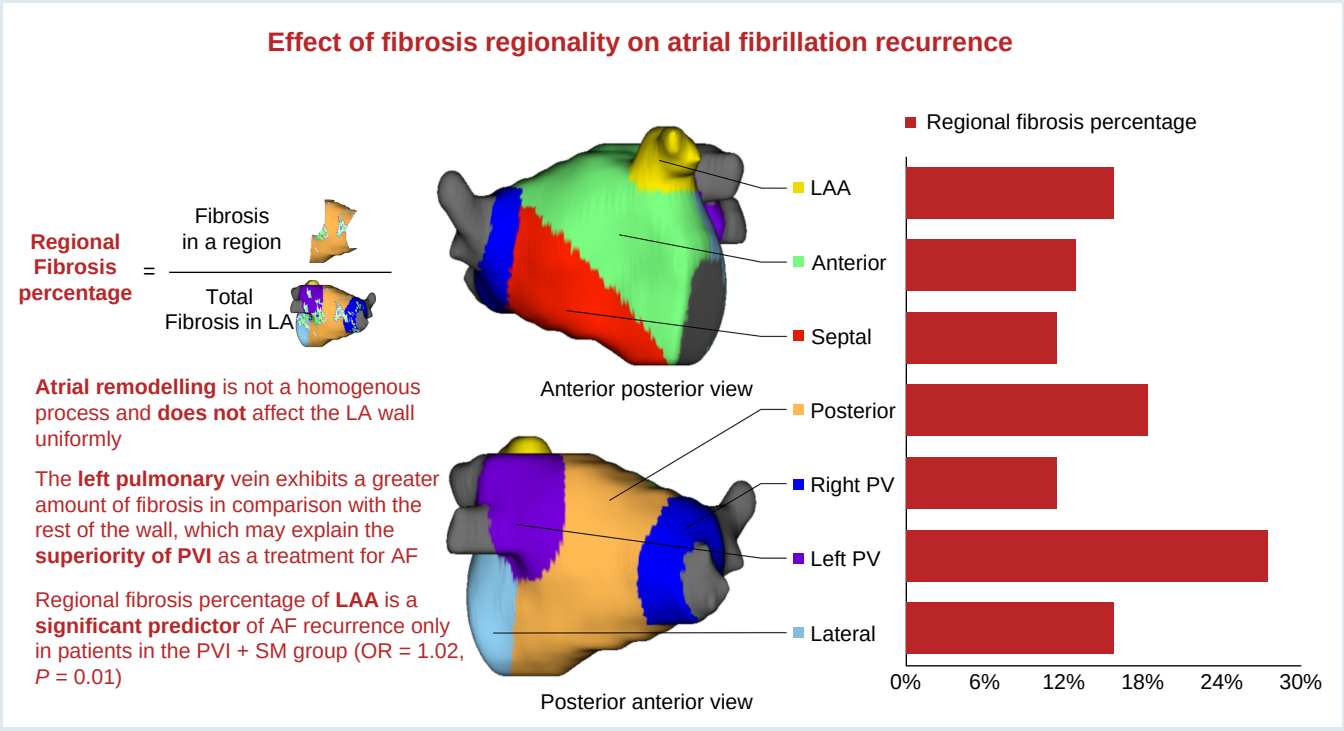
Aims The amount of fibrosis in the left atrium (LA) predicts atrial fibrillation (AF) recurrence after catheter ablation (CA). We aim to identify whether regional variations in LA fibrosis affect AF recurrence.

Methods and results This *post hoc* analysis of the DECAAF II trial includes 734 patients with persistent AF undergoing first-time CA who underwent late gadolinium enhancement magnetic resonance imaging (LGE-MRI) within 1 month prior to ablation and were randomized to MRI-guided fibrosis ablation in addition to standard pulmonary vein isolation (PVI) or standard PVI only. The LA wall was divided into seven regions: anterior, posterior, septal, lateral, right pulmonary vein (PV) antrum, left PV antrum, and left atrial appendage (LAA) ostium. Regional fibrosis percentage was defined as a region's fibrosis prior to ablation divided by total LA fibrosis. Regional surface area percentage was defined as an area's surface area divided by the total LA wall surface area before ablation. Patients were followed up for a year with single-lead electrocardiogram (ECG) devices. The left PV had the highest regional fibrosis percentage (29.30 ± 14.04%), followed by the lateral wall (23.23 ± 13.56%), and the posterior wall (19.80 ± 10.85%). The regional fibrosis percentage of the LAA was a significant predictor of AF recurrence post-ablation (odds ratio = 1.017, $P = 0.021$), and this finding was only preserved in patients receiving MRI-guided fibrosis ablation. Regional surface area percentages did not significantly affect the primary outcome.

