Differences in Post Ablation Cardiac MRI Scar Between Radiofrequency and Cryoballoon Ablation: A DECAAF II Sub-analysis

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Abstract

Introduction: Pulmonary vein isolation (PVI) using radiofrequency (RF) and cryoballoon (Cryo) ablation are standard approaches for rhythm control of symptomatic atrial fibrillation. Both strategies involve scar formation of the left atrium (LA). There have been few studies investigating the differences in residual fibrosis and scar formation in patients undergoing RF and Cryo using cardiac magnetic resonance imaging (CMR). **Methods:** The current study is a sub-analysis of the control arm of the Delayed-Enhancement MRI Determinant of Successful Catheter Ablation of Atrial Fibrillation study (DECAAF II). The study was a multicenter, randomized, controlled, single blinded trial that evaluated atrial arrhythmia recurrence (AAR) between PVI alone and PVI plus CMR atrial fibrosis guided ablation. Pre-ablation CMR and 3–6-month post ablation CMR were obtained to assess baseline LA fibrosis and scar formation respectively. **Results:** Of the 843 patients randomized in the DECAAF II trial, we analyzed the 408 patients in the primary analysis control arm that received standard PVI. Five patients received combined RF and Cryo ablations so were excluded from this sub-analysis. Of the 403 patients analyzed, 345 underwent RF and 58 Cryo. The average procedure duration was 146 minutes for RF and 103 minutes for Cryo ($p = 0.001$). The rate of AAR at ˜15 months occurred in 151 (43.8%) patients in the RF group and 28 (48.3%) patients in the Cryo group ($p = 0.62$). On 3-month post CMR the RF arm had significantly more covered fibrosis (3.6% vs. 3.0%, $p = 0.04$) and scar (8.8% vs. 6.4%, $p = 0.001$) compared to Cryo. Patients with [?] 6.5% LA scar on 3-month post CMR had less AAR independent of ablation technique (RF $p = 0.009$, Cryo $p = 0.02$). Cryo caused a greater percentage of right and left pulmonary vein (PV) scar ($p = 0.04$, $p = 0.02$) and less non-PV scar ($p = 0.009$) compared to RF. On Cox regression Cryo patients free of AAR had a greater percentage of left PV scar ($p = 0.01$) and less non-PV scar ($p = 0.004$) compared to RF free of AAR. **Conclusion:** In this sub-analysis of the control arm of the DECAAF II trial, there was no significant difference in the rate of AAR in patients undergoing PVI alone between RF vs. Cryo. Post ablation LA scar [?] 6.5% predicted freedom from AAR, independent of ablation technique. Cryo formed a greater percentage of PV scar and less non-PV scar compared to RF, which may have prognostic implications.

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Patient Consent: Written informed consent was obtained from all participants prior to study inclusion.

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Conclusion: In this sub-analysis of the control arm of the DECAAF II trial, there was no significant difference in the rate of AAR in patients undergoing PVI alone between RF vs. Cryo. Post ablation LA scar [?] 6.5% predicted freedom from AAR, independent of ablation technique. Cryo formed a greater percentage of PV scar and less non-PV scar compared to RF, which may have prognostic implications.

Keywords: atrial arrhythmia recurrence, PVI, radiofrequency, cryoballoon, CMR, fibrosis, scar

Introduction:

Catheter ablation in patients with symptomatic persistent atrial fibrillation (AF) is effective in maintaining sinus rhythm and is a class I indication in symptomatic patients who have failed antiarrhythmic drug therapy.[1] Standard pulmonary vein isolation (PVI) remains the main-stay treatment while additional ablations such as posterior wall isolation, left atrial roof line ablation, targeting atrial rotors, complex fractionated electrograms, low voltage/complex electrograms, or baseline left atrial (LA) fibrosis have not shown added benefit.[2-7] The two most common ablation techniques for PVI include radiofrequency (RF) ablation using thermal tissue heating, and cryoballoon (Cryo) using cryogenic freezing to cause cellular necrosis.[8]

Cryo is gaining popularity as a treatment modality for AF, given its relatively simpler technique, shorter procedure duration, and promising clinical results.[9-11] In patients with symptomatic paroxysmal AF, Cryo has been shown to be noninferior to RF and superior to drug therapy at maintaining sinus rhythm, reducing healthcare utilization, and delaying progression to persistent AF.[9,12-14] Most prospective comparisons between RF and Cryo have included mostly paroxysmal AF patients so further evaluation in the persistent AF population is warranted.[9,15]

The difference in ablation induced scar formation by the two techniques is also not well studied. Cardiac magnetic resonance (CMR) imaging has been shown to reliably assess LA fibrosis, with post-ablation late gadolinium enhancement (LGE) showing predictiveness for atrial arrhythmia recurrence (AAR) or even sites of breakthrough conduction at repeat ablation.[16-19] Hence it would be interesting to see if the two techniques have different effects on the LA post ablation.

The current sub-analysis from the control arm of the DECAAF II trial was designed to compare 1) the rate of AAR after standard RF and Cryo PVI ablation in patients with persistent AF 2) the effect standard RF and Cryo PVI ablation have on post ablation scar using CMR 3) if scar on post ablation CMR can be used to predict AAR.

Materials & Methods:

Study Design: This study is a sub-analysis of the control arm of the DECAAF II trial evaluating the rate of AAR and CMR results between patients with persistent AF who underwent standard RF and Cryo PVI ablation. A full discussion of the DECAAF II methods can be found at DOI: 10.1111/jce.14957. In brief, the DECAAF II trial was a prospective, randomized, investigator initiated, industry sponsored, multicenter, international, controlled, single blinded trial that randomized persistent AF patients to standard PVI ablation or PVI plus CMR guided atrial fibrosis ablation. Of the 843 patients who were randomized, 417 patients were included in the control arm. Nine patients were lost to follow up and 5 patients received both RF and Cryo ablations so were excluded, resulting in 403 patients which were included in this as treated sub-analysis. Of these 403 patients, 345 underwent RF and 58 Cryo ablation (Figure 1). All patients had LGE-CMR before and 3-6 months post ablation. Patients were followed for 12-18 months using daily smartphone electrocardiogram (ECG) recordings to assess for AAR. A Data Coordinating Center at the University of Utah was responsible for recording and analysis. Written informed consent was obtained from all participants prior to study inclusion. The study was approved by the ethics review committee at all sites.

