Original Investigation

Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation
The DECAAF Study

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IMPORTANCE Left atrial fibrosis is prominent in patients with atrial fibrillation (AF). Extensive atrial tissue fibrosis identified by delayed enhancement magnetic resonance imaging (MRI) has been associated with poor outcomes of AF catheter ablation.

OBJECTIVE To characterize the feasibility of atrial tissue fibrosis estimation by delayed enhancement MRI and its association with subsequent AF ablation outcome.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, prospective, observational cohort study of patients diagnosed with paroxysmal and persistent AF (undergoing their first catheter ablation) conducted between August 2010 and August 2011 at 15 centers in the United States, Europe, and Australia. Delayed enhancement MRI images were obtained up to 30 days before ablation.

MAIN OUTCOMES AND MEASURES Fibrosis quantification was performed at a core laboratory blinded to the participating center, ablation approach, and procedure outcome. Fibrosis blinded to the treating physicians was categorized as stage 1 (<10% of the atrial wall), 2 (≥10%-<20%), 3 (≥20%-<30%), and 4 (≥30%). Patients were followed up for recurrent arrhythmia per current guidelines using electrocardiography or ambulatory monitor recording and results were analyzed at a core laboratory. Cumulative incidence of recurrence was estimated by stage at days 325 and 475 after a 90-day blanking period (standard time allowed for arrhythmias related to ablation-induced inflammation to subside) and the risk of recurrence was estimated (adjusting for 10 demographic and clinical covariates).

RESULTS Atrial tissue fibrosis estimation by delayed enhancement MRI was successfully quantified in 272 of 329 enrolled patients (57 patients [17%] were excluded due to poor MRI quality). There were 260 patients who were followed up after the blanking period (mean [SD] age of 59.1 [10.7] years, 31.5% female, 64.6% with paroxysmal AF). For recurrent arrhythmia, the unadjusted overall hazard ratio per 1% increase in left atrial fibrosis was 1.06 (95% CI, 1.03-1.08; $P < .001$). Estimated unadjusted cumulative incidence of recurrent arrhythmia by day 325 for stage 1 fibrosis was 15.3% (95% CI, 7.6%-29.6%); stage 2, 32.6% (95% CI, 24.3%-42.9%); stage 3, 45.9% (95% CI, 35.5%-57.5%); and stage 4, 51.1% (95% CI, 32.8%-72.2%) and by day 475 was 15.3% (95% CI, 7.6%-29.6%), 35.8% (95% CI, 26.2%-47.6%), 45.9% (95% CI, 35.6%-57.5%), and 69.4% (95% CI, 48.6%-87.7%), respectively. Similar results were obtained after covariate adjustment. The addition of fibrosis to a recurrence prediction model that includes traditional clinical covariates resulted in an improved predictive accuracy with the C statistic increasing from 0.65 to 0.69 (risk difference of 0.05; 95% CI, 0.01-0.09).

CONCLUSIONS AND RELEVANCE Among patients with AF undergoing catheter ablation, atrial tissue fibrosis estimated by delayed enhancement MRI was independently associated with likelihood of recurrent arrhythmia. The clinical implications of this association warrant further investigation.

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Atrial tissue fibrosis affecting the left atrium is a major determinant of the progression of atrial fibrillation (AF)[1]; thus, a more extensively remodeled atrium represents the substrate needed for the arrhythmia to persist. A clear correlation has been shown between AF and the degree of atrial fibrosis in postmortem histological analysis.[2] Atrial fibrosis is also a major determinant for success of rhythm control strategies in AF,[3,4] including catheter ablation, one of the most efficacious methods to treat patients with AF.[5,6] However, this knowledge has never been incorporated into treatment plans for patients with different degrees of fibrosis.

Delayed enhancement magnetic resonance imaging (MRI) is an effective modality to identify fibrotic nonviable ventricular myocardium.[7-9] Delayed enhancement MRI has also been used in patients who have undergone ablation procedures[10,11] to assess for ablation-induced scarring in the left atrial wall. More recently, delayed enhancement MRI has been used to image the left atrium prior to AF ablation procedures to estimate the degree of atrial tissue fibrosis. Single-center studies have shown that extensive fibrosis of the left atrial wall quantified by delayed enhancement MRI is associated with recurrent arrhythmia following catheter ablation.[12,13] In this study, we hypothesized that atrial fibrosis estimation by delayed enhancement MRI is feasible in multiple centers, and that it is associated with ablation outcomes after adjusting for known covariates.

Methods

Study Design

Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF) is a multicenter, prospective, observational cohort study of patients with AF undergoing catheter ablation. All enrolled patients with history of AF and who were scheduled for their first ablation procedure underwent a delayed enhancement MRI scan of the left atrium. The data were deidentified and sent to a core processing facility with an image processing team blinded to the participating center, the ablation approach, and the procedure outcome. The participating centers were blinded to the delayed enhancement MRI quantification of atrial fibrosis and followed their routine protocol for ablation techniques and patient management. Patient follow-up data were collected for at least 1 year after the ablation procedure to assess for maintenance of sinus rhythm or recurrent arrhythmias.

