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Lesion delivery and scar formation in catheter ablation for atrial fibrillation: The DECAAF II trial

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ABSTRACT

BACKGROUND The Efficacy of Delayed Enhancement MRI-Guided Fibrosis Ablation vs Conventional Catheter Ablation of Atrial Fibrillation randomized trial showed no difference in atrial fibrillation (AF) recurrence with additional delayed enhancement magnetic resonance imaging (DE-MRI) fibrosis-targeted ablation to pulmonary vein isolation (PVI) in persistent AF.

OBJECTIVE We evaluated the effect of lesion delivery on ablation-induced scarring and AF recurrence.

METHODS Lesions delivered, targeting fibrotic and nonfibrotic areas identified from preablation DE-MRI, were studied in relation to ablation-induced scarring on 3-month DE-MRI, including their association with arrhythmia recurrence.

RESULTS A total of 593 patients treated with radiofrequency were analyzed: 293 (49.4%) underwent PVI and 300 (50.6%) underwent additional fibrosis-guided ablation. Lesion analysis showed that 80.9% in the MRI fibrosis-guided group vs 16.5% in the PVI group ($P < .001$) had ≥40% of baseline fibrosis targeted. MRI assessment of ablation-induced scar showed that 44.8% of fibrosis-guided ablation and 15.5% of PVI had ≥40% of their fibrosis covered by scar ($P < .001$), demonstrating significant attenuation from lesions delivered to scar formed. In the overall population, fibrosis coverage with scar was not associated with recurrence (hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.80–1.01; $P = .08$ per 20% increase). In patients with baseline fibrosis < 20%, fibrosis coverage with scar was associated with lower recurrence than PVI (HR 0.85; 95% CI 0.73–0.97; $P = .03$), whereas the association was not significant when baseline fibrosis ≥ 20% (HR 0.97; 95% CI 0.80–1.17; $P = .77$). Significant center variation was observed in fibrosis targeting and coverage with scarring.

CONCLUSION Radiofrequency ablation lesions do not uniformly result in scar formation. A post hoc analysis suggests reduced arrhythmia recurrence when ablation-induced scarring covers fibrotic regions in patients with low baseline fibrosis.

KEYWORDS Atrial fibrillation; Cardiac magnetic resonance imaging; Catheter ablation; Atrial fibrosis; Lesion delivery

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Introduction

Catheter ablation outcomes in persistent atrial fibrillation (AF) are modest despite numerous approaches to ablation.[1] Pulmonary vein isolation (PVI) remains the most consistent approach for persistent AF, and clinical trials have demonstrated that additional ablation beyond PVI, such as linear left atrial ablation, electrogram-based targeting of abnormal fractionated signals, and processed electrogram signals to identify and target focal or rotational activity, did not yield a significant improvement in arrhythmia-free outcomes.[2–5]

These results notwithstanding, the role of the atrial substrate in the pathophysiology of persistent AF is widely recognized,[6] with atrial fibrosis quantified using delayed enhancement magnetic resonance imaging (DE-MRI) identifying patients not likely to respond to ablation therapy.[7]

Substrate modification, in addition to PVI, based on DE-MRI fibrosis ablation was recently investigated in the Efficacy of Delayed Enhancement MRI-Guided Fibrosis Ablation vs Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II) clinical trial.[8] The results of this large randomized prospective ablation trial demonstrated that, similar to other approaches for substrate modification, targeting atrial fibrosis detected on DE-MRI was not superior to PVI alone in decreasing atrial arrhythmia recurrence in persistent AF.[8]

A systematic approach to identify the contributing factors to the underwhelming results of catheter ablation in persistent AF is needed. The DECAAF II trial protocol included a systematic collection of electroanatomic maps demonstrating lesions delivered, as well as second DE-MRI, 3 months after ablation, to assess the extent of ablation-induced scarring. In this article, we took this unique opportunity to dissect the relation of delivered ablation and durable scar formation, their relation to preexisting fibrosis, and associations with catheter ablation outcomes.

Methods

Study design

This is a secondary analysis of the DECAAF II randomized prospective clinical trial (ClinicalTrials.gov identifier NCT02529319), which enrolled 843 patients with persistent AF who underwent their first catheter ablation from July 2014 through January 2020. Patients were randomized to undergo ablation targeting left atrial fibrosis detected on DE-MRI in addition to PVI as compared to conventional PVI alone. A computerized central randomization design was generated and stratified according to center and level of atrial fibrosis at baseline (fibrosis <20% and ≥20%). Patients were followed for 12–18 months after randomization and underwent a second DE-MRI scan at 3 months after ablation for evaluation of ablation-induced scarring. The trial rationale, design, and protocol have been described previously.[9] The study protocol was approved by the institutional committee on human research at the investigators' respective institutions. The primary end point of the trial was occurrence of atrial arrhythmia lasting at least 30 seconds after observing a 90-day blanking period. The outcomes of interest in this analysis are the evaluation of ablation-induced scarring and the association between delivered ablation lesions and arrhythmia recurrence.