Patient Population: To enroll, patients had to be at least 18 years old and have documented persistent AF without prior ablation. Persistent AF was defined as lasting 7 days or more on rhythm strip or chart

review. Exclusion criteria included patients with prior ablation, contraindication for CMR or beta blockers, inability to be positioned in CMR scanner, pregnant women, terminally ill, or those without smartphone capability.[20]

Imaging Protocol: All patients underwent LGE-CMR within 30 days prior to ablation and between 90-180 days post. Merisight delayed CMR protocol (MARREK Inc) and image processing software were used. If the patient's heart rate was greater than 90 beats per minute, he or she was pre-medicated with a beta blocker. Images were transmitted to MARREK Inc where they were reviewed, processed, and quantified with respect to LA fibrosis (pre-ablation) and LA scar formation (post-ablation). LA fibrosis was defined using the previously described Marrek Inc, LGE-CMR protocol (MRI and image processing software).[21,22]Post-ablation CMR findings for the LA were classified as post ablation scar, covered fibrosis, and non-covered fibrosis. Post ablation scar was the percentage of the entire LA which enhanced at a higher LGE threshold and constituted iatrogenic scar induced by the PVI. Of note, post ablation scar had higher intensity signals that effectively masked the fibrosis pattern noted on pre-ablation scans. The pre-ablation CMR was overlaid on the 3–6-month post-ablation CMR and areas of baseline fibrosis which overlapped with areas of scar were termed covered fibrosis, whereas areas of baseline fibrosis not covered by scar were termed non-covered fibrosis (Figure 2). Suboptimal images were not processed. The site physician could opt to reimage patients who had images below quality standards.

PVI: In this sub-analysis all patients underwent standard PVI ablation with either RF or Cryo. The operator created lesions around the pulmonary vein (PV) antra as described by the HRS consensus statement.[23] Standard techniques were used to confirm entrance, and at the discretion of the operator, exit block. If normal sinus rhythm was not achieved post ablation, patients were cardioverted. Additional non-PV trigger ablation lesions could be performed at the discretion of the operator if normal sinus rhythm could not be restored post cardioversion.[20]

Cryoballoon ablation: Cryo ablation was chosen at the operator's discretion. A 28-mm Arctic Front Advance balloon was recommended to maximize antral ablation. Termination of energy was recommended if Cryo temperatures were below -55 degrees °C with 28-mm Arctic Front and -60 degrees °C with 23-mm Arctic Front.[20] If Cryo was unsuccessful after 540 seconds of therapy, the operator was encouraged to cannulate a different vein branch, use a different size cryoballoon, try focal cryocatheter, or employ RF.

Primary and Secondary Outcomes: The primary outcome was first AAR (AF, atrial flutter, atrial tachycardia) after the 90-day blanking period confirmed with at least one valid ECG tracing, 2 consecutive smartphone ECG tracings more than 6 hours apart, or another continuous monitoring device (Holter). Patients were told to submit ECGs daily and these transmissions were reviewed at the central location. Secondary outcomes after the 90-day blanking period included the rates of antiarrhythmic use, repeat ablation, and cardioversion.

Safety Outcome: The primary safety composite outcome was the occurrence of at least one of the following within the 30-day period after the ablation procedure: stroke, heart failure, bleeding requiring transfusion, PV stenosis, or death from any cause. Additional safety outcomes include the individual components of the primary safety composite, occurrence of esophageal injury, perforation, or tamponade, and serious adverse events including cardiovascular, cerebrovascular, and gastrointestinal events. The safety end points were adjudicated by a 3-member outcomes committee based on the 2017 HRS Consensus Statement.[23]

Statistical Analysis: Statistical analysis was performed in the as treated control arm of the DECAAF II study in patients who received PVI ablation alone. The group was analyzed between those who received RF and Cryo. Categorical data, expressed as a number and percent, were compared using the chi-squared test. For data with sample size < 5, the Fischer exact test was used. Continuous data, expressed as mean +/- SD, were compared using the independent Student$t$ test. For the survival analysis, follow-up time began 90-days after the date of ablation and ended at the diagnosis of an atrial arrhythmia event. For the Kaplan-Meier curves, the log-rank test was used for significance. The multivariate analysis used a Cox proportional hazards model to obtain the appropriate estimates and confidence intervals of hazard ratios. Proportionality

assumptions were confirmed by graphical methods. The primary analysis was performed with a two-sided significance level of 0.05. Analysis was performed using R version 3.3.2 GUI Mavericks build.

Results:

Baseline Results: Enrollment started in July 2016 and was completed in February 2021. In the RF arm, all 345 patients underwent the baseline CMR and 313 (90.7%) underwent the follow up CMR. In the Cryo arm, all 58 patients underwent the baseline CMR and 51 (87.9%) underwent the follow-up CMR. In the RF group, 341 patients (98.8%) completed the 3-month follow up visit and 335 (97.1%) completed the 12-month follow up visit. In the Cryo group, 55 patients (94.8%) and 53 patients (91.4%) completed the 3 and 12-month follow up respectively. The average number of days with transmitted ECGs was 193.9 +/- 139.5 days in the RF group and 134.4 +/- 136.5 days in the Cryo group (p = 0.003). The characteristics of the patients at baseline were balanced between the two groups, except for the number of patients on antiarrhythmic and anticoagulation therapy was higher in the RF group and the baseline brain natriuretic peptide level was higher in the Cryo group (Table 1A).

Baseline CMR Results: The pre-ablation CMR left atrial volume index (LAVI) was comparable between RF and Cryo (p = 0.57) (Table 2A). Additionally, the baseline fibrosis on the pre-ablation CMR was similar between the two groups (Table 2A). The RF group had an average of 18.5 +/- 7.2% LA fibrosis while the Cryo group had an average of 20.8 +/- 8.4% LA fibrosis (p = 0.08). The percentage of atrial fibrosis around the right and left PVs as well as fibrosis not located around the PVs was similar between RF and Cryo groups (Table 2A). The percentage of patients across Utah Stages 1, 2, 3, and 4 was also balanced between RF and Cryo (Supplemental Table 1).