Conclusion We have confirmed that atrial cardiomyopathy and remodelling are not a homogenous process, with variations in different regions of the LA. Atrial fibrosis does not uniformly affect the LA, and the left PV antral region has more fibrosis than the rest of the wall. Furthermore, we identified regional fibrosis of the LAA as a significant predictor of AF recurrence post-ablation in patients receiving MRI-guided fibrosis ablation in addition to standard PVI.

* Corresponding author. Tel: +12162133097, *E-mail address*: edonnellan@tulane.edu

Graphical Abstract



Keywords Atrial fibrillation • Fibrosis • Regional • Left atrial wall • Scar

What's new?

- Atrial cardiomyopathy has regional variations in fibrosis within the left atrium, with prognostic value for predicting atrial fibrillation (AF) recurrence.
- Patients with persistent AF have increased fibrosis in the left pulmonary vein region compared with the rest of the left atrium wall.
- Preferential fibrosis of the left atrial appendage, i.e. regional fibrosis percentage, is a marker of more advanced atrial cardiomyopathy and is predictive of AF recurrence.

Introduction

Pulmonary vein isolation (PVI) is an effective treatment for persistent atrial fibrillation (AF).[1] Despite advances in ablation techniques and modalities, AF recurrence after catheter ablation (CA) remains high.[2] Atrial fibrosis has been identified as a predictor of incident AF and AF burden.[3] Moreover, the amount of atrial fibrosis prior to CA predicts AF recurrence after the procedure.[4] Cardiac late gadolinium enhancement magnetic resonance imaging (LGE-MRI) has been shown to identify atrial fibrosis and scar,[3,5] and this has been correlated and validated with pathological specimens.[6] The Efficacy of MRI-Guided Fibrosis Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II) trial showed that MRI-guided ablation of fibrosis does not decrease AF recurrence after CA when compared with conventional PVI alone.[2] This prompts the question of whether atrial cardiomyopathy affects the left atrium (LA) uniformly, whether atrial remodelling is a homogenous process, and whether these variations provide prognostic value. For example, the posterior wall in particular is thought to be a source of arrhythmogenic triggers for patients with persistent AF and is readily amenable to electrical isolation.[7] In addition, the left atrial appendage (LAA) has been identified as an important source of extra-pulmonary vein (PV) arrhythmogenic triggers in patients with persistent AF.[8] Therefore, multiple adjunct therapies to standard PVI targeting these potentially arrhythmogenic regions have been described, with varying degrees of success.[9–11]

While the heterogeneity of myopathy distribution across the LA wall has been suggested in the literature,[12–14] there exists a paucity of data regarding regional fibrosis as detected by LGE-MRI and its relationship with recurrence after CA. We sought to leverage the extensive imaging data of the DECAAF II trial database to study these regional variations and their associated prognostic values.

Methods

Study population

This is a *post hoc* analysis of patients enrolled in the DECAAF II clinical trial, which has been previously described.[2] Eight hundred forty-three patients with persistent AF and undergoing AF CA were randomized to receive PVI plus MRI-guided ablation or PVI alone. Patients with contraindications to gadolinium or MRI and patients who had a previous AF ablation or valvular cardiac surgery were excluded from the study. Late gadolinium enhancement magnetic resonance imaging was performed in both groups within 1 month before the ablation procedure to assess baseline atrial fibrosis and at 3 months post-ablation to assess for ablation scar. Physicians were encouraged but not required to discontinue anti-arrhythmic drugs (AADs) after the 90-day blanking period. Participants were followed for a period of 12–18 months using daily smartphone electrocardiogram (ECG) device recordings (ECG Check Device, Cardiac Designs Inc.) to assess the primary outcome of AF recurrence after ablation. Patients who had non-regional LGE-MR images were excluded from this study. This study was approved by the Tulane University Biomedical IRB.