Abbreviations

AF: atrial fibrillation

CI: confidence interval

DECAAF II: Efficacy of Delayed Enhancement MRI-Guided Fibrosis Ablation vs Conventional Catheter Ablation of Atrial Fibrillation

DE-MRI: delayed enhancement magnetic resonance imaging

HR: hazard ratio

PVI: pulmonary vein isolation

Imaging

All patients underwent baseline DE-MRI to quantify preablation left atrial fibrosis within 30 days of the ablation procedure using previously described protocols. DE-MRI images were also obtained at 3 months after ablation to detect and quantify ablation-induced scarring. Image processing of baseline (fibrosis) and 3-month (scarring) MRI images was done with Merisight (Marrek Inc., Salt Lake City, UT). Of note, fibrosis quantification was derived only from baseline imaging and not postablation imaging, as the threshold for ablation-induced scarring assessment is typically higher than that used for preablation native fibrosis because of the known hyperenhancement of ablated tissue in the 3-month period between the scans.[10] Image processors were blinded to ablation randomization.

Catheter ablation

For patients randomized to the fibrosis-guided ablation group, processed 3-dimensional images obtained using DE-MRI were used during the procedure by merging and registration with virtual geometries of the left atrium obtained from electroanatomic mapping systems. All patients underwent PVI with either cryoballoon or radiofrequency ablation. After PVI had been confirmed, additional ablation was pursued in patients randomized to undergo fibrosis-guided ablation, where the operator either encircled or overlapped all fibrotic lesions observed on DE-MRI. Cardioversion was performed at the end of ablation to restore sinus rhythm as needed.

Evaluation of fibrosis targeting and scar coverage

Delivered lesion distribution in patients undergoing radiofrequency ablation for PVI or fibrosis-guided ablation was exported for analysis from the electroanatomic mapping systems. Patients undergoing cryoballoon ablation were excluded from this analysis because of the lack of a standardized electroanatomic method of tracking the cryoballoon location and delivered freezes. Therefore, the analysis and results discussed below focus on ablation lesions delivered, ablation-induced scar, and arrhythmia recurrence in patients treated using radiofrequency ablation.

Left atrial ablation lesions collected from electroanatomic maps were superimposed on 3-dimensional left atrial MRI images of fibrosis. The ablation lesion size was set at 2 mm. *Targeted* fibrosis represented baseline fibrosis that was overlapped or encircled by ablation lesions delivered during

the ablation procedure. *Scar-covered* fibrosis was determined on the basis of ablation-induced scar, which overlapped or encircled baseline fibrosis, when superimposing the 3-month DE-MRI image on the baseline DE-MRI image (Figure 1). We analyzed image-processing computed percentage of the overlap between baseline fibrosis and ablation lesions, as well as ablation-induced scar. In addition, 5 independent reviewers were trained to classify the amount of fibrosis that was targeted (based on ablation point maps) and covered with scar (based on 3-month MRI) on a 5-level scale (level 1: <20% of fibrosis targeted/scar covered or encircled; level 2: 20%–40%; level 3: 40%–60%; level 4: 60%–80%; level 5: >80%). For encirclement, the presence of any visible gap >1.4 mm was considered not encircled.[11] This scale was not prespecified in the original trial protocol and was used to provide a graded assessment of fibrosis encirclement, targeting, and coverage. Reviewers were blinded to treatment assignment.

Statistical analysis

The clinical end point of the study was the first confirmed recurrence of atrial arrhythmia (AA) (including AF, atrial flutter, or atrial tachycardia) lasting for at least 30 seconds, after observing a 90-day blanking period, and demonstrated by at least 2 smartphone electrocardiographic device tracings, or 1 positive reading on a clinical electrocardiographic tracing, ambulatory monitor, or if the patient underwent repeat ablation. The analyses in this report considered 3 different measures of achievement of the intended therapy:

1. The raw percentage of fibrosis covered and computed automatically from MRI image processing.
2. Mean *level of fibrosis targeted*: This is the mean across raters of the 5-level scale for fibrosis targeted, as indicated by baseline MRI.
3. Mean *level of fibrosis covered*: This is the mean across raters of the 5-level scale for fibrosis covered by ablation-induced scarring, as indicated by 3-month MRI.

Descriptive summaries of baseline clinical and demographic characteristics were provided by randomized treatment assignment.

We summarized the overall levels of fibrosis targeting and scar coverage based on the 5-level scales by providing the average proportion (across the 5 raters) of subjects with ratings of $\geq$3, indicating that at least 40%–60% of fibrosis was targeted or covered, respectively, within the MRI-guided and PVI-only randomized treatment groups. We used scatterplots with superimposed local regression curves to describe the association of baseline fibrosis with each of the 3 measures of scar coverage or fibrosis targeting within the 2 randomized groups. For the fibrosis targeting and scar coverage measures based on the 5-level ratings, we performed separate random effects analyses within the 2 randomized groups, with a fixed intercept and random center effects to estimate the proportion of the total variation in the measure that was accounted for by variation between centers. We computed *P* values to test for the presence of nonzero center variation using a likelihood ratio test with a mixture of χ^2 distributions as the reference sampling distribution.[11] As mentioned in the primary article on the DECAAF II trial, we used the weighted Kappa and Gwet's agreement coefficient to assess the intra- and interrater agreement. The interrater agreement on the level of coverage was 92% on fibrosis targeting and 90% on scar coverage.