Study Patients

Patients from 15 centers in 6 countries across 3 continents were enrolled in the DECAAF study. Patients were eligible if they were scheduled to undergo a first AF ablation procedure per the recent consensus recommendations.[14] All eligible patients underwent a delayed enhancement MRI scan before their ablation procedure. Key exclusion criteria were a contraindication for delayed enhancement MRI with a full dose of gadolinium-based contrast agent (with an estimated glomerular filtration rate ≥30 mL/min), a previous left atrial ablation or surgical procedure for the treatment of AF, and morbid obesity (body mass index >35 or inability to be placed in an MRI scanner due to body mass). The full list of inclusion and exclusion criteria appears in the Supplement. All patients provided written informed consent. The institutional review board or independent ethics committee at each participating clinical center approved the study.

Magnetic Resonance Imaging

The 15 participating centers from Europe (8 centers), the United States (6 centers), and Australia (1 center) had different degrees of expertise in cardiac MRI. Customized pulse sequences and imaging protocol for the atrial MRI (Marrek Inc) were installed on 18 Siemens MRI scanners (Siemens Healthcare). Nine centers used 1.5-Tesla scanners, 5 centers used 3-Tesla scanners, and 1 center used both 1.5- and 3-Tesla scanners. A detailed description of the atrial imaging protocol is provided in the Supplement (see Atrial MR Image Acquisition; eTable 1).

All patients underwent delayed enhancement MRI of the left atrium less than 30 days prior to the AF ablation procedure. The purpose of the MRI study for DECAAF was to quantify the degree of atrial fibrosis from delayed enhancement MRI; however, other MRI sequences (such as an MR angiogram) were available to provide anatomical guidance prior to and during the ablation procedure for mapping and image integration.

Delayed Enhancement MRI Assessment of Left Atrial Fibrosis

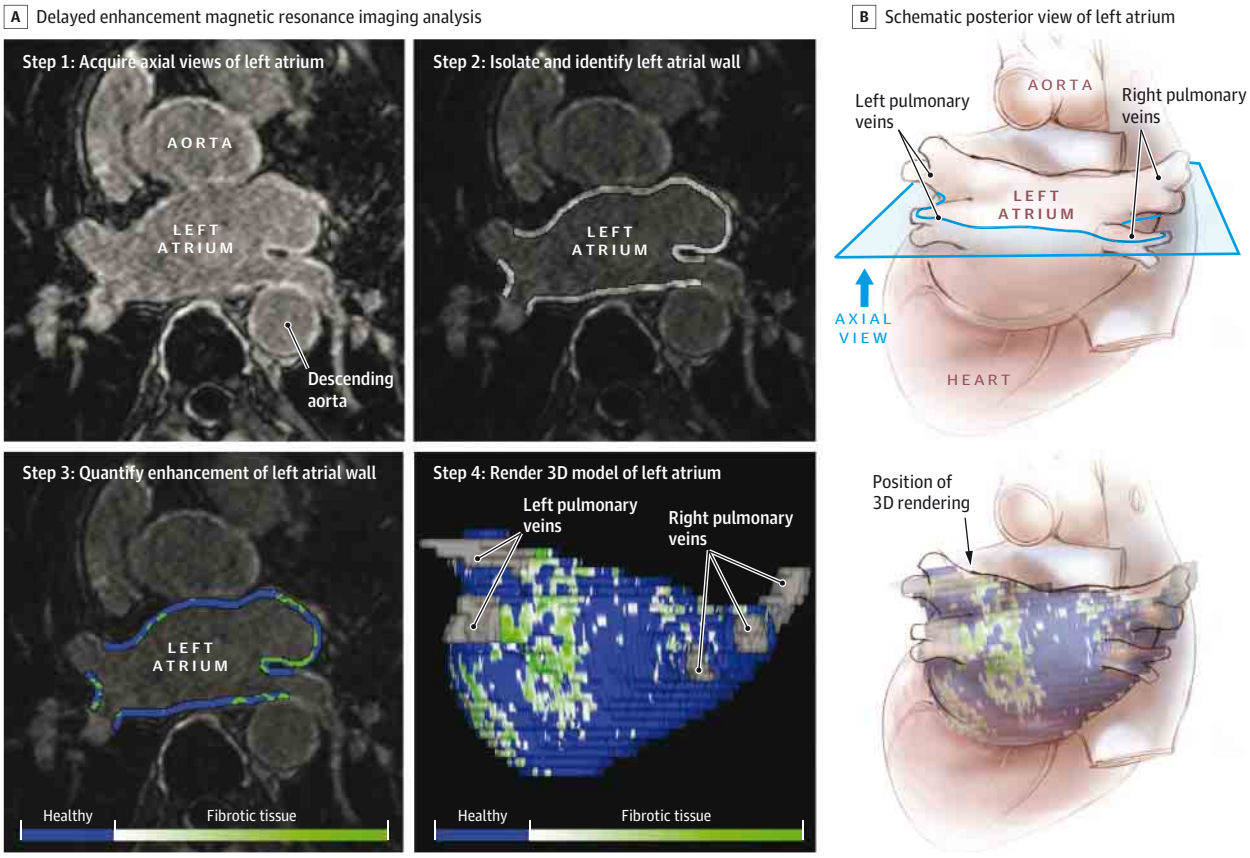
Quantification of left atrial fibrosis was obtained using the methods previously described.[12] To delineate regions of fibrosis in delayed enhancement MRI images prior to ablation, enhancement was defined by an intensity threshold that was determined by expert inspection. To assist in this process, initial visualization used a volume-rendering tool in Corview (Marrek) that allowed the distribution of enhancement in 3D. A custom transfer function allowed the definition of gradations of enhancement while suppressing blood and normal tissue. The image processing flow is illustrated in **Figure 1**. Patients were assigned to 1 of 4 groups (fibrosis stages 1-4) based on the volumetric percentage of left atrial wall enhancement as illustrated in **Figure 2**.