3-Month Post Ablation CMR Results: We observed a significant reduction in LAVI in all patients undergoing ablation regardless of technique (Table 2A). Reduction in LAVI was significantly greater in the RF group compared to Cryo (10.1 +/- 11.6 cc vs. 5.7 +/- 11.4 cc, p = 0.01). Covered LA fibrosis was higher in RF compared to Cryo (3.6 +/- 2.2% vs. 3.0 +/- 1.8%, p = 0.04) while non-covered LA fibrosis was lower in RF compared to Cryo (14.9 +/- 6.3% vs. 17.8 +/- 7.8%, p = 0.01). The follow up LA scar was higher in the RF group compared to Cryo (8.8 +/- 4.2% vs. 6.4 +/- 3.6%, p = 0.001). Similar results were seen after stratifying by Utah Stage (Table 2B).

When comparing the regionality of LA scar, the Cryo group had a greater percentage of scar formed around the right and left PVs while the RF group had a greater percentage of non-PV scar (Table 2A). We also noted a significantly greater percentage of scar formed around the left PVs when compared to the right PVs. This finding was significant for the total cohort (37.7 +/- 16.3% vs. 5.2 +/- 8.6%, p < 0.001) as well as the Cryo (43.7 +/- 20.0% vs. 8.5 +/- 12.9%, p < 0.001) and RF (36.7 +/- 15.4% vs. 4.6 +/- 7.6%, p < 0.001) subgroups.

Primary End Points: The primary efficacy endpoint, AAR after the blanking period, was similar between groups, occurring in 151 RF patients and 28 Cryo patients (43.8% vs. 48.3%, p = 0.52) (Table 3A) (Figure 3). The use of antiarrhythmics 90 days post blanking period was similar, with 45 patients (13.0%) in the RF arm and 10 patients (17.2%) in the Cryo arm receiving antiarrhythmics (p = 0.51) (Table 3A). Likewise, the groups were comparable with respect to the number undergoing repeat ablation and repeat cardioversion (Table 3A). Stratified by Utah Stages 1, 2 and 3, 4 showed comparable rates of AAR between RF and Cryo (Table 3B).

Predictive Value of Scar Formation:

Total Scar:

For the entire cohort, we noted a trend towards a greater percentage of LA scar in patients free of AAR compared to those with AAR (8.8 +/- 4.2% vs. 8.0 +/- 4.2%, p = 0.09) (Table 4A). Cryo patients free of AAR had a significantly higher percentage of LA scar than those with AAR (7.4 +/- 4.2% vs. 5.4 +/- 2.5%, p = 0.04) (Table 4A). This difference was not seen in the RF subgroup (9.0 +/- 4.1% vs. 8.5 +/- 4.3%, p = 0.34) (Table 4A).

Univariate analysis showed that post ablation LA scar [?] 6.5% predicted freedom from AAR (p = 0.005) (Figure 4). Multivariate Cox regression analysis accounting for CHA_2DS_2VASC, age, sex, antiarrhythmic medications, and baseline fibrosis reaffirmed the prior finding that post ablation LA scar [?] 6.5% predicted freedom from AAR in the entire cohort (HR 0.59 [95% CI, 0.43-0.81]; p = 0.001). This threshold of [?] 6.5% LA scar was predictive of freedom from AAR independently in both RF and Cryo groups (p = 0.003) (Figure 5). RF patients with [?] 6.5% LA scar had less left PV scar and more non-PV scar compared to Cryo patients with [?] 6.5% LA scar (Table 4B).

Regional Scar :

Scar regionality was predictive of AAR as patients with a greater percentage of LA scar around the PVs had less AAR. Univariate (Figure 6) and multivariate Cox regression analysis accounting for CHA_2DS_2VASC, age, sex, antiarrhythmic medications, and baseline fibrosis showed that in the entire cohort, patients with [?] 2.3% absolute LA scar around the PVs (PV scar) had less AAR (HR 0.663 [95% CI, 0.48-91]; p = 0.01). This inverse relationship between PV scar and AAR was statistically significant in the RF group (p = 0.01) and showed a trend towards significance in the Cryo group (p = 0.29) (Supplemental Figures 1 and 2).

Analyzing regional scar further we divided total LA scar into PV scar (left PV, right PV) and non-PV scar (Figure 7). Cryo patients free of AAR had a greater percent left PV scar (45.5 +/- 18.7% vs. 37.5 +/- 15.3%, p = 0.01) and less non-PV scar compared to RF patients free of AAR (48.2 +/- 12.9% vs. 57.9 +/- 11.6%, p = 0.004) (Table 4C) (Figure 8). There was no difference in right PV scar between RF patients free of AAR and Cryo patients free of AAR (p = 0.38) (Figure 8).

Safety End Points: The procedural characteristics showed similar fluoroscopy time between the groups but increased total sheath and total transseptal time in RF compared to Cryo (Table 1B). The primary composite safety outcome (stroke, heart failure, bleeding requiring transfusion, PV stenosis, and death within 30 days) did not occur in either group (0 RF vs. 0 Cryo, p = 1.0) (Supplemental Table 2). The total number of deaths from any cause between 31 – 451 days post ablation was equivalent with both arms having 1 death (p = 0.27) (Supplemental Table 2). With respect to esophageal injury and perforation or tamponade there was no difference between RF and Cryo (Supplemental Table 2). The number of serious adverse events was balanced, with 14 RF patients (4.1%) and 4 Cryo patients (6.9%) having a serious adverse event (p = 0.31) (Supplemental Table 2).

Discussion:

In this sub-analysis of the DECAAF II trial of patients with persistent AF who underwent routine PVI, there was no significant difference in AAR between RF and Cryo. Patients with [?] 6.5% LA scar on post ablation CMR had less AAR. Cryo patients had a greater percentage of scar formation around the PVs and less non-PV scar compared to RF.