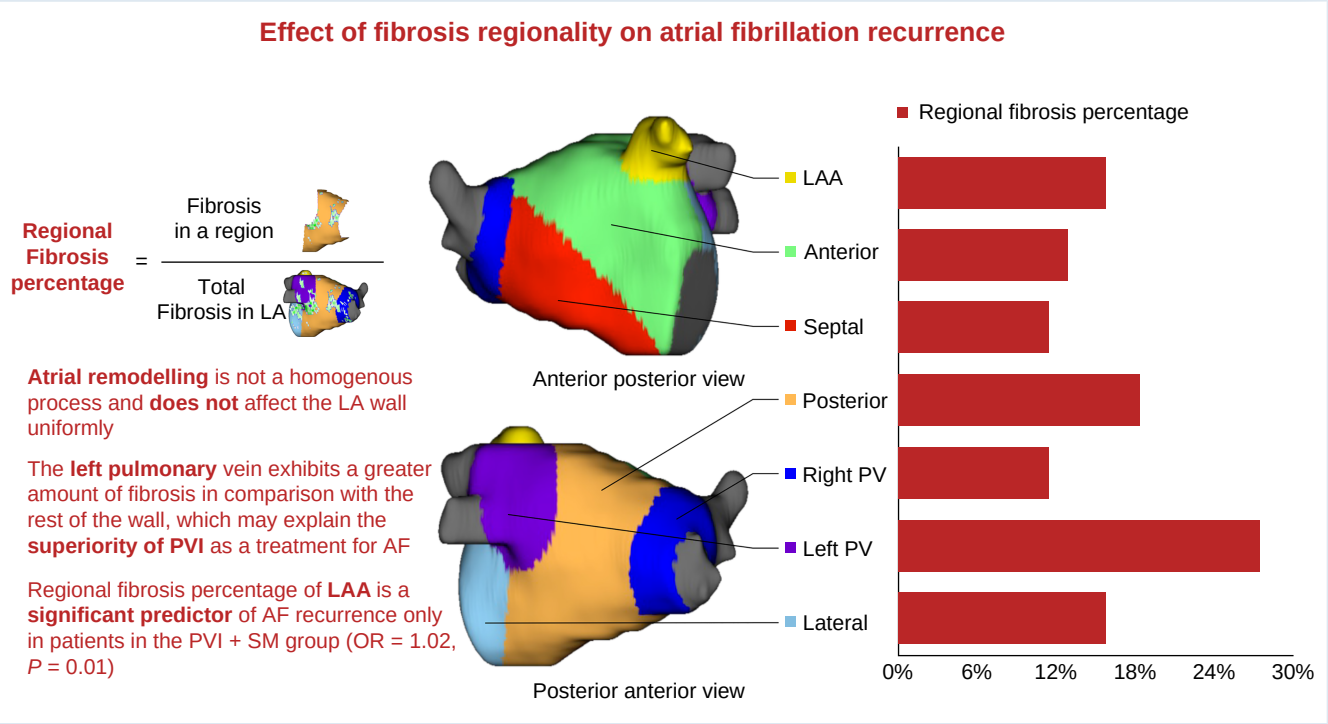


Figure 1 Central figure, effect of fibrosis regionality on atrial fibrillation recurrence.

Table 1 Baseline characteristics of the study cohort

N		734
Sex (% males)		78.2
Age (mean ± SD)		62.0 ± 9.0
History of tobacco use (%)		38.7
Congestive heart failure (%)		18.8
Hypertension (%)		59.1
Diabetes mellitus (%)		9.4
Coronary artery disease (%)		12.7
Stroke (%)		8.4
Taking anti-arrhythmic medications (%)		46.7
Long-standing persistent AF (%)		61.1
Baseline fibrosis percentage (mean ± SD)		18.6 ± 7.2
Baseline Utah stage (%)	I	11.7
	II	46.9
	III	32.7
	IV	10
Preablation LA size (mean ± SD)		131.2 ± 41.0
Post-ablation scar percentage (mean ± SD)		9.6 ± 5.1
Post-ablation LA Size (mean ± SD)		108.1 ± 35.4