Clinical Follow-up

The participating centers were required to send patient data and deidentified MR images to the core center online. A website was specifically designed to accept all uploaded data, including baseline demographics and clinical comorbidities, follow-up information at the specified time points for clinic visits, and information from visits due to an event (http://www.decaaf.org). Unique patient identifiers were assigned for data tracking and analysis.

Procedural information, drug prescription, and electrocardiographic results (12-lead and ambulatory monitors) were collected at 3, 6, and 12 months after the procedure and at any time available thereafter. The electrocardiogram or ambulatory monitor recordings from clinical follow-up visits were sent to the core center for confirmation of the analysis and the out-

Figure 1. Process for Quantification of Left Atrial Wall Fibrosis



High-resolution 3D delayed enhancement magnetic resonance imaging (MRI) scans of the left atrium are acquired (step 1). Epicardial and endocardial borders are contoured in each MRI slice to define the left atrial wall segmented region (step 2). Wall segmentations include the 3D extent of both the left atrial wall and the antral regions of the pulmonary veins, but exclude the mitral valve. Quantification of fibrosis is based on relative intensity of contrast enhancement (step 3). The 3D model of the left atrium is rendered from the endocardial (left atrial cavity) and left atrial wall segmentations, and the maximum enhancement intensities are projected on the surface of the model (step 4). Interactive 3D model at jama.com.

comes were measured per the guidelines in the recent consensus document.[14] Any episode of AF, atrial flutter, or tachycardia lasting at least 30 seconds and occurring after the 90-day blanking period was classified as a recurrence.

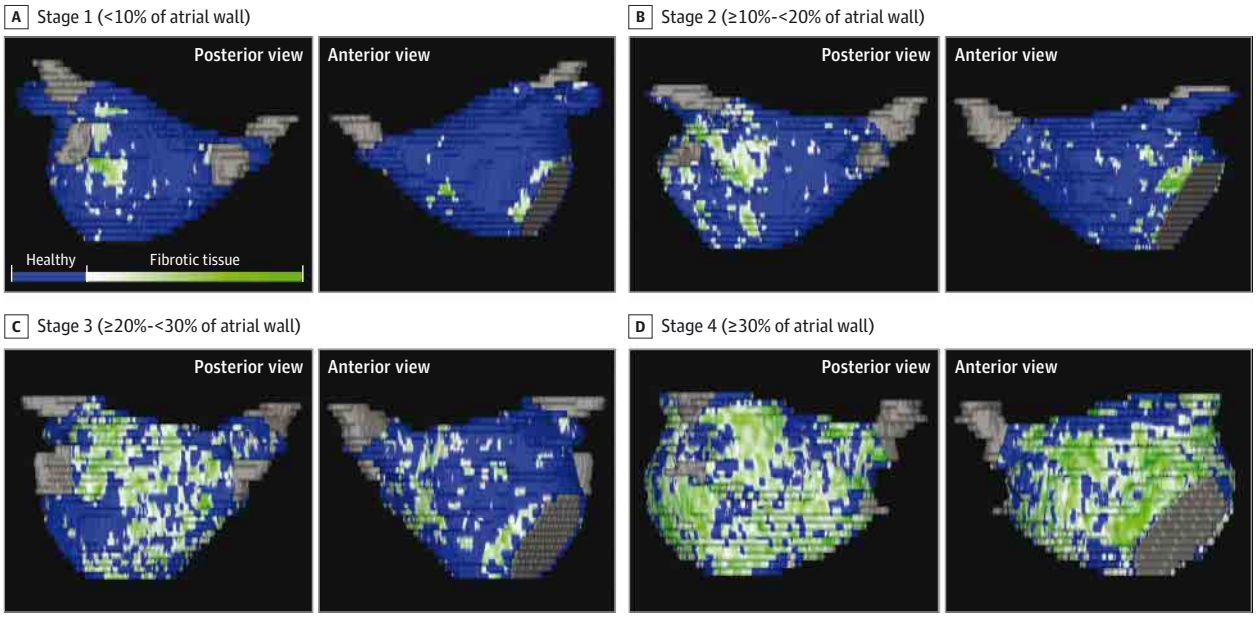
Statistical Methods

Baseline characteristics were summarized for 260 patients who were included in the prospective cohort study and for the 69 remaining enrolled participants who were not included in the prospective cohort using means and standard deviations for continuous variables and frequencies and percentages for categorical factors. Separate simple linear regression analyses were performed to relate fibrosis to individual demographic and clinical covariates. Time to AF recurrence was related to the individual demographic and clinical covariates using separate univariable Cox proportional hazard regression models.