Cryo ablation is gaining popularity as the preferred method of ablation given the shorter procedure duration, ease of ablation delivery, and equivalent safety profile. When comparing RF to Cryo for paroxysmal AF, both techniques appear to be equally efficacious with respect to AAR.[9,24] However, there is a paucity of data comparing RF to Cryo in patients with persistent AF. In the prospective cluster FREEZE Cohort study evaluating the effectiveness and safety of Cryo compared to RF in patients with paroxysmal and persistent AF, subgroup analysis of patients with persistent AF showed no difference in AAR after 3 months between Cryo and RF (Hazard ratio 1.01, CI 0.70-1.46, p = 0.95).[25] Moreover, a pooled registry trial studying Cryo vs. RF as an initial AF ablation procedure showed that in patients with persistent AF, Cryo was as effective as RF with respect to the rate of repeat AF ablation at 12-month follow up (Hazard ratio 0.92, confidence interval 0.631-1.343).[26] The present sub-analysis adds to the growing evidence that Cryo is noninferior to RF with respect to AAR in patients with persistent AF undergoing their first ablation procedure (p = 0.62).

This DECAAF II sub-analysis is one of the first studies to observe the effects RF and Cryo have on the LA by CMR.[17,27] It strengthens the evidence that greater extent of LA scarring after PVI ablation may be associated with less AAR.[18,19]Univariate (Figure 4) and multivariate analysis showed that patients with [?]

6.5% LA scar had less AAR, and this trend was seen in both RF and Cryo groups (Figure 5). In addition to finding predictive value in the percentage of total LA scar, we found that the location of scar around the PVs has prognostic value (Figure 6). These findings suggest that patients with a higher percentage of LA scar, specifically around the PVs, may have more durable and continuous lesions that result in better PVI, thus improving freedom from AAR. Scar formation is not without risk however, and clinicians must balance the benefits of ablation with the risk of stiff left atrial syndrome, esophageal injury, and stroke.[28-30] Overall, the percentage and location of post ablation LA scar may help clinicians predict which patients recur after PVI and consider additional strategies for rhythm control.

Interestingly in our cohort, RF and Cryo had similar rates of AAR despite RF having a greater percentage of LA scar. This may be explained by the regionality of LA scar formation. Cryo patients had more PV scar and less non-PV scar compared to RF patients (Table 2A). Furthermore, Cryo patients free of AAR had a greater percentage of left PV scar and less non-PV scar than RF patients free of AAR (Figure 8, Table 4C). This same trend of Cryo patients having more left PV scar and less non-PV scar was also seen in the subset of patients with [?] 6.5% total LA scar (Table 4B). This may allude to a difference in the efficacy and durability of scar formation between RF and Cryo. A study by Wieczorek et al. examining early pulmonary vein reconnection (PVR) showed that Cryo had less PVR compared to RF ablation 30 minutes post PVI (7% vs. 18%, $p < 0.0001$).[31] Kurose et al. showed that Cryo resulted in wider and more continuous ablation lesions with less ablation gaps on 1–3-month post ablation CMR compared to RF.[32] The more extensive and continuous ablation lesions formed by Cryo may explain the lower rate of PVR observed post ablation. This study supports the above findings because Cryo had a greater percentage of PV scar compared to RF, suggesting that Cryo ablation may more efficiently and uniformly target the PVs while causing less non-PV scar. The more targeted PV scar formed via Cryo helps explain the similar rate of AAR between modalities despite RF having a greater total LA scar percentage.

Initial CMR studies in patients with AF showed that baseline and residual fibrosis were strong predictors of AAR.[16,17]However, PVI plus CMR guided fibrosis ablation compared to routine PVI ablation, evaluated in the ALICIA and DECAAF II trials, did not lead to improved freedom from AAR.[7,33] In this sub-analysis, despite RF covering a greater percentage of LA fibrosis compared to Cryo (3.6 +/- 2.2 vs. 3.0 +/- 1.8, $p = 0.04$), the AAR rates were similar between groups. Although there appears to be a link between fibrosis and AF, the underlying pathophysiology of AF is not fully understood. The arrhythmogenic nature of fibrosis is variable and depends on many factors. Current imaging software is unable to effectively differentiate arrhythmogenic from non-arrhythmogenic fibrosis, limiting the utility of targeting fibrosis with ablation. Moreover, targeting fibrosis with thermal injury might not be an effective strategy to nullify its arrhythmogenicity, especially in patients with more advanced/transmural fibrosis that is difficult to reach. Operators also utilize different RF ablation techniques even when performing standard PVI, resulting in variable recurrence rates. On the contrary, Cryo ablation is more standardized which decreases inter-operator variability.

Limitations:

The current sub-analysis has several limitations. First, this is a sub-analysis of the DECAAF II trial, evaluating patients in the control arm who received PVI alone. More patients in the control arm received RF ablation ($n = 345$) compared to Cryo ($n = 58$), resulting in selection bias. While the baseline characteristics were well matched, more patients in the RF arm received antiarrhythmic therapy and anticoagulation prior to ablation, which could affect the rate of AAR and bleeding post ablation. Additionally, RF patients had more days of transmitted ECGs, which may have resulted in less atrial arrhythmia detection in Cryo patients. Being an international study, there were operators of varying skill levels and expertise, which may have affected the efficacy of RF ablation more than Cryo given the former's inherent complexity. Also, while the CMR protocol was standardized, the CMR machines varied between study sites, influencing the reproducibility of the images. Lastly, the follow-up period was relatively short (12-18 months) which may have been insufficient time to see a difference in the primary outcome.

Conclusion:

In patients with persistent AF, routine PVI with Cryo was non-inferior to RF in terms of atrial arrhythmia recurrence. Patients with [?] 6.5% total LA scar on post ablation CMR had less AAR. Cryo ablation formed a greater percentage of PV scar compared to RF, suggesting more effective scar localization that may have important prognostic implications.