We used separate Cox proportional hazards analyses to relate the primary AA recurrence outcome to the average level of targeted fibrosis and to the average level of scar coverage across the 5 raters, with covariate adjustment for age, sex, baseline percent fibrosis, and baseline left atrial

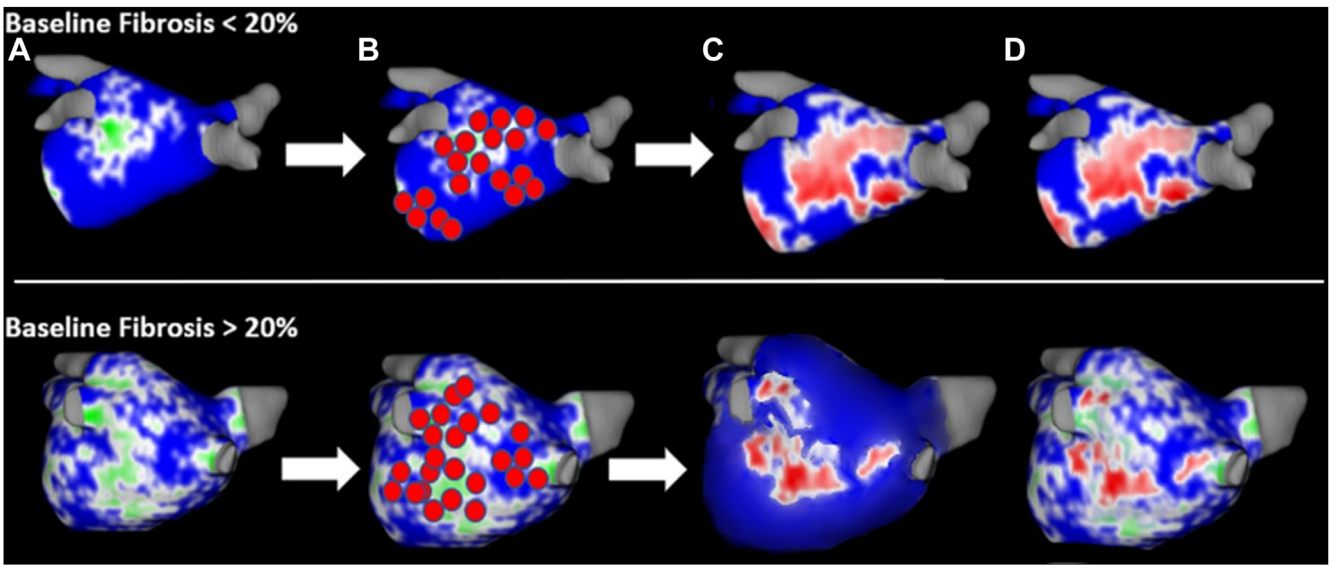

Figure 1
Imaging assessment of (**A**) baseline fibrosis, (**B**) ablation lesions targeting fibrosis, (**C**) ablation-induced scarring, and (**D**) covered fibrosis.

volume index in the full cohort, irrespective of the randomized group. A natural cubic spline model was used to display the functional forms of these relationships with 95% pointwise confidence intervals (CIs), with the medians of the respective fibrosis targeting or scar coverage used as the reference. The Cox models included gamma distributed random frailty terms to account for clustering by clinic. We used associated Cox models with the same covariates and linear terms for targeted fibrosis and scar coverage to estimate hazard ratios (HRs) to summarize the change in the hazard of the primary outcome for each 1-unit increase on the 5-level scales for targeted fibrosis and scar coverage.

All statistical analyses included all available randomized patients with nonmissing measurements on fibrosis targeting, or scar coverage variable used in that analysis, without imputation of missing data. The proportionality of hazards was confirmed. All analyses involving statistical inference were performed with a 2-sided significance level of .05 without adjustment for multiple comparisons. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC) or R version 3.4.1 (RStudio, Boston, MA).

Results

Analysis cohort

A Consolidated Standards of Reporting Trials (CONSORT) diagram is provided in the Online Supplement to explain the 3 cohorts analyzed in this study. Of the 823 patients analyzed in the main trial, 47 underwent cryoballoon ablation procedures and were excluded from the analyses of targeted fibrosis. One hundred eighty-three patients were missing data on ablation lesions, and therefore the fibrosis targeting analysis was performed in 593 patients. In this first cohort, 300 underwent PVI plus fibrosis-guided ablation and 293 underwent PVI only. Their characteristics are summarized in Table 1. Three-month MRI and the covered fibrosis rating were missing in 88 and 91 patients, and therefore analyses of the covered fibrosis rating and of the automated covered fibrosis measured using MRI were performed in 732 and 735 patients, respectively (second and third cohorts). A comparison of the characteristics of the 3 cohorts used for the respective fibrosis targeted and coverage analyses is provided in Online Supplemental Table S1.

Primary outcome

The event rate for the primary end point of AA recurrence after ablation did not differ significantly between the fibrosis-guided group and the PVI group and was previously reported.[8]

Assessment of fibrosis targeting and scar coverage

Lesions were analyzed in the 593 patients with available electroanatomical data. Using the 5-level rating scale described in the Methods section, more extensive targeting of fibrosis by ablation lesions is demonstrated in the MRI fibrosis-guided group than in the PVI group: 80.9% vs 16.5% of patients in the intervention vs conventional arms, respectively, had an average rating of $\geq$3 (indicating that at least 40%–60% of fibrosis was targeted).