Cox regression analyses were also performed to relate time to recurrence of arrhythmia to percent fibrosis without covariate adjustment (model 1) and again after adjusting for the following sets of covariates: clinical center (model 2), clinical center, age, and sex (model 3); clinical center, age, sex, hypertension, congestive heart failure, mitral valve disease, and diabetes status (model 4); and all covariates in model 4 plus AF type (paroxysmal or persistent), left atrial volume, and left ventricular ejection fraction (model 5). The Harrell concordance C statistic for survival outcomes was used to assess the increase in prognostic accuracy resulting from adding fibrosis to the Cox model with the final set of covariates.

To test whether the C statistics of 2 models were statistically significantly different, we used the bootstrap method to derive the standard error of the difference in the C statistics of the 2 models and used the normal z test to derive the P value. The proportionality assumption required by Cox regression was checked using Schoenfeld residual plots and linear proportionality tests.[15] Natural cubic splines with 3 knots were used to evaluate the shape of the relationship of the log-transformed hazard for AF recurrence with fibrosis, adjusting for the final set of covariates. Clinical centers with fewer than 20 patients in the United States and Europe were combined, leaving the 6 largest centers along with a combined US center with a total of 50 patients and a combined European center with 30 patients.

Figure 2. Four Stages of Left Atrial Tissue Fibrosis Based on 3D Delayed Enhancement Magnetic Resonance Imaging Scans



Representative example from 4 different patients of each stage of left atrial tissue fibrosis. Normal left atrial wall is displayed in blue; fibrotic changes are in green and white. Stages 1 through 4 show increasing amounts of fibrosis as a percentage of the total left atrial wall volume. The pulmonary veins and mitral valve are shown in gray.

The completion of the blanking period (ie, 90 days after ablation) was defined as time zero for all analyses of time to recurrence per the consensus statement.[14] The primary analyses of time to recurrence administratively censored follow-up at day 325 or at the date of last contact for those patients who were lost to follow-up prior to day 325. The above analyses were repeated using each patient's complete follow-up period, including any additional follow-up time after day 325. We also estimated the absolute risk of recurrence for the 4 Utah fibrosis stages (defined in the Results section) at days 325 and 475 after the blanking period. The unadjusted risks were estimated using the Kaplan-Meier estimator with 95% confidence intervals computed on the log-log scale.

The adjusted risks were estimated from a Cox proportional hazard model controlling for covariates defined in model 5. We used the Breslow estimator to obtain the baseline hazards under the Cox model. Relationships were designated as statistically significant if the 2-sided *P* value was less than .05 without adjustment for multiple comparisons. We used SAS version 9.3 (SAS Institute Inc), Stata version 11 (StataCorp), and R version 2.11.1 (R Project for Statistical Computing) to perform all statistical analyses.

Results

Baseline Characteristics and Ablation

There were 329 patients enrolled in the DECAAF study between August 2010 and August 2011. Fifty-seven patients (17.3%) were excluded due to poor MRI quality by consensus of 3 observers from the core center. Atrial wall fibrosis was quantified for 272 patients who had preablation delayed enhancement MR images of acceptable quality. We lost contact with 12 of these 272 patients during the blanking period. Thus, 260 were included in the final cohort for analysis. The mean (SD) follow-up time prior to day 325 after the blanking period was 213 (120) days and the total follow-up time was 255 (178) days.

Table 1 summarizes demographic and clinical characteristics of this final cohort (n = 260) and of the remaining 69 enrolled patients who were excluded from the final cohort. Notable characteristics of the prospective cohort included a mean (SD) patient age of 59.1 (10.7) years with a male majority (68.5%); 64.6% had paroxysmal AF and 63.9% received antiarrhythmic treatment prior to ablation. Ten percent of patients had a history of coronary artery disease, whereas the prevalence was 5% for congestive heart failure and 11% for diabetes.

The patients underwent ablation per their institutional protocols. Of the final cohort, 16 patients underwent cryoballoon ablation (6.2%), and the remainder underwent radiofrequency ablation. There were 177 patients (68.1%) who underwent pulmonary vein isolation alone. Forty-three patients (16.5%) underwent cavotricuspid isthmus and pulmonary vein isolation ablation. The ablation procedures performed on the patient cohort are summarized in eTable 2 in the Supplement. At 12 months postablation, 53 of 213 patients (24.9%) were receiving a class 1 or 3 antiarrhythmic drug.