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Table 1A)

Baseline Characteristic	**All (n = 403)**	**RF (n = 345)**	**Cryo (n = 58)**	**p value**
Age - year	62.3 +/- 9.1	62.2 +/- 9.1	63.1 +/- 8.8	p = 0.46
Male sex - no (%)	321 (79.7)	274 (79.4)	47 (81.0)	p = 0.91
Race - white	374 (92.8)	318 (92.2)	56 (96.6)	p = 0.41
CHF	66 (16.4)	53 (15.4)	13(22.4)	p = 0.25
HTN	237 (58.8)	202 (58.6)	35 (60.3)	p = 0.91
Vascular Disease	39 (9.7)	31 (9.0)	8 (13.8)	p = 0.37
Diabetes	43 (10.7)	36 (10.4)	7 (12.1)	p = 0.89
Prior Stroke/TIA	34 (8.4)	28 (8.1)	6 (10.3)	p = 0.61
CAD	49 (12.2)	42 (12.2)	7 (12.1)	p = 1.0
CABG	8 (2.0)	8 (2.3)	0 (0)	p = 0.61
CHA_2DS_2VASC	1.9 +/- 1.4	2.0 +/- 1.4	1.8 +/- 1.3	p = 0.45
Tobacco	159 (39.5)	133(38.6)	26 (44.8)	p = 0.45
Hyperlipidemia	136 (3.4)	122 (35.4)	14 (24.1)	p = 0.13
Mitral Valve Disease	25 (6.2)	21 (6.1)	4 (6.9)	p = 0.77
Rheumatic Fever	3 (0.7)	3 (0.9)	0 (0)	p = 1.0
Antiarrhythmic use prior	191 (47.4)	172 (49.9)	19 (32.8)	**p = 0.02**
Beta Blocker	296 (73.4)	256 (74.2)	40 (69.0)	p = 0.50
ACEi	113 (28.0)	98 (28.4)	15 (25.9)	p = 0.81
ARB	100 (24.8)	90 (26.1)	10 (17.2)	p = 0.20
Statin	131 (32.5)	108 (31.2)	23 (39.7)	p = 0.27
Anticoagulation drug	387 (96.0)	335 (97.1)	52 (89.7)	**p = 0.02**
Antiplatelet	17 (4.2)	15 (4.3)	2 (3.4)	p = 1.0
BNP	252.7 +/- 327.6	218.8 +/- 285.8	407.1 +/- 448.8	**p = 0.05**

Table 1B)

Baseline Procedural Characteristics	**All (n = 403)**	**RF (n = 345)**	**Cryo (n = 58)**	**p value**
Total fluoroscopy time	14.1 +/- 10.6	13.9 +/- 11.1	15.6 +/- 7.4	p = 0.14
Total sheath time	140.2 +/- 61.4	146.4 +/- 63.2	103.4 +/- 29.6	**p = 0.001**
Total transseptal time	112.6 +/- 50.5	117.4 +/- 52.0	84.4 +/- 26.4	**p = 0.001**

Data are represented as mean +/- SD or number and percent. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; Cryo = cryoballoon;

HTN = hypertension; RF = radiofrequency; TIA = transient ischemic attack

Table 2A) MRI Outcomes

Table 2A) MRI Outcomes **MRI Outcomes All (n = 364) RF (n = 313) Cryo (n = 51) p value** Pre-LAVI 61.5 +/-

&

Table 2A) MRI Outcomes

MRI Outcomes	**All (n = 364)**	**RF (n = 313)**	**Cryo (n = 51)**	**p value**
Pre-LAVI	61.5 +/- 17.8	61.7 +/- 17.5	60.1 +/- 19.4	p = 0.57
Post-LAVI	52.0 +/- 16.2	51.6 +/- 15.6	54.4 +/- 19.7	p = 0.41
LAVI Change	9.5 +/- 11.7	10.1 +/- 11.6	5.7 +/- 11.4	**p = 0.01**
Baseline Fibrosis	18.8 +/- 7.4	18.5 +/- 7.2	20.8 +/- 8.4	p = 0.08
Fibrosis around RPV	10.6 +/- 8.7	10.6 +/- 8.8	10.8 +/- 8.2	p = 0.87
Fibrosis around LPV	19.7 +/- 8.4	19.8 +/- 8.5	19.3 +/- 8.1	p = 0.65
Fibrosis not around PV	69.7 +/- 8.7	69.6 +/- 8.8	69.9 +/- 8.3	p = 0.89
Covered Fibrosis	3.5 +/- 2.1	3.6 +/- 2.2	3.0 +/- 1.8	**p = 0.04**
Non-covered Fibrosis	15.3 +/- 6.6	14.9 +/- 6.3	17.8 +/- 7.8	**p = 0.01**
Follow Up Ablation scar	8.5 +/- 4.2	8.8 +/- 4.2	6.4 +/- 3.6	**p = 0.001**
% Scar around RPV	5.2 +/- 8.6	4.6 +/- 7.6	8.5 +/- 12.9	**p = 0.04**
% Scar around LPV	37.7 +/- 16.3	36.7 +/- 15.4	43.7 +/- 20.0	**p = 0.02**
% Scar not around PV	57.1+/- 11.5	58.7 +/- 11.4	47.8 +/- 12.2	**p = 0.009**
Table 2B)				
Utah Stage 1 and 2	**All (n = 210)**	**RF (n = 184)**	**Cryo (n = 26)**	**p value**
Baseline Fibrosis	13.6 +/- 3.7	13.6 +/- 3.7	13.8 +/- 4.0	p = 0.79
Covered Fibrosis	2.7 +/- 1.8	2.7 +/- 1.9	2.3 +/- 1.2	p = 0.10
Non-covered Fibrosis	10.9 +/- 3.6	10.8 +/- 3.6	11.5 +/- 3.8	p = 0.40
Scar	8.6 +/- 4.2	8.9 +/- 4.2	6.7 +/- 3.7	**p = 0.008**
Utah Stage 3 and 4	**All (n = 154)**	**RF (n = 129)**	**Cryo (n = 25)**	**p value**
Baseline Fibrosis	26.0 +/- 4.6	25.6 +/- 4.5	28.0 +/- 4.7	**p = 0.02**
Covered Fibrosis	4.6 +/- 2.0	4.8 +/- 2.0	3.6 +/- 2.1	**p = 0.01**
Non-covered Fibrosis	21.4 +/- 4.8	20.8 +/- 4.5	24.4 +/- 5.0	**p =0.002**
Scar	8.2 +/- 4.1	8.6 +/- 4.1	6.1 +/- 3.6	**p = 0.003**