Fibrosis coverage by ablation-induced scar was assessed using 3-month MRI, which was available in 735 patients. The 5-level rating of ablation-induced scar showed that 44.8% of patients who underwent fibrosis-guided ablation and 15.5% of patients who underwent PVI had an average rating of $\geq$3 (indicating that least 40%–60% of fibrosis was covered). This demonstrates significant attenuation from fibrosis targeting (80.9%) to scar formation (44.8%), as fibrosis targeting did not consistently result in ablation-induced scarring in the fibrosis targeting group. Examples of fibrosis targeting by ablation lesions and coverage by ablation scar are shown in Figure 1.

The pattern of higher targeted compared to covered fibrosis was also apparent when the average rates for each are presented in relation to baseline fibrosis. In Figure 2A, fibrosis targeting is shown to be rated higher than PVI, as more ablation lesions are delivered in the former group; however, the rating of fibrosis coverage by ablation-induced scar is significantly lower and closer to that observed in PVI, as shown in Figure 2B.

Studying the association between baseline fibrosis, fibrosis targeting with ablation lesions, and subsequent scar formation also revealed that the degree of baseline fibrosis affects scar formation and coverage. Patients randomized to undergo MRI fibrosis-guided ablation demonstrated higher fibrosis targeting, as mentioned above; however, ablation resulted in less scar formation when delivered in patients with high vs low fibrosis. When ablation-induced scarring was assessed across the full range of baseline fibrosis by using the automated measure of scarring, the 2 treatment groups were indistinguishable (Figure 3), indicating that in the overall cohort, despite more ablation in the MRI group, scarring was the same compared to the PVI group and that more ablation in fibrotic areas was not effective in increasing scar formation.

Correlation of targeted and covered fibrosis with arrhythmia recurrence

In the overall cohort, targeted fibrosis was not significantly associated with arrhythmia recurrence (HR 0.94 per 1-unit increase in the average rating on the 5-level scale; 95% CI 0.84–1.04 per 1-unit increase in the average rating on the 5-level scale; $P = .21$). We observed a slightly stronger association for covered fibrosis, which also was not statistically significant (HR 0.90 per 1-unit increase; 95% CI 0.80–1.01 per 1-unit increase; $P = .07$) (Figure 4). In a prespecified subgroup analysis, in patients with baseline fibrosis < 20%, Cox regression analysis demonstrated an HR of 0.85 (95% CI 0.73–0.99; $P = .03$) for AA recurrence associated with 1-unit increase in the mean covered fibrosis rating (Figure 5A). This suggests a possible reduction in AA recurrence with fibrosis coverage with ablation-induced scar in the low baseline fibrosis group. This association was not observed in the subgroup with baseline fibrosis $\geq$ 20%

Table 1 Baseline characteristics of the analytical sample for targeted fibrosis

Variable	MRI guided (n = 300)	Conventional PVI (n = 293)	*P*
Utah stage at baseline			
I (fibrosis <10%)	39 (13)	35 (11.9)	.88*
II (10% ≤ fibrosis < 20%)	135 (45)	134 (45.7)	–
III (20 ≤ fibrosis < 30%)	105 (35)	99 (33.8)	–
IV (fibrosis ≥ 30%)	21 (7)	25 (8.5)	–
Age at randomization (y)			
Mean ± SD	61.4 ± 8.9	62.0 ± 9.5	–
Median (interquartile range)	61.9 (56.9–67.8)	63.1 (55.9–69.3)	.25†
Range	29.4–80.9	31.6–81.6	–
Sex	61 (20.3)	57 (19.5)	.79*
Ethnicity			
Hispanic or Latino	14 (4.7)	10 (3.4)	.74*
Not Hispanic or Latino	261 (87)	258 (88.1)	–
Unknown or not reported	25 (8.3)	25 (8.5)	–
Race			
Asian	2 (0.7)	0 (0)	.29‡
Black or African American	2 (0.7)	3 (1.1)	–
Native Hawaiian or other Pacific Islander	0 (0)	2 (0.7)	–
White	278 (98.6)	271 (98.2)	–
Coronary artery disease	40 (13.3)	35 (11.9)	.61*
History of tobacco use	108 (36)	113 (38.6)	.52*
Mitral valve disease	15 (5)	17 (5.8)	.67*
Hyperlipidemia	97 (32.3)	95 (32.4)	.98*
Congestive heart failure/left ventricular dysfunction	64 (21.3)	48 (16.4)	.12*
Age > 75 y	14 (4.7)	19 (6.5)	.33*
Hypertension (defined as systolic pressure > 160 mm Hg)	178 (59.3)	175 (59.7)	.92*
Diabetes mellitus	21 (7)	31 (10.6)	.12*
Stroke/transient ischemic attack/thromboembolism	26 (8.7)	22 (7.5)	.61*
Antiarrhythmic medications	152 (50.7)	143 (48.8)	.65*
Vascular disease	29 (9.7)	23 (7.8)	.43*
Coronary artery bypass graft	3 (1)	8 (2.7)	.12*
Rheumatic fever	4 (1.3)	2 (0.7)	.69‡
Cardioverted	253 (84.3)	240 (81.9)	.43*
Prior failed antiarrhythmic medication	173 (57.7)	170 (58)	.93*

Values are presented as n (%) unless specified otherwise.
Missing values: Race: 18/17.
MRI = magnetic resonance imaging.
*χ^2 test.
†Wilcoxon rank sum test.
‡Fisher exact test.