Complications

There were complications observed in 5% of the analyzed cohort with 6 reported cases of cardiac tamponade, 1 case of pulmonary vein narrowing, 1 case of esophageal injury, 1 case of

Table 1. Demographic and Clinical Characteristics of Patients Included or Excluded From the Final Cohort

	No. (%) of Patients in Final Cohort	
	Included (n = 260)	Excluded (n = 69)
Sex		
Male	178 (68.5)	51 (73.9)
Female	82 (31.5)	18 (26.1)
AF type[a]		
Paroxysmal	168 (64.6)	36 (52.2)
Persistent	75 (28.8)	28 (40.6)
Permanent	17 (6.5)	3 (4.3)
Missing	0	2 (2.9)
Paroxysmal AF by fibrosis stage[b]		
1	49 (18.8)	
2	107 (41.2)	
3	80 (30.8)	
4	24 (9.2)	
Coronary artery disease	26 (10.0)	4 (5.8)
Myocardial infarction	9 (3.5)	1 (1.5)
Tobacco use	23 (8.9)	5 (7.3)
Mitral valve disease	14 (5.4)	4 (5.8)
Hyperlipidemia	78 (30.0)	23 (33.3)
$CHADS_2$		
Congestive heart failure	15 (5.8)	2 (2.9)
Age >75 y	13 (5.0)	1 (1.5)
Hypertension (>160 mm Hg)	143 (55.0)	43 (62.3)
Diabetes mellitus	32 (12.3)	12 (17.4)
Prior stroke or TIA	13 (5.0)	6 (8.7)
Preablation antiarrhythmic drug therapy	166 (63.9)	39 (56.5)

Abbreviations: AF, atrial fibrillation; TIA, transient ischemic attack.

[a] Paroxysmal defined as recurrent AF (≥2 episodes) that terminates spontaneously within 7 days; persistent, recurrent AF that is sustained for more than 7 days; permanent (or longstanding persistent AF), continuous AF lasting longer than 1 year.[14]

[b] Stage 1 defined as fibrosis of less than 10% of the atrial wall; stage 2, 10% or greater fibrosis but less than 20%; stage 3, 20% or greater fibrosis but less than 30%; stage 4, fibrosis of 30% or greater.

femoral hematoma, and 4 cases of femoral arterial-venous fistula. All the patients who experienced complications had recovered without long-term sequelae at the conclusion of the study.

Imaging and Baseline Characteristics

The MRI data were analyzed at the core laboratory for image quality and for quantification of atrial fibrosis. Based on the degree of detected fibrosis from delayed enhancement MRI, 4 stages were defined: stage 1, less than 10% of the atrial wall; stage 2, 10% or greater but less than 20%; stage 3, 20% or greater but less than 30%; and stage 4, 30% or greater. There were 49 patients in stage 1 (18.9%), 107 in stage 2 (41.2%), 80 in stage 3 (30.8%), and 24 in stage 4 (9.2%).

The percentage of patients with paroxysmal AF was 65.3% for stage 1, 63.6% for stage 2, 61.3% for stage 3, and 79.2% for stage 4. The selected patient baseline characteristics for each of the fibrosis disease stages are described in eTable 3 in the Supplement. The bivariate analyses relating fibrosis to the background covariates revealed that the only factor with a statistically significant association with the amount of atrial fibrosis was a history of hypertension (eTable 4 in the Supplement).

Arrhythmia Recurrence Analysis

The hazard ratios (HRs) relating time of arrhythmia recurrence to individual demographic and clinical factors are reported in **Table 2**. Among these factors, only percent atrial fibrosis and history of mitral valve disease (reported cases of history of mitral valve disease were mainly mitral valve insufficiency of ≥2 or moderate severity, except 1 reported case of mitral and tricuspid repair due to mitral valve prolapse) had statistically significant associations with arrhythmia recurrence. For a 1% increase in atrial fibrosis, the HR was 1.06 (95% CI, 1.03-1.08; $P < .001$) compared with patients without a mitral valve disease history. The comparison of those with mitral valve disease history yielded an HR of 3.45 (95% CI, 1.78-6.68; $P < .001$).

The percent atrial fibrosis was strongly associated with arrhythmia recurrence when age, sex, hypertension, congestive heart failure, mitral valve disease, diabetes, type of atrial fibrillation (paroxysmal vs persistent), left atrial volume, left ventricular ejection fraction, and participating center were adjusted for (model 5 in eTable 5 in the Supplement). The overall HR was 1.06 (95% CI, 1.03-1.09; $P < .001$) per 1% increase in atrial fibrosis. **Figure 3** depicts the relationship of AF recurrence with percent fibrosis based on the cubic spline model after controlling for the covariates in model 5.