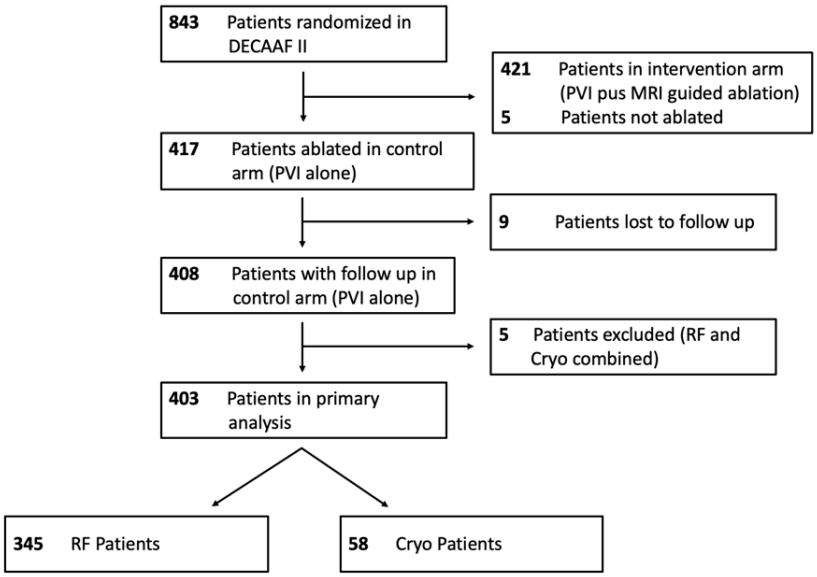
Table 3A) Primary End Points

Primary End Points	**All (n = 403)**	**RF (n = 345)**	**Cryo (n = 58)**	**p value**
AAR	179 (44.4)	151 (43.8)	28 (48.3)	p = 0.52
Antiarrhythmic use	55 (13.6)	45 (13.0)	10 (17.2)	p = 0.51
Repeat ablation	73 (18.1)	65 (18.8)	8 (13.8)	p = 0.46
Cardioversion	75 (18.6)	63 (18.3)	12 (20.7)	p = 0.80
Table 3B)				
AAR by Utah Stage				
Utah Stage 1+2	**All (n = 232)**	**RF (n = 200)**	**Cryo (n = 32)**	**p value**
AAR	103 (44.4)	88 (44.0)	15 (46.9)	p = 0.91
Utah Stage 3+4	**All (n = 171)**	**RF (n = 145)**	**Cryo (n = 26)**	**p value**
AAR	76 (44.4)	63 (43.4)	13 (50.0)	p = 0.69

Data are presented as number and percent. AAR = atrial arrhythmia recurrence; Cryo = cryoballoon; RF = radiofrequency.

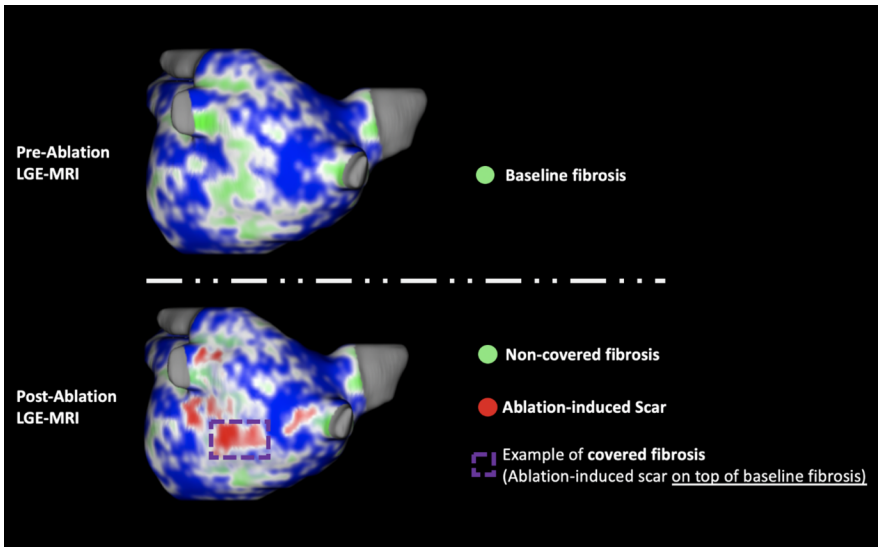
Table 4A) RF and Cryo Scar

Table 4A) RF and Cryo Scar **Entire Cohort All (n = 364) Free of AAR (n = 203) AAR (n = 161) p value** Basel



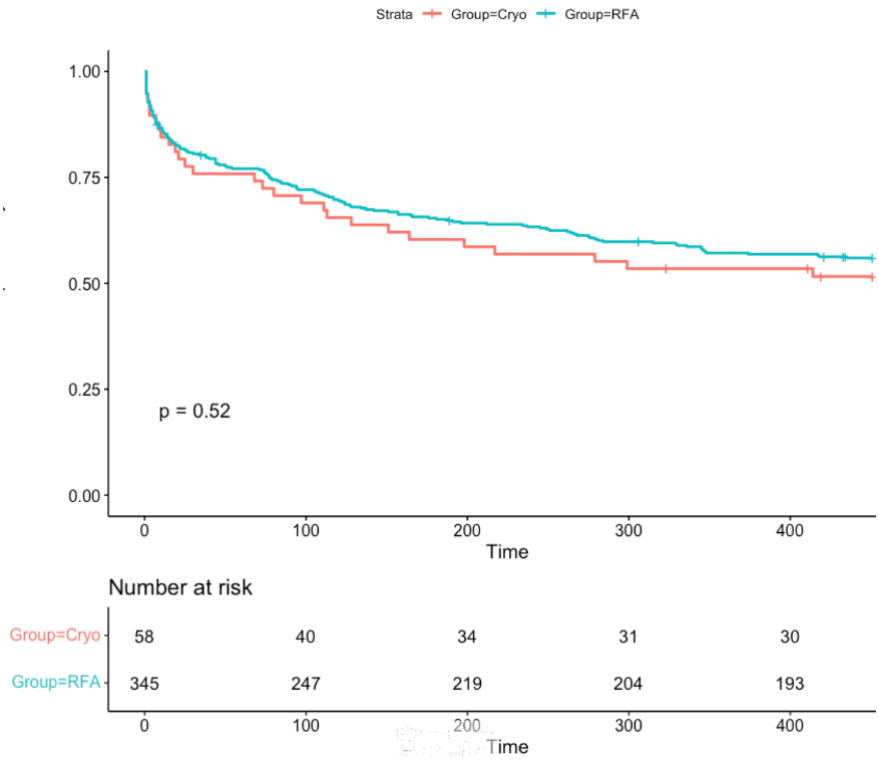
Abbreviations: Cryo = cryoballoon; PVI = pulmonary vein isolation; MRI = magnetic resonance imaging; RF = radiofrequency.