(HR 0.97; 95% CI 0.80–1.18; *P* = .77) (Figure 5B). The Cox models were adjusted for age, sex, baseline fibrosis, and left atrial volume and included a frailty term to account for clustering by center. Figure 6 provides Kaplan-Meier curves for arrhythmia recurrence for 4 subgroups defined by baseline fibrosis (<20% vs ≥20%) and the average 5-level coverage rating (<3 vs ≥ 3).

Variations across participating centers

A random effects analysis was performed to examine whether the center at which the ablation procedure was performed had any effect on the 5-level scale ratings of fibrosis targeting and coverage. We found significant variation across participating centers, with some centers demonstrating clear separation and others demonstrating significant overlap in fibrosis targeting, with center variation accounting for 33% of the total variation in the PVI-only group (*P* < .001) and 30% of the total variation in the MRI fibrosis-guided group (*P* < .001) (Online Supplemental Figure 1A). Fibrosis coverage by ablation-induced scar also differed significantly across centers (*P* < .001 for both the PVI-only and MRI fibrosis-guided groups), but center variation accounted for smaller percentages of the total variation (15% in the PVI-only group and 19% in the MRI fibrosis-guided group), and substantial overlap can be seen in fibrosis coverage between the randomization groups in nearly all the participating centers (Online Supplemental Figure 1B and Online Supplemental Table S2), consistent with the findings described in the analysis above.

Discussion

In this analysis of the DECAAF II trial, we studied ablation-induced scar formation associated with delivered

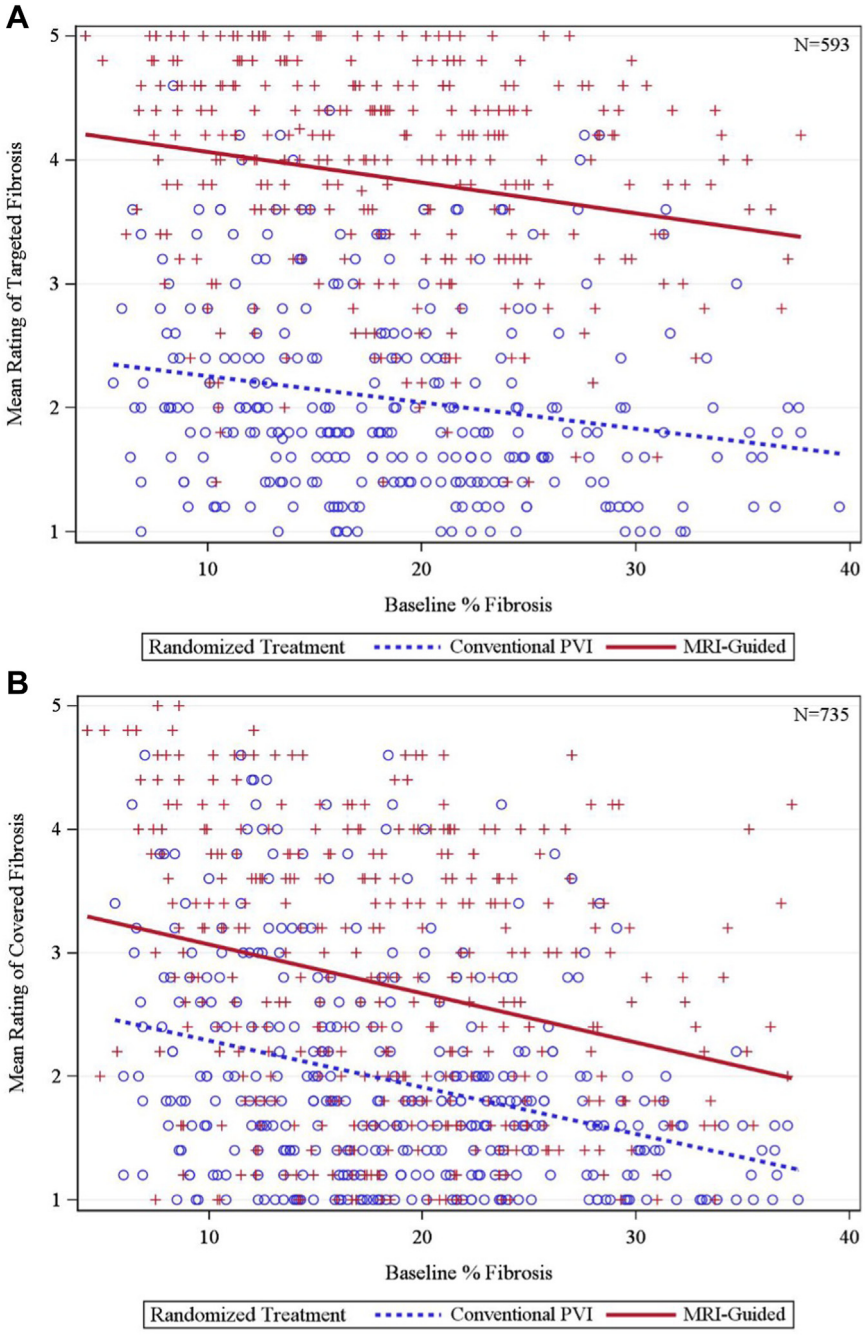

Figure 2

A: Scatterplot illustration of the 5-level scale rating of targeted fibrosis with conventional pulmonary vein isolation (PVI) (*blue circles*) and magnetic resonance imaging (MRI)–guided fibrosis ablation (*red plus signs*), demonstrating significantly higher targeting in the MRI fibrosis-guided group ($P < .0001$). **B:** Scatterplot of covered fibrosis demonstrates a significantly attenuated difference between the 2 groups ($P < .0001$).