The relationship was significantly stronger at lower compared with higher levels of fibrosis (test of nonlinearity $P = .03$), with the estimated HR per 1% increase in fibrosis decreasing from 1.15 (95% CI, 1.06-1.25) when fibrosis was 10% of the atrial wall to 1.02 (95% CI, 0.97-1.06) when fibrosis was 30%. The Harrell C statistic characterizing the discrimination of time to AF recurrence at 325 days by fibrosis was 0.65 when atrial fibrosis was considered as a single factor; however, adding fibrosis to the covariates in model 5 increased the C statistic from 0.65 to 0.69. The difference between these 2 C statistics was 0.05 (95% CI, 0.01-0.09). A similar result was found for the entire follow-up period. The C statistic characterizing discrimination of time to AF recurrence for the entire follow-up was 0.65 when atrial fibrosis was considered as a single factor. The addition of fibrosis to a recurrence prediction model (model 5) that includes traditional clinical covariates resulted in an improved predictive accuracy with the C statistic increasing from 0.64 to 0.69 with a risk difference of 0.05 (95% CI, 0.01-0.09).

Table 3 provides estimates of the absolute risks of arrhythmia recurrence by stage at days 325 and 475 with and without adjustment for the covariates in model 5. The estimated unadjusted cumulative incidence of recurrent arrhythmia by day 325 for stage 1 fibrosis was 15.3% (95% CI, 7.6%-29.6%); stage 2, 32.6% (95% CI, 24.3%-42.9%); stage 3, 45.9% (95% CI, 35.5%-57.5%); and stage 4, 51.1% (95% CI, 32.8%-72.2%) and by day 475 was 15.3% (95% CI, 7.6%-29.6%), 35.8% (95% CI, 26.2%-47.6%), 45.9% (95% CI, 35.6%-57.5%), and 69.4% (95% CI,

48.6%-87.7%), respectively. **Figure 4** depicts the Kaplan-Meier cumulative incidence of arrhythmia recurrence over the follow-up period through 475 days after the blanking period.

Discussion

In the DECAAF multicenter, prospective, observational cohort study, noninvasive evaluation of left atrial fibrosis using delayed enhancement MRI was independently associated with procedural outcomes in patients undergoing AF ablation after accounting for known baseline covariates. A statistically significant association between atrial fibrosis and history of hypertension was also shown. The results from DECAAF were obtained in a setting in which left atrial fibrosis was quantified using 3D delayed enhancement MRI from separate clinical practices around the world and in which different ablation approaches were used.

To our knowledge, this study is the first multicenter study to demonstrate the feasibility and potential clinical value of delayed enhancement MRI in the management of patients with AF considered for ablation. In current practice, criteria for selecting good candidates for AF ablation are limited. This study contributes to the wide range of procedure success rates reported.[14] Because essentially all patients in the study population would be expected to have recurrent arrhythmia without ablation treatment, the large variation in estimated recurrence probabilities between stages (ranging from 15.3% for stage 1 to 69.4% for stage 4 at day 475; Table 3) can be interpreted as characterizing a corresponding dependence in the probability of ablation treatment failure on fibrosis. Hence, the degree of left atrial wall fibrosis estimated by delayed enhancement MRI has the potential to offer a noninvasive and effective method in determining which patients with AF are likely to benefit from ablation while avoiding performing procedures in patients likely to have arrhythmia recurrence.

The addition of atrial fibrosis to the arrhythmia recurrence prediction model resulted in a statistically significant increase in the C statistic compared with a traditional risk factor model. The C statistic value of the model including fibrosis (0.69) closely approached 0.70, which is the traditional cutoff value used in statistical models.

Atrial Fibrosis and AF

Atrial fibrotic disease and AF are intertwined. Data from animal models and human studies show that AF leads to atrial fibrosis.[4,16] It is also known that atrial fibrosis is essential to perpetuate atrial arrhythmias and leads to increased AF burden as demonstrated in studies performed in experimental models.[17,18]

The relationship between atrial fibrotic changes and AF has recently been demonstrated in postmortem and open-heart surgery histological analyses obtained from surgical specimens.[19,20] In these studies, the authors showed that atrial tissue disease and fibrosis assessed from biopsy obtained during open-heart surgery predicted postoperative AF recurrence. Postmortem analysis of atrial tissue demonstrated a correlation between atrial fibrosis and a history of AF. In the same study, authors also demonstrated lack of significant fibrosis in control patients of similar age with no history of AF. Previous retrospective analyses using delayed enhancement MRI to assess the degree of atrial disease based on fibrotic changes confirmed these findings. These analyses also showed that every patient with AF possesses some degree of atrial fibrotic changes that varies between minimal and severe or extensive,[12,13] including patients with lone AF.[21] DECAAF confirmed these findings in a multicenter, prospective study.