Figure 2: CMR Imaging Depicting Pre-Ablation Fibrosis and Post-Ablation Scar, Covered Fibrosis, and Non-Covered Fibrosis



Abbreviations: CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging.

Figure 3: Kaplan Meier Curve Showing Freedom from AAR Between RF and Cryo



The analysis was performed in RFA and Cryo patients who remained in follow-up after the 90-day blanking period. Follow up times are expressed in days. Number at risk indicates the number of patients remaining at risk at the indicated follow-up times without a prior atrial arrhythmia-recurrence event. Abbreviations: Cryo = cryoballoon; RFA = radiofrequency ablation.

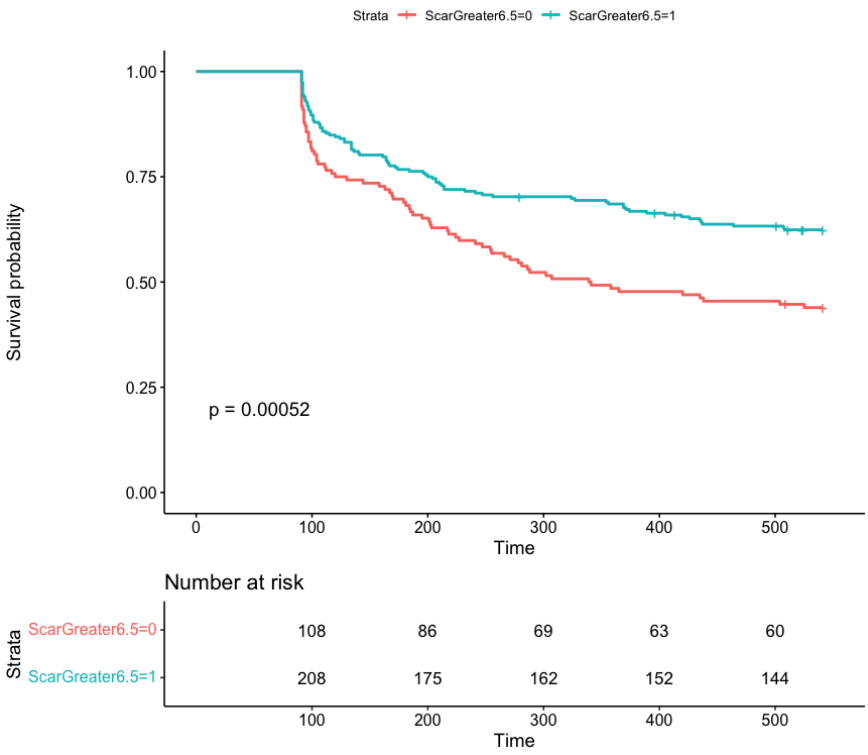
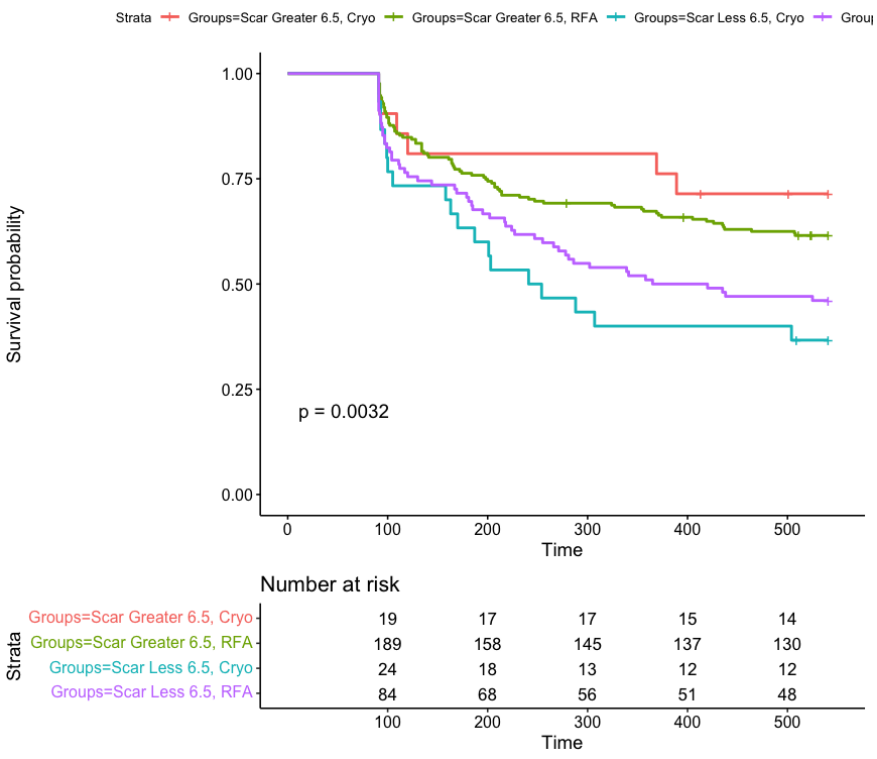