radiofrequency ablation lesions and their association with atrial arrhythmia recurrence. We showed that (1) radiofrequency ablation lesions delivered, especially over fibrotic regions, do not uniformly result in scar formation; (2) radiofrequency ablation was more likely to result in scar when delivered over low baseline fibrosis; and (3) arrhythmia recurrence appeared to be reduced, when ablation-induced scarring covered fibrotic areas in patients with low baseline fibrosis, in this post hoc subgroup analysis.

The main determinants of success of catheter ablation include selection of the appropriate candidate for ablation, identification of ablation targets, and adequate scar formation at the intended ablation sites in addition to adjunctive lifestyle interventions targeting AF risk factors. Durable PVI, which requires scarring surrounding the pulmonary veins, is the cornerstone of ablation for AF.[12] Several clinical trials in persistent AF have failed to demonstrate a clear superiority of the empirical addition of linear ablation or electrogram-

based targeting of additional areas beyond PVI.[13,14] The fibrosis targeting strategy hypothesis was born from prior observations that ablation-induced scarring overlapping baseline fibrosis was associated with reduced arrhythmia recurrence.[15] The intention-to-treat analysis of the DECAAF II trial demonstrated that this approach was not superior in a prospective randomized fashion.[8] Next, we examined lesion formation, assessed by late gadolinium enhancement-MRI 3 months after ablation, and its association with arrhythmia recurrence.

Lesion formation is the ultimate determinant of the effect of catheter ablation on the desired outcome of arrhythmia suppression.[16] There are many factors that contribute to lesion formation in radiofrequency ablation. These include catheter size, irrigation, power, duration, stability, and force used when delivering an ablation lesion.[17,18] All radiofrequency ablation procedures in this trial were performed using open irrigation catheters; however, the study protocol left other ablation parameters at the discretion of the operators. With this limitation, this analysis suggests that despite adequate lesion delivery, scar formation was significantly less than the lesions delivered. While this discrepancy was previously described in radiofrequency ablation targeting atrial tissue,[19] the findings in this analysis suggest a wider discrepancy in ablation delivered over fibrotic tissue. In other words, the fibrotic nature of the underlying tissue being ablated may also affect the likelihood of scar formation. This is also a question often raised when other methods of assessment of atrial disease are used, such as voltage mapping, as in the ERASE-AF trial.[20] It remains to be determined how radiofrequency ablation parameters need to be adjusted, or whether other ablation energy sources may perform better, when ablating over fibrotic tissue to ensure adequate lesion formation.

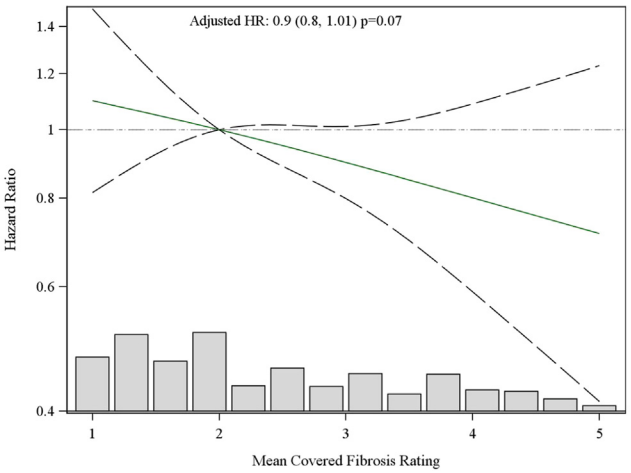

Figure 4
Estimated hazard ratios (HRs) with pointwise 95% confidence intervals comparing the rate of atrial arrhythmia (AA) recurrence for each covered fibrosis rating to the median covered fibrosis rating in the full cohort, irrespective of the randomized group. The hazard ratio curves were estimated using a cubic spline Cox regression model. The hazard ratios and *P* values were determined from a linear Cox regression model for the covered fibrosis rating. Both analyses included sex, age, baseline fibrosis, and baseline left atrial volume index as covariates and a random frailty effect for a center.

The other main finding in this study is that ablation targeting fibrotic areas in patients with early fibrotic remodeling measured by fibrosis < 20% were associated with lower arrhythmia recurrence compared to conventional PVI. At the

