

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Committees: Steering Committee, Data Safety and Monitoring Board, End Point Adverse Event Committee, Data Coordinating Center

Steering Committee (in alphabetical order)

The Steering Committee is composed of investigators who are expert in the field of electrophysiology, cardiac imaging and atrial fibrillation ablation. The committee was responsible for supporting the design and reviewing the conduct of the study. It helped to identify and resolve problems with recruitment and performance, and evaluated the recommendations of the Data and Safety Monitoring Board. It was also responsible for the early termination of the trial, and advised on appropriate adjudication of major events by the End Point and Adverse Events Committee. It reviewed the final report, and is accountable for presenting and publishing the study results in close collaboration with the sponsor, as well as for evaluating the proposed sub-studies.

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Data Safety and Monitoring Board

The Data and Safety Monitoring Board is composed of four independent members.

The Data Safety and Monitoring Board was primarily responsible for ensuring the safety of the patients. Further responsibilities were to inform the sponsor about survival curve in the trial after the determined interim analysis, to formulate guidelines for the possible early termination of the study, to trigger unscheduled interim analysis if safety data indicate that treatment is associated with important adverse events, and to advise to stop the trial in case of an unacceptable patient risk exposure.

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End Point Adverse Event Committee

eAppendix (continued). Committees: Steering Committee, Data Safety and Monitoring Board, End Point Adverse Event Committee, Data Coordinating Center

The End Point and Adverse Event Committee is constituted of three experts in the field of ablation of atrial fibrillation. They have received blinded data regarding all serious adverse events, all deaths, all cerebrovascular accidents, and all first recurrences of atrial fibrillation, from the Contact Research Organization. The classification principles have been determined by the End Point and Adverse Event Committee in conjunction with the Steering Committee. The End Point and Adverse Event Committee was responsible for the classification of all received events, for the determination of which events fulfill the efficacy and safety end point criteria and for the classification of first atrial episode (atrial fibrillation recurrence or not).

Dhiraj Gupta, MD

Jason G. Andrade, MD

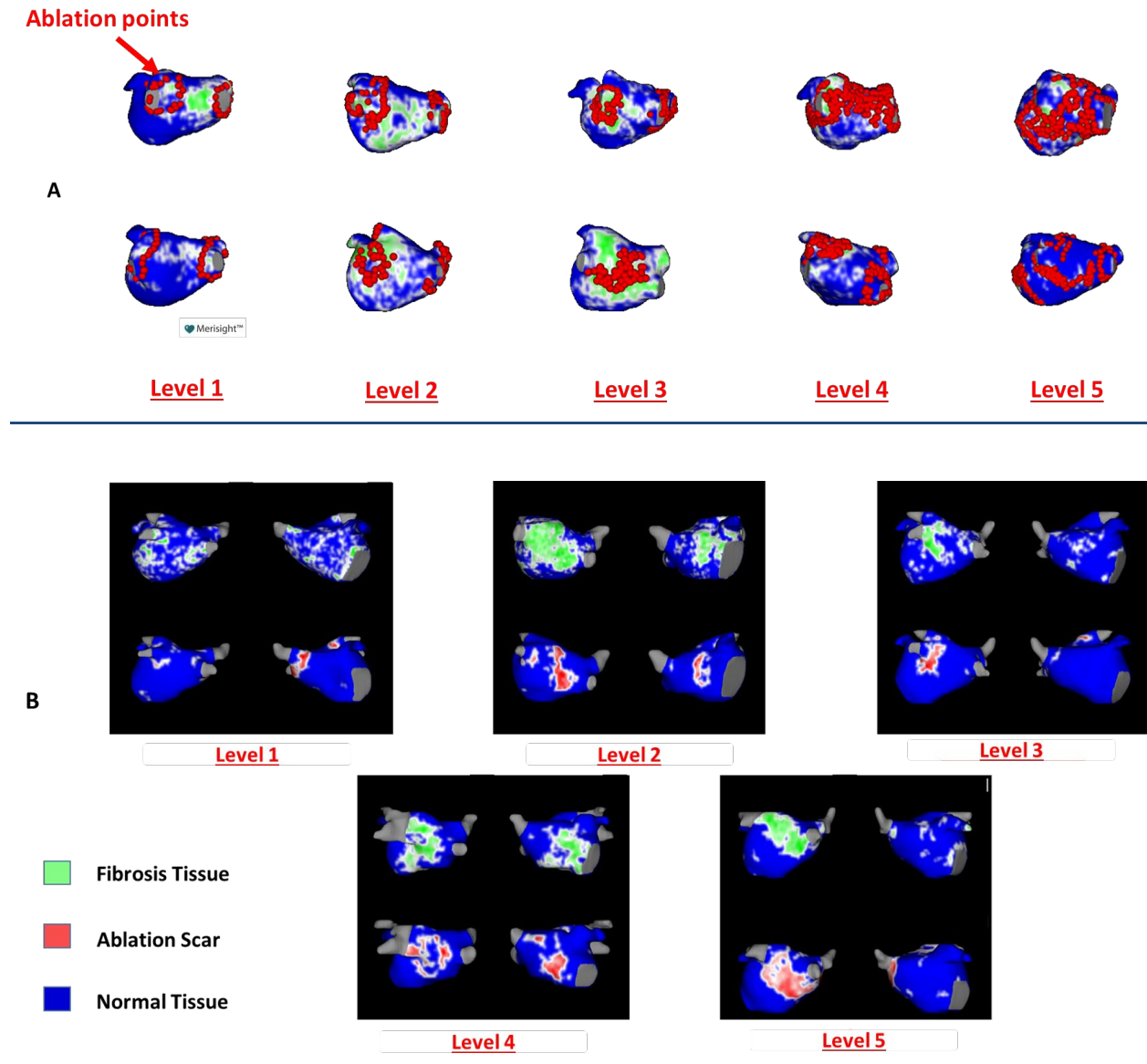
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Figures*