The relationship between high blood pressure and AF is well described.[22,23] Systemic hypertension can lead to atrial pressure and volume overload and subsequent atrial tissue

Table 2. Individual Demographic and Clinical Factors Related to Arrhythmia Recurrence

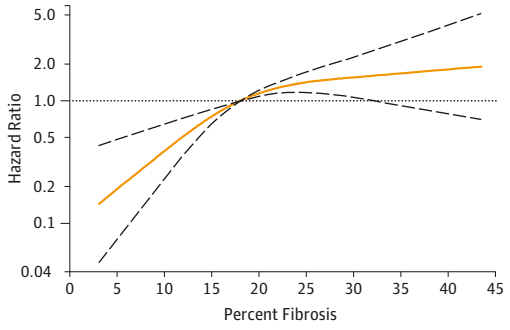
	Hazard Ratio (95% CI)[a]	*P* Value
Female sex	1.46 (0.95-2.25)	.08
Age at ablation per 10 y	1.05 (0.86-1.28)	.61
AF type[b]	1.22 (0.80-1.88)	.36
Initial body mass index, per unit	1.03 (0.99-1.08)	.11
History		
Coronary artery disease	1.24 (0.64-2.39)	.53
Congestive heart failure	1.45 (0.63-3.33)	.37
Diabetes mellitus	1.24 (0.64-2.39)	.53
Tobacco use	1.24 (0.64-2.39)	.53
Mitral valve disease	3.45 (1.78-6.68)	<.001
Hyperlipidemia	1.01 (0.64-1.58)	.98
Stroke	0.81 (0.26-2.57)	.73
$CHADS_2$ score		
1 vs 0	1.13 (0.70-1.82)	.63
2 vs 0	1.17 (0.63-2.17)	.62
3 vs 0	1.27 (0.39-4.15)	.69
4 vs 0	2.83 (0.86-9.26)	.09
Congestive heart failure	0.82 (0.30-2.24)	.70
Age >75 y	1.19 (0.48-2.93)	.71
Hypertension (>160 mm Hg)	1.36 (0.88-2.09)	.16
Diabetes mellitus	1.33 (0.72-2.44)	.37
Prior stroke or TIA	1.19 (0.48-2.92)	.71
Antiarrhythmic drug therapy	0.87 (0.56-1.33)	.51
Left atrial volume (per 10 mL)	1.05 (1.00-1.09)	.05
LVEF per 1%	1.02 (0.99-1.05)	.16
Catheter type		
Radiofrequency	1 [Reference]	.73
Cryo	0.85 (0.35-2.10)	
Ablation type		
Pulmonary vein isolation	1 [Reference]	.57
Other	1.14 (0.73-1.77)	
Arrhythmia recurrence per 1% increase in left atrial fibrosis	1.06 (1.03-1.08)	<.001

Abbreviations: LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

[a] The hazard ratios relate to the time of atrial fibrillation recurrence by day 325, individual demographic and clinical factors, and percent fibrosis based on separate univariable Cox regression analyses.

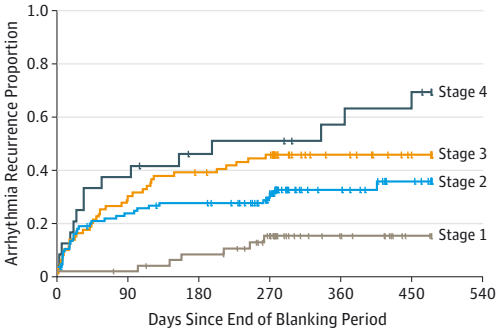
[b] Persistent or permanent vs paroxysmal.

Figure 3. Relationship of Atrial Fibrillation Recurrence With Percent Fibrosis



Adjusted for age, sex, hypertension, congestive heart failure, mitral valve disease, diabetes, atrial fibrillation type (paroxysmal or persistent), left atrial volume, left ventricular ejection fraction, and participating center (model 5) based on a cubic spline analysis with follow-up censored at day 325 after the blanking period. The strength of the association was greater at lower levels of fibrosis than at higher levels (P = .03 for test of nonlinearity). Blue dashed lines indicate 95% CI.

Figure 4. Cumulative Incidence of Arrhythmia Recurrence Without Covariate Adjustment Through Day 475 After the Blanking Period



No. at risk

Stage 4	24	15	11	10	7	6
Stage 3	80	56	47	41	19	12
Stage 2	107	79	74	58	26	15
Stage 1	49	47	43	33	13	4

Small vertical ticks on curves indicate where a patient's follow-up has completed without recurrent atrial fibrillation.

Table 3. Absolute Arrhythmia Risk at 325 and 475 Days After Blanking Period

Stage	Absolute Risk (95% CI) by No. of Days After 90-d Blanking Period: 325 d	475 d
Without covariate adjustment[a]		
1	0.15 (0.08-0.30)	0.15 (0.08-0.30)
2	0.33 (0.24-0.43)	0.36 (0.26-0.48)
3	0.46 (0.36-0.58)	0.46 (0.36-0.58)
4	0.51 (0.33-0.72)	0.69 (0.49-0.88)
With covariate adjustment[b]		
1	0.12 (0.03-0.21)	0.14 (0.03-0.23)
2	0.31 (0.21-0.39)	0.36 (0.25-0.48)
3	0.45 (0.33-0.55)	0.49 (0.35-0.60)
4	0.55 (0.28-0.71)	0.65 (0.39-0.80)

[a] The absolute risk was calculated using the Kaplan-Meier method and the 95% confidence interval was based on survival estimate at the log-log scale.