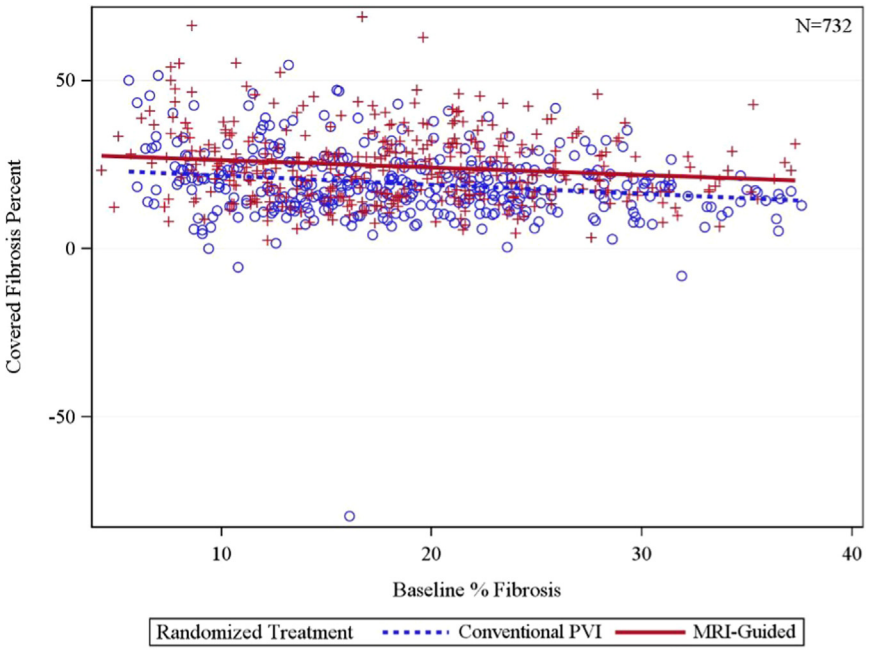

Figure 3
Scatterplot of covered fibrosis percentage. It demonstrates significant overlap between the 2 ablation groups, and no significant difference in covered fibrosis across a wide range of baseline fibrosis, despite more ablation delivered in the higher fibrosis group. MRI = magnetic resonance imaging; PVI = pulmonary vein isolation.

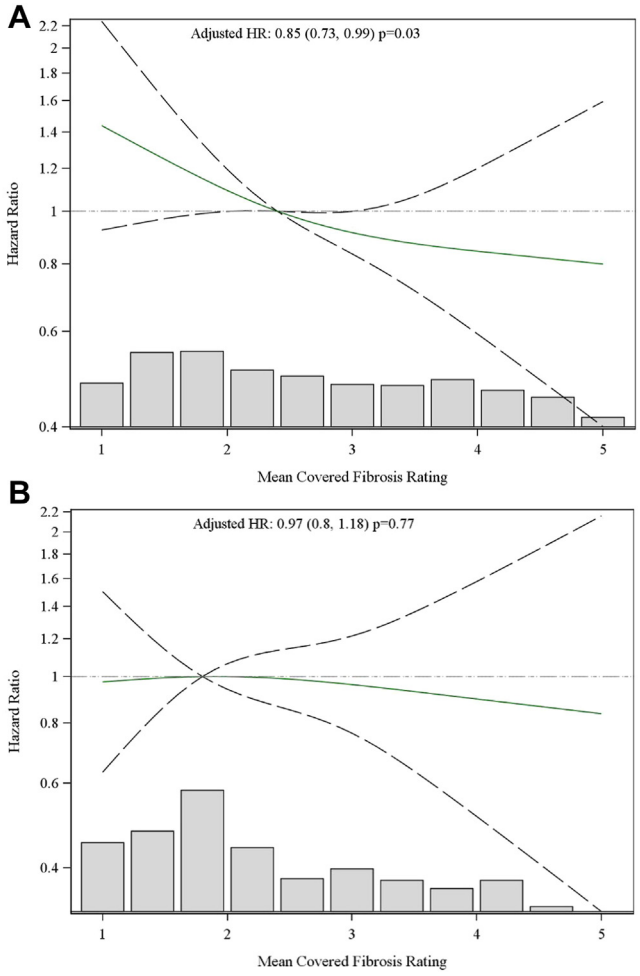

Figure 5
Estimated hazard ratios (HRs) with pointwise 95% confidence intervals comparing the rate of atrial arrhythmia (AA) recurrence for each covered fibrosis rating to the median covered fibrosis rating for (**A**) subjects with baseline fibrosis < 20% (n = 429) and (**B**) those with baseline fibrosis ≥ 20% (n = 305), irrespective of the randomized treatment group. The hazard ratio curves were estimated using separate cubic spline Cox regression models applied to the 2 baseline fibrosis subgroups. The hazard ratios and *P* values were determined from linear Cox regression models for the covered fibrosis rating. Both analyses included sex, age, baseline fibrosis, and baseline left atrial volume indices as covariates and a random frailty effect for a center.

same time, we showed that PVI plus fibrosis ablation was not associated with improved outcomes in patients with advanced fibrosis > 20%. This finding affirms our previous observations that catheter ablation is less likely to result in successful arrhythmia suppression in advanced, highly fibrotic atrial substrates.[7] This may be due to inadequate scar formation in this advanced stage, as discussed above. In addition, while small areas of fibrosis can be adequately covered, wider and more diffuse areas of fibrosis may be more difficult to target. The nature of fibrotic remodeling may also vary regionally within the atrium and between individuals.[21] This heterogeneity includes transmurality of fibrotic remodeling, which may play a role in the endocardial to epicardial dissociation demonstrated in AF.[22] Transmurality may also be an important factor in ablation-induced scarring as a result of the various ablation parameters used.[23,24] Moreover, contributions of other factors such as atrial blood supply and epicardial adipose tissue, which includes ganglia providing parasympathetic input and adipokines affecting fibrosis generation and development, can have an effect on the atrial substrate, as well as lesion formation, and are not factored into the ablation approach.