eFigure1.- Examples of Ablation Points Targeting Fibrosis (A) and Scar-Coverage/Encirclement of Fibrosis at 3 Months (B) in Each Level on the 5-Level Scale as Assessed on 3-Month MRI

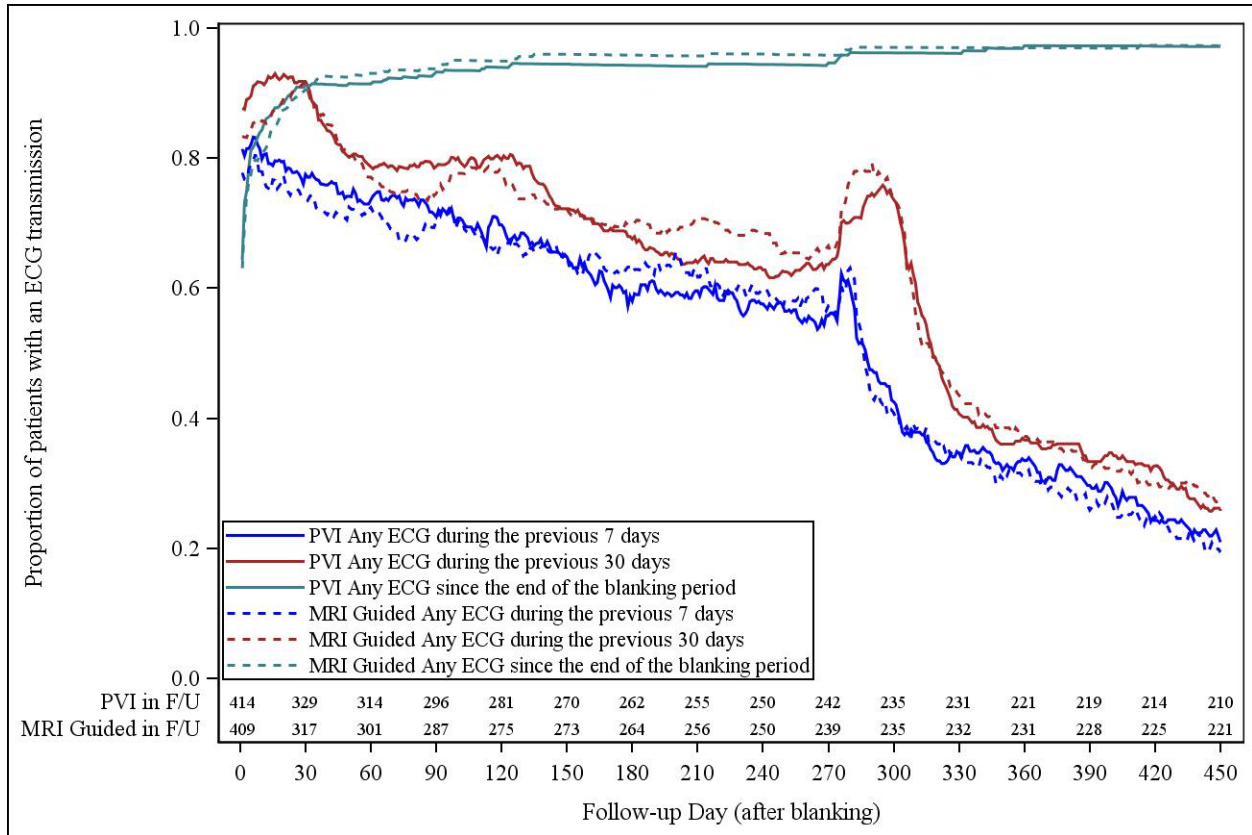


Level 1: No or little fibrosis covered/encircled Level 2 Some fibrosis covered/encircled Level 3: About half of fibrosis covered/encircled Level 4: Majority