[b] The absolute risk was calculated based on the Cox proportional hazard model and baseline hazard was obtained using the Breslow estimator. All covariates in model 5 (see Statistical Methods section of text for definition of model 5) were used for the adjustment. Mean values for each of the covariates were used to calculate adjusted absolute risks.

change. In DECAAF, hypertension was the only baseline factor associated with atrial fibrosis in patients with AF. None of the known AF risk factors, including the composite $CHADS_2$ score, predicted fibrosis burden. This possibly could be accounted for by the relatively younger AF patient population enrolled in DECAAF (mean [SD] age, 59.1 [10.7] years) and the low prevalence of significant comorbidities in these patients. Nevertheless, the DECAAF population seems to be representative of the AF ablation population.[24,25]

Current clinical practice evaluates AF using a classification system that describes the pattern of arrhythmia and need for treatment, including electrical and chemical cardioversion.[14] Patient comorbidities including echocardiographic evaluation of atrial size and ventricular function also play a role in formulating an overall prediction in response to treatment.[26,27] It was recently demonstrated that AF clinical phenotype and AF-related fibrotic changes or atrial disease progression are not interchangeable or equivalent. For example, patients with a short known history of paroxysmal AF could have extensive atrial fibrosis and conversely patients diagnosed with persistent AF for many years could have a minimal amount of fibrosis. Until data from recent publications[12,13] became available, there was no insight into the underlying atrial fibrosis associated with different phenotypes of AF. The weak correlation between the temporal pattern of AF and degree of fibrosis was confirmed in DECAAF.

Ablation Outcome for AF

Since the introduction of catheter ablation as a viable treatment option for AF more than a decade ago, reported long-term procedural success in suppressing AF has ranged between 20% and 50%.[14] Although both procedure time and safety have improved substantially, the success rate has not seen a concomitant meaningful improvement despite significant advancement in the technology used in the ablation procedure.[28] Another major challenge facing the AF ablation approach is the need for repeat ablations,[14,29] with some patients requiring up to 4 interventional procedures to achieve suppression of recurrent arrhythmias.[30] In a prospective, randomized, multicenter study comparing ablation with antiarrhythmic drug therapy, it was demonstrated that 66% of patients had better health outcomes due to ablative treatment of paroxysmal AF after 9 months of follow-up.[31] Most of the published ablation studies, similar to this one, are short-term (≤1 year) follow-up reports.[32,33] Longer follow-up suggests a lower success rate.[34,35]

A recent report[19] described the effect of atrial fibrosis on surgical AF ablation outcome in an open-heart surgery

patient series. Kainuma et al[19] described a correlation between procedural failures and progressive atrial disease and fibrosis evaluated from biopsies taken during surgery. These and other studies highlight the fact that ablation therapy may not be the optimal treatment option for all AF patients. Therefore, it would be clinically useful if patients likely to respond could be identified and selected for ablation while other patients not likely to respond to ablation could be counseled against this procedure. The DECAAF study demonstrates the feasibility and potential clinical value of such a concept by evaluating atrial fibrosis noninvasively using MRI prior to the ablation procedure in a multicenter setting.

The consensus document[14] published in 2012 did not dictate a specific energy source or ablation approach to treat AF; the decision is left to the discretion of the physician performing the procedure. The same model was adopted for DECAAF. Despite the various ablation approaches and energy sources applied in the DECAAF study population, atrial fibrosis remained associated with procedural outcome. The feasibility of implementing delayed enhancement MRI screening to detect left atrial fibrosis into clinical practice could potentially improve patient selection for AF ablation and could translate into cost-savings by avoiding unnecessary AF ablation procedures.[36] Individualizing the type of invasive treatment for AF based on the association between fibrosis and arrhythmia recurrence merit further investigation in future studies aimed at demonstrating that exclusion of patients with extensive fibrosis leads to improved procedural outcomes.

Study Limitations

The exclusion of 17.3% (n = 57 patients) of the initial cohort was attributed to poor quality of delayed enhancement MR images due to varying levels of cardiac MRI expertise at the participating centers. Upon further analysis of the nondiagnostic images, it was found that 63.2% (n = 36) of the poor quality images were due to MRI technologist error, 29.8% (n = 17) were related to individual patients (arrhythmia, fast heart rate [>120 beats/min]), irregular respiration, and high body mass index), and the remaining 7.0% (n = 4) were due to hardware limitations. Knowing these reasons for poor image quality could help to improve image acquisition in future studies. Although the study demonstrated an association between atrial fibrosis and arrhythmia recurrence following ablation, it did not provide evidence of an effect of testing on clinical outcomes.

Conclusions

The DECAAF multicenter, prospective study demonstrated that among patients with atrial fibrillation undergoing catheter ablation, atrial fibrosis estimated by delayed enhancement MRI was independently associated with likelihood of recurrent arrhythmia. The clinical implications of this association warrant further investigation.

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