Image processing

All patients underwent cardiac LGE-MR imaging using previously described methods.[4,15–17] The LA wall was manually segmented, and regions of fibrosis were delineated using an intensity threshold set by expert inspection of each image. Regions exhibiting enhancement intensity two to three standard deviations (SD) above the mean intensity of normal tissues were considered fibrotic. The LA wall was divided into seven regions using previously described methods[17]: anterior, posterior, septal, lateral, right PV antrum, left PV antrum, and LAA ostium (*Figure 1*). The left PV antrum was defined as the LA wall extending 10 mm from the left PV–LA junction, the right PV antrum was defined as the LA wall extending 10 mm from the right PV–LA junction, the posterior wall as the posterior LA extending from the LA floor to the LA roof and bordered by both PV antra, the septum wall as the wall between LA and right atrium, the anterior wall as the anterior part of the LA, and the left lateral wall as the left side of the LA that is not covered by other areas. After sub-segmentation, the LGE area (mm^2) and LGE coverage (%) in each LA sub-region were calculated using the Corview image analysis software (MARREK, Inc., Salt Lake City, Utah, USA).[17] The amount of fibrosis in the LA was stratified into four Utah stages, as previously described.[2] Baseline fibrosis was defined as the total amount of fibrosis in the LA wall prior to ablation divided by the surface area of the LA wall. Regional fibrosis percentage was defined as the amount of fibrosis in a particular region of the LA wall before ablation divided by the total amount of fibrosis in the LA wall (*Figure 1*). Surface area percentage was defined as the surface area of a particular region, divided by the total surface area of the LA wall.

Primary outcome

The primary outcome for this study was the first confirmed recurrence of AF lasting for at least 30 s after the 90-day blanking period, demonstrated by at least two consecutive 1-lead smartphone ECG device tracings, one positive reading on a clinical 12-lead ECG tracing, ambulatory monitor, or if the patient underwent repeat CA.[2]

Statistical analysis

Continuous variables were reported as mean ± SD. Binary logistic regression was used to perform the univariate and multivariate analysis with the dependent variable being the primary outcome and regional fibrosis percentages as independent variables. A *P*-value <0.05 was considered