of fibrosis covered/encircled and Level 5: Nearly all or all fibrosis covered/encircled

Targeted Fibrosis: Baseline atrial fibrosis (green) covered by ablation points during the procedure

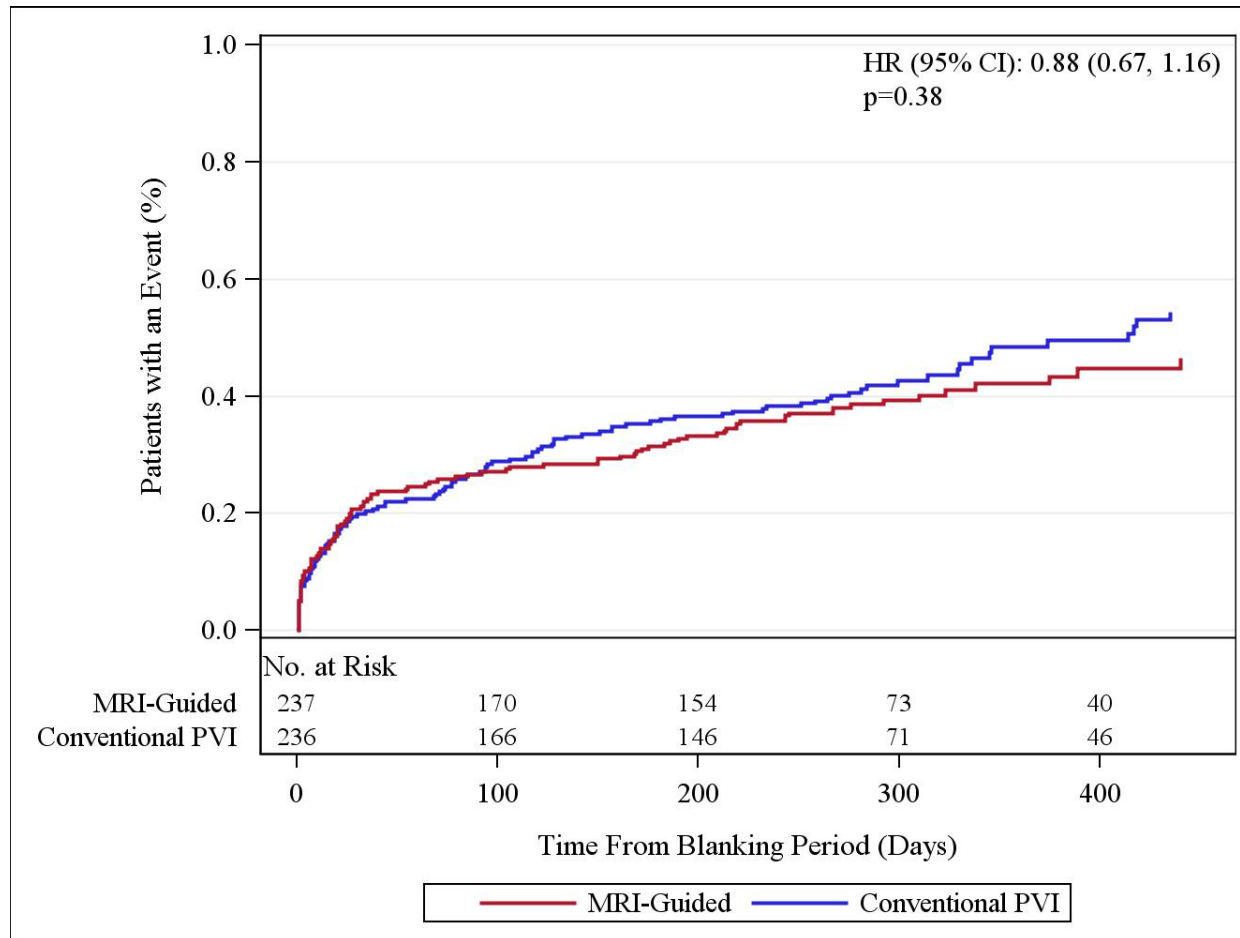
Scar-Covered/Encircled Fibrosis: Baseline atrial fibrosis (green) covered or encircled by the ablation induced scar as assessed on the 3-month MRI (red)