Figure 4: Kaplan Meier Curve: Post Ablation Scar Predicting Freedom from AAR

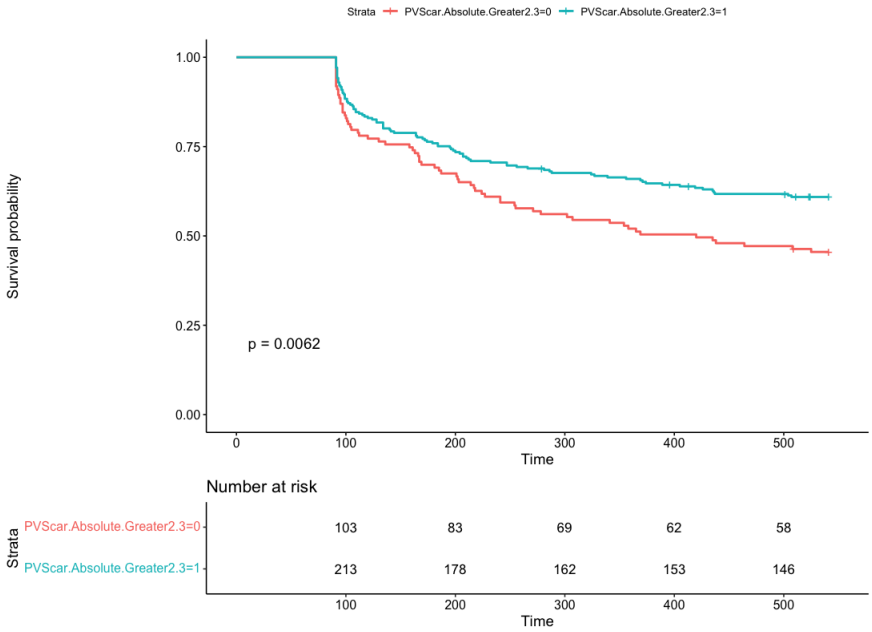
The analysis was performed in patients who remained in follow-up after the 90-day blanking period. Follow up times are expressed in days. Number at risk indicates the number of patients remaining at risk at the indicated follow-up times without a prior atrial arrhythmia-recurrence event.

Figure 5: Kaplan Meier Curves: Post Ablation Scar Predicting Freedom from AAR in RF and Cryo Subgroups



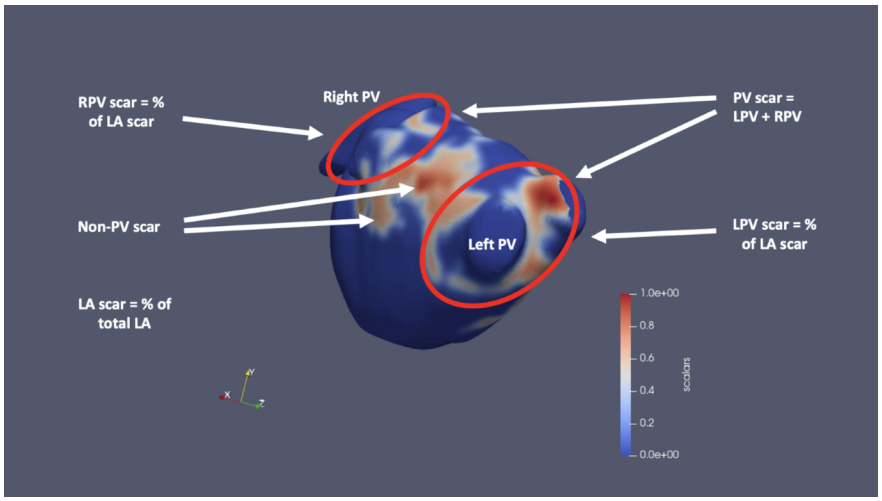
The analysis was performed in RFA and Cryo patients who remained in follow-up after the 90-day blanking period. Follow up times are expressed in days. Number at risk indicates the number of patients remaining at risk at the indicated follow-up times without a prior atrial arrhythmia-recurrence event. Abbreviations: Cryo = cryoballoon; RFA = radiofrequency ablation.

Figure 6: Post Ablation Absolute PV Scar Regionality Predicting Freedom From AAR



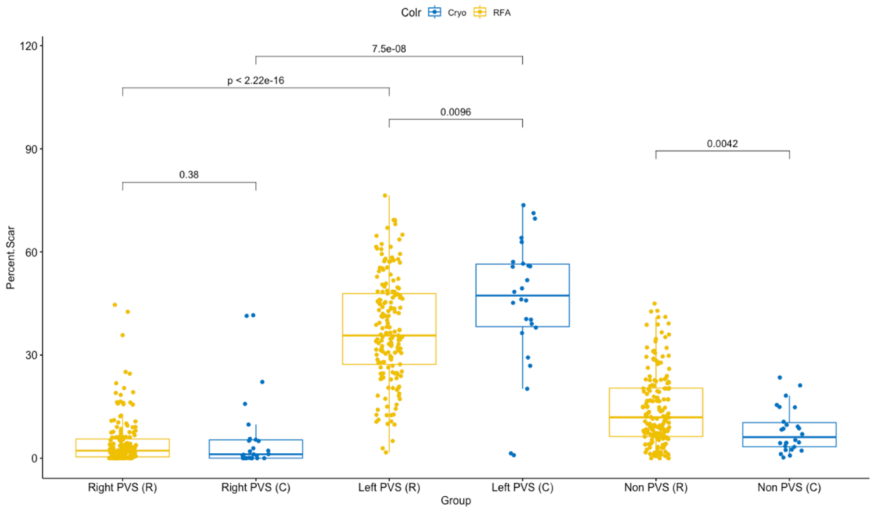
The analysis was performed in patients who remained in follow-up after the 90-day blanking period. Follow up times are expressed in days. Number at risk indicates the number of patients remaining at risk at the indicated follow-up times without a prior atrial arrhythmia-recurrence event. Abbreviations: PV = pulmonary veins.

Figure 7: LA Scar Regionality



Abbreviations: LA = left atrium; LPV = left pulmonary veins; PV = pulmonary veins; RPV = right pulmonary veins.

Figure 8: Bar Graph Showing Patients Free of AAR Post Ablation Scar Regionality



Abbreviations: AAR = atrial arrhythmia recurrence; Cryo = cryoballoon; PVS = pulmonary veins scar; RFA = radiofrequency ablation.