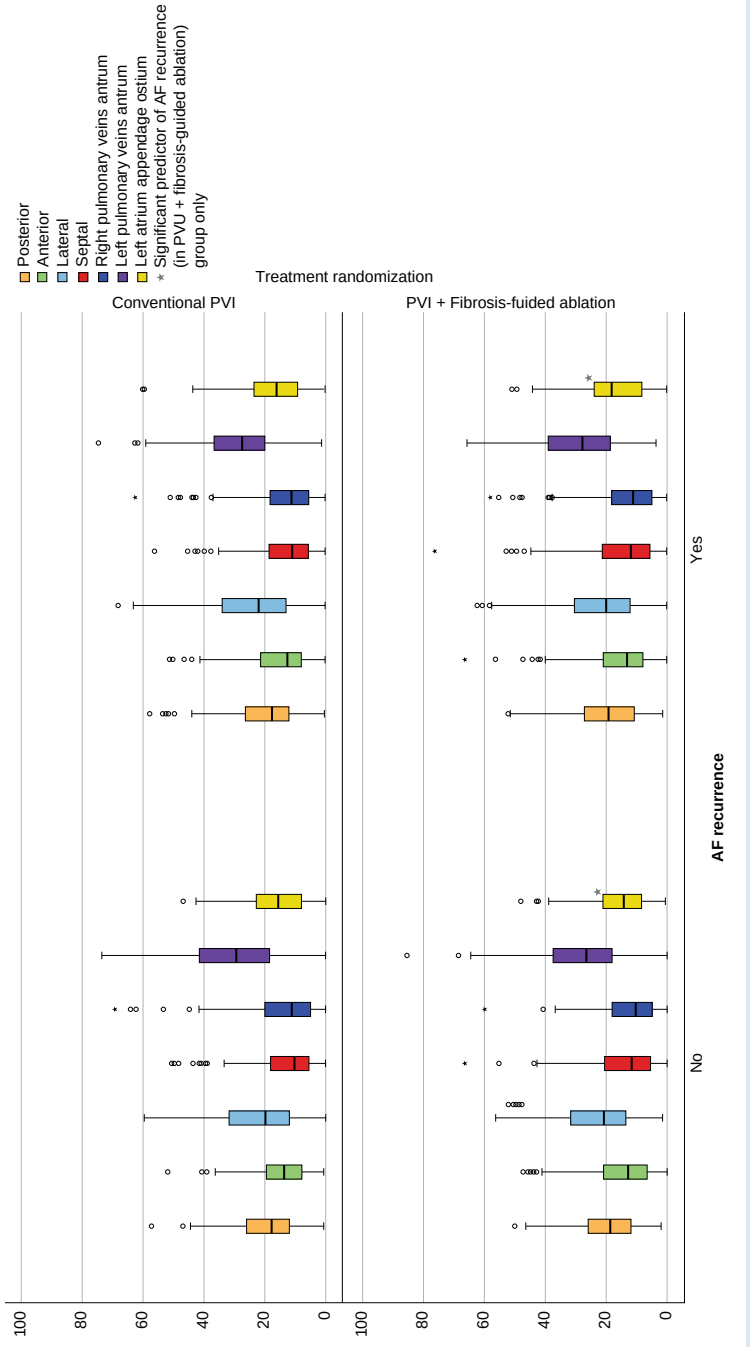


Figure 2 Boxplot figure showing regional fibrosis percentages of different regions of the LA wall, stratified by treatment randomization and AF recurrence.

Table 2 Regional distribution of pre-ablation regional fibrosis percentages

LA wall region	All patients (mean ± SD)	Standard PVI group (mean ± SD)	MRI-guided fibrosis ablation (mean ± SD)	*P* value
Anterior wall	15.32 ± 10.48	15.35 ± 10.32	15.30 ± 10.65	0.941
Posterior wall	19.80 ± 10.85	19.69 ± 11.18	19.91 ± 10.53	0.793
Lateral wall	23.23 ± 13.56	23.46 ± 13.76	23.00 ± 13.38	0.648
Septal wall	14.02 ± 11.17	13.66 ± 10.61	14.38 ± 11.71	0.383
Right pulmonary vein antrum	13.75 ± 11.64	14.19 ± 11.97	13.31 ± 11.30	0.309
Left pulmonary vein antrum	29.30 ± 14.04	29.78 ± 13.84	28.82 ± 14.24	0.355
LAA ostium	16.70 ± 10.08	16.69 ± 10.04	16.71 ± 10.14	0.980

Table 3 Regional fibrosis percentages as predictors of the primary outcome

LA wall region	Odds ratio	95% confidence interval	*P* value
Univariate analysis			
Anterior wall	1.009	0.991–1.027	0.332
Posterior wall	0.998	0.981–1.016	0.807
Lateral wall	1.002	0.990–1.014	0.682
Septal wall	0.993	0.976–1.011	0.419
Right pulmonary vein antrum	0.999	0.985–1.127	0.857
Left pulmonary vein antrum	0.994	0.981–1.008	0.322
LAA ostium	1.021	1.003–1.039	0.019
Multivariate analysis			
LAA ostium	1.017	1.003–1.031	0.021

statistically significant. Statistical analysis was done using Software Package for Social Sciences (SPSS Inc., Chicago, Illinois) version 27.0.1.

Results

Baseline characteristics

The DECAAF II study included 843 patients. One hundred nine patients had inadequate MRI data and were excluded from this study. This study included 734 patients, and 333 (45.4%) of them achieved the primary outcome. The mean age of patients was 62.0 ± 9.0 years, and 78.2% of patients were males. At baseline, pre-ablation fibrosis percentage ranged from a minimum of 4.3% to a maximum of 37.6%, and had a mean of 18.6 ± 7.3%; 11.7% of patients had Utah Stage I fibrosis, 46.9% had Stage II, 32.7% had Stage III and 10% had Stage IV fibrosis. Age ($\beta = 0.13$, $P < 0.001$) and body mass index ($\beta = 0.09$, $P = 0.047$) were identified as significant predictors of baseline fibrosis. At baseline, 46.7% of patients were taking AADs, and 25.1% continued AADs through the 90-day blanking period post-ablation. Further description of baseline patient demographics can be found in *Table 1*.

Regional distribution of fibrosis

The mean fibrosis percentage prior to ablation was highest in the left PV antrum (29.30 ± 14.04%), followed by the lateral wall (23.23 ± 13.56%), and the posterior wall (19.80 ± 10.85%) (*Figure 2*). Time from first diagnosis with AF to CA and baseline AAD use did not significantly affect the distribution of fibrosis. There was no significant difference in the distribution of fibrosis between the two treatment arms. Further description of the regional distribution of fibrosis can be found in *Table 2* and *Figure 2*.