Study limitations

One of the main limitations of this analysis, common to all on-treatment analyses, is bias from uncontrolled confounding, which makes these results hypothesis generating. Other limitations include the subjective nature of the coverage ratings and the lack of lesion level analysis of individual parameters such as power and duration in scar formation.

Conclusion

This analysis highlights the effect of delivered lesions on scar formation in fibrotic areas, which are an important part of the AF substrate in the challenging group of persistent AF. Patients with lower levels of atrial fibrosis have better scar formation and may have less arrhythmia recurrence if fibrosis coverage was actually achieved. Future studies should further analyze operator- and ablation-dependent determinants of scar formation.

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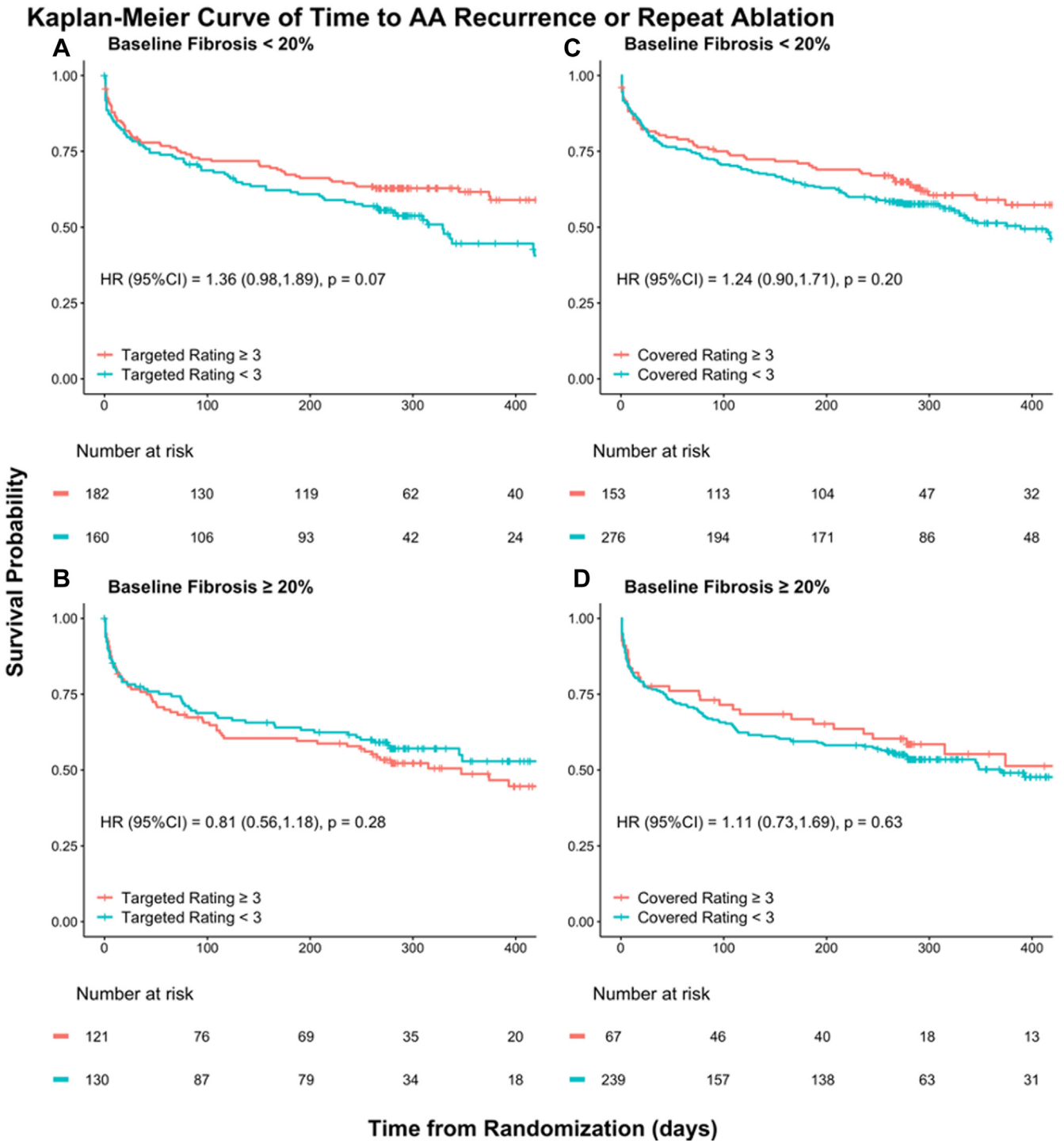

Figure 6
Proportions of patients free of atrial arrhythmia (AA) recurrence or repeat ablation if mean fibrosis targeted rating ≥ 3 and < 3 for the (**A**) subgroups with baseline fibrosis < 20% and (**B**) those with baseline fibrosis $\geq 20\%$ and if mean fibrosis covered rating ≥ 3 (40%) and < 3 for the (**C**) subgroups with baseline fibrosis < 20% and (**D**) those with baseline fibrosis $\geq 20\%$. The hazard ratios (HRs) compare the 2 targeted or covered fibrosis groups while accounting for a gamma distributed random frailty term to account for clustering by center. The *vertical hash marks* indicate right censoring.

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