Effect of regional fibrosis on primary outcome

Univariate analysis showed that the pre-ablation regional fibrosis percentage of the LAA ostium affects the primary outcome {odds ratio [OR] = 1.021 [95% confidence interval (CI) 1.003–1.039], $P = 0.019$}. On multivariate analysis, the regional fibrosis percentage of the LAA ostium was predictive of the primary outcome [OR = 1.017 (CI 1.003–1.032), $P = 0.021$]. The rest of the results of the univariate and multivariate analyses of regional fibrosis percentages are shown in *Table 3*.

Effect of treatment randomization

In patients randomized to receive MRI-guided fibrosis ablation, multivariate analysis showed that the pre-ablation regional fibrosis percentage of the LAA ostium remains a significant predictor of the primary outcome [OR = 1.02 (95% CI 1.006–1.047), $P = 0.01$] (*Figure 3*), while the regional distribution of fibrosis does not affect the primary outcome in patients receiving standard PVI only. *Table 4* shows the results of the univariate and multivariate analyses stratified by the treatment randomization group.

Regional surface area percentages

The posterior wall had the highest pre-ablation surface area percentage of the LA wall (20.71 ± 3.50%), followed by the anterior wall (17.71 ± 2.53%). Further description of these parameters can be found in *Table 5*. Regional surface area distribution did not affect the primary outcome, and this was preserved when stratifying patients by treatment randomization (*Table 6*).

Discussion

In the present study, we confirmed the non-homogeneity of atrial remodelling and cardiomyopathy. Patterns of fibrosis variation between

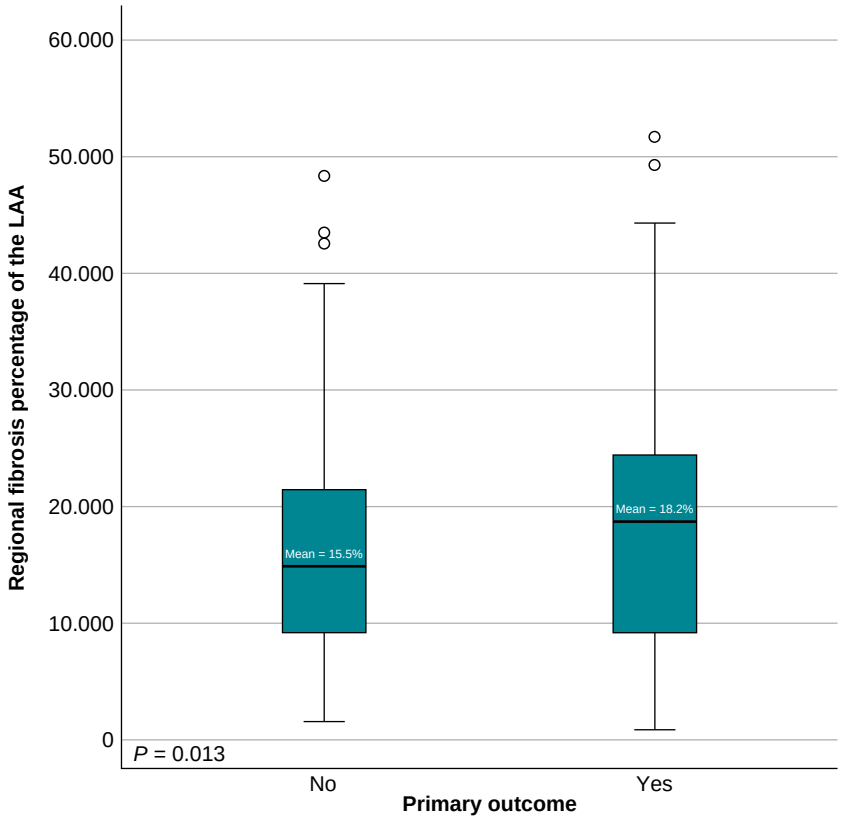


Figure 3 Difference in fibrosis percentage of the LAA in patients randomized to receive PVI + MRI-guided fibrosis ablation.

different LA wall regions in persistent AF patients were described using LGE-MRI. In addition, we demonstrated that pre-ablation fibrosis of the LAA is a positive predictor of AF recurrence after CA (*Figure 1*).

We have shown that the left PV antrum demonstrates a significant percentage of fibrosis when compared with the rest of the LA (*Figure 1*), followed by the lateral and posterior walls. Cochet *et al.*[18] have also used LGE-MRI to describe fibrosis distribution in 190 patients and showed that fibrosis was more commonly found below the left inferior PV ostium than in any other region of the LA. However, it must be noted that this study included AF and non-AF patients, whereas our study cohort consists of persistent AF patients only. These findings are supported by previous histologic findings by Hassink *et al.*,[19] who have exhibited greater amounts of fibrosis in the PV antra in AF patients than in non-AF patients. These findings may help explain the superiority of PVI as a treatment for patients with AF.[1]

While there is a paucity of data on regional LA wall fibrosis as detected by LGE-MRI, several studies have described it using electroanatomical voltage mapping (EAVM). A study by Teh *et al.*[20] reported that patients with persistent AF had more atrial fibrosis in the septum and the roof of the LA wall than in any other region. Meanwhile, Lin *et al.*[21] found more fibrosis in the anterior wall followed by the posterior wall in patients with persistent AF, and Chang *et al.*[22] found the low anteroseptal wall to have more fibrosis than any other region, followed by the right PV. While there is no consensus across these studies, it must be noted that none of these studies have used LGE-MRI to assess for fibrosis. The discrepancy in results between these studies may be due to different operator techniques, contact force, different catheters, or interelectrode spacing. While fibrosis assessment using LGE-MRI is associated with low-voltage areas on EAVM,[23] Sim *et al.*[24] showed the use of LGE-MRI to identify atrial fibrosis may be a better predictor of AF recurrence than EAVM. Therefore, evaluating the relationship between regional fibrosis patterns and AF recurrence after CA might be better using LGE-MRI.

The LAA is an important source of arrhythmogenic triggers in patients with persistent AF.[25] Electrical isolation of the LAA has been studied thoroughly, and the results are contradicting and non-confirmatory. A meta-analysis by AlTurki *et al.*[26] showed a significant reduction in AF recurrence in patients who underwent electrical isolation of the LAA in addition to PVI when compared with those who underwent PVI alone. On the other hand, a more recent meta-analysis by Wang *et al.* showed that the addition of LAA isolation to PVI does not provide incremental benefit with respect to freedom from atrial arrhythmia.

While the benefit of LAA isolation remains unclear, the LAA seems to be of a significant role in the prediction of CA ablation outcomes, and the extent of fibrosis in the LAA may be indicative of advanced atrial myopathy.[13] Our data show that a higher regional fibrosis percentage in the LAA, which may be indicative of advanced atrial myopathy,[13] significantly predicts AF recurrence post-ablation in patients with persistent AF undergoing MRI-guided fibrosis ablation in addition to standard PVI. This finding was not observed in the patients treated with PVI only.

The differential effect observed between the two treatment groups may be explained by the association of advanced atrial myopathy with less lesion formation during fibrosis-guided ablation, as shown in previous work by our group.[27] Therefore, patients with more preferential fibrosis of the LAA, indicating more advanced atrial myopathy, may derive less benefit from additional, fibrosis-guided ablation. These results

highlight the need for further investigation into the role of LAA fibrosis and its implications for treatment strategies in AF.

A recent meta-analysis has identified multiple structural and functional attributes of the LAA to be predictive of AF recurrence post-ablation, namely LAA volume, orifice area, orifice long/short axis, and volume index, as well as LAA emptying flow velocity, filling flow velocity and ejection fraction.[28] Pinto Teixeria *et al.* have also demonstrated that the volume of the LAA, as measured by computed tomography (CT) scanning, is a significant predictor of AF recurrence post-ablation in patients with paroxysmal or persistent AF.[29] Moreover, Istratoaie *et al.*[30] used echocardiography to demonstrate that a lower LAA emptying velocity predicts AF recurrence post-ablation in patients with paroxysmal AF. These studies, as well as our data, emphasize the predictive value intrinsic to the LAA as an indicator of advanced atrial cardiomyopathy.

The posterior wall of LA is considered an arrhythmogenic focus in patients with persistent AF. It has been postulated that posterior wall isolation (PWI) as an adjunct to standard PVI may improve outcomes. While multiple meta-analyses have confirmed the superiority of this approach in preventing AF recurrence in patients with persistent AF,[31–33] other studies found opposing results.[34,35] However, our data show that atrial fibrosis and dilation of the posterior wall do not predict AF recurrence after CA and may not explain why PWI decreases AF recurrence. This may mean that other factors specific to the posterior wall may be driving its arrhythmogenicity, and further studies on this matter are required.

There are several limitations to this study. First, only patients with persistent AF undergoing CA were included, which may be selected for patients with more advanced AF, and the effect of fibrosis regionality at earlier disease stages cannot be inferred from our data. Further studies should include other patient populations with and without AF to better understand the effect of the aforementioned factors on the

Table 4 Regional fibrosis percentages as predictors of the primary outcome, stratified by treatment randomization

LA wall region	Odds ratio	95% confidence interval	*P* value
Univariate analysis (PVI-only group)			
Anterior wall	1.008	0.988–1.028	0.45784617
Posterior wall	1.004	0.986–1.023	0.65882351
Lateral wall	1.011	0.996–1.026	0.16228285
Septal wall	1.005	0.986–1.025	0.60722093
Right pulmonary vein antrum	0.993	0.976–1.010	0.40868463
Left pulmonary vein antrum	0.992	0.977–1.006	0.2653776
LAA ostium	1.010	0.989–1.031	0.35281304
Univariate analysis (PVI + MRI-guided fibrosis ablation)			
Anterior wall	1.008	0.989–1.028	0.415
Posterior wall	1.006	0.987–1.026	0.554
Lateral wall	0.998	0.983–1.013	0.797
Septal wall	1.005	0.988–1.023	0.583
Right pulmonary vein antrum	1.009	0.991–1.027	0.344
Left pulmonary vein antrum	1.005	0.990–1.019	0.522
LAA ostium	1.026	1.006–1.048	0.013
Multivariate analysis (PVI + MRI-guided fibrosis ablation)			
LAA ostium	1.02643567	1.006–1.048	0.0135

Table 6 Regional surface area percentages as predictors of the primary outcome

LA wall region	Odds ratio	95% confidence interval	*P* value
Univariate analysis			
Anterior wall	0.886	0.135–5.831	0.900
Posterior wall	0.844	0.128–5.549	0.860
Lateral wall	0.854	0.130–5.616	0.870
Septal wall	0.888	0.135–5.841	0.961
Right pulmonary vein antrum	0.843	0.126–5.439	0.843
Left pulmonary vein antrum	0.797	0.121–5.244	0.813
LAA ostium	0.813	0.124–5.349	0.830

Table 5 Regional distribution of pre-ablation surface area percentages

LA wall region	All patients (mean ± SD)	Standard PVI group (mean ± SD)	MRI-guided fibrosis ablation (mean ± SD)	*P* value
Anterior wall	17.71 ± 2.53	17.8 ± 2.61	17.60 ± 2.61	0.411
Posterior wall	20.71 ± 3.50	20.61 ± 3.45	20.82 ± 3.54	0.432
Lateral wall	9.09 ± 2.21	9.11 ± 2.26	9.08 ± 2.17	0.861
Septal wall	12.04 ± 1.83	12.07 ± 1.82	12.01 ± 1.84	0.703
Right pulmonary vein antrum	17.05 ± 4.56	16.97 ± 4.65	17.13 ± 4.47	0.628
Left pulmonary vein antrum	10.74 ± 2.38	10.73 ± 2.47	10.75 ± 2.29	0.910
LAA ostium	12.69 ± 2.92	12.76 ± 3.10	12.61 ± 2.73	0.510

development as well as the recurrence of AF. Furthermore, the technique used to segment LA fibrosis is dependent upon operator experience, and the follow-up period was relatively limited. In addition, 109 patients in the DECAAF II cohort had suboptimal image quality that hindered the extraction of regional fibrosis patterns due to technical issues and thus were excluded from this study.

Conclusion

In summary, our study has provided new insights into the heterogeneous nature of atrial cardiomyopathy and remodelling. We found significant variations in the distribution of atrial fibrosis across different regions of the LA, with the left PV antral region showing a higher propensity for fibrosis. Furthermore, our results suggest that regional fibrosis in the LAA may be associated with AF recurrence after ablation, particularly in patients who received substrate modification. These findings underscore the importance of taking into account the regional heterogeneity of atrial remodelling in developing personalized treatment strategies for AF patients.

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Conflict of interest: N.M. reports having received consulting fees from Biosense Webster, as well as research funding from Abbot. N.M. also reports having a family member as the CEO of Cardiac Designs. N.M. also reports being the founder of MARREK, being named in a patent issued for MRI fibrosis imaging, and being a previous shareholder of Cardiac Designs. All other co-authors have no relevant conflict of interest.

Data availability

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

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