eFigure 2.- Completeness of ECG Transmissions in Both Treatment Arms

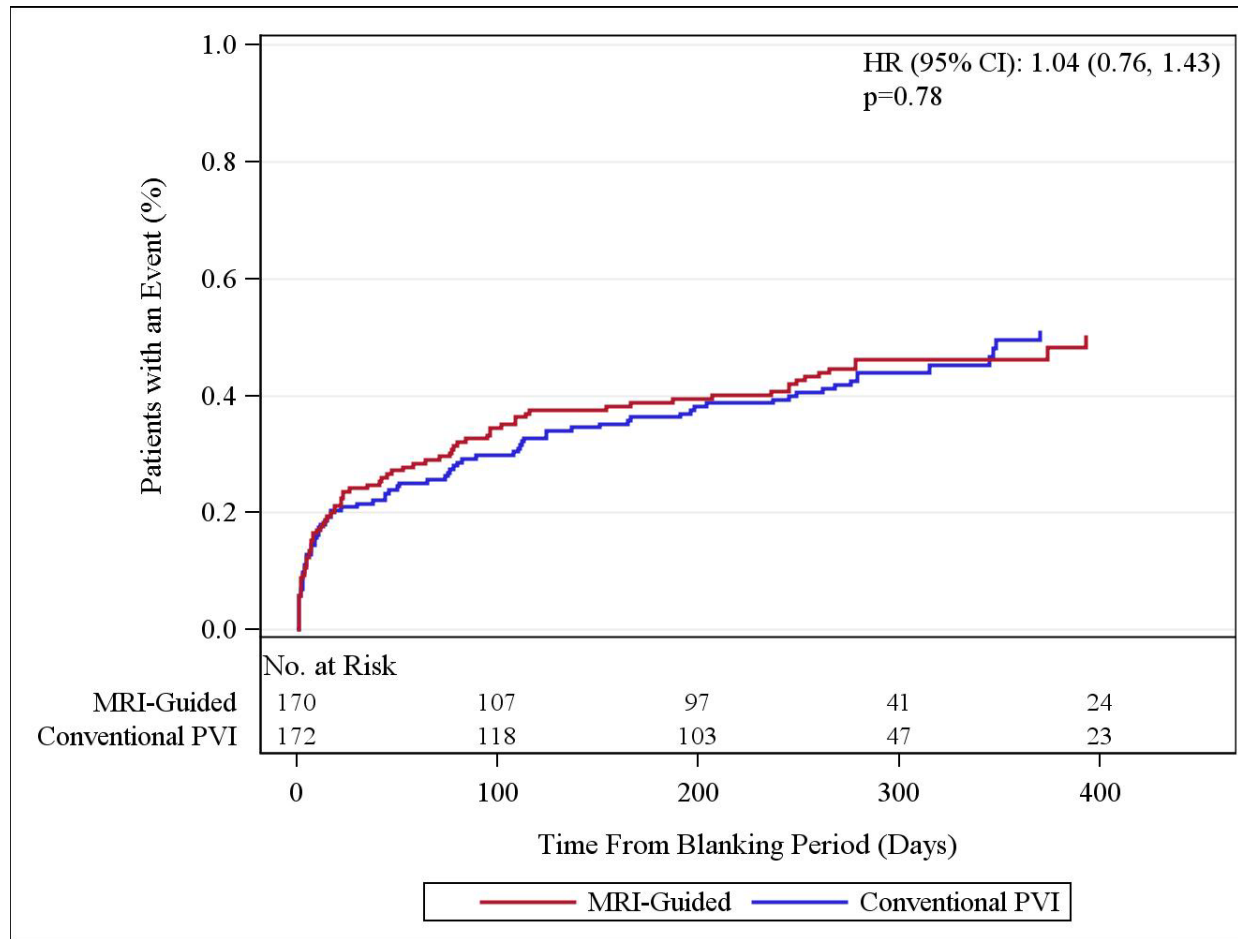


The horizontal axis in the plot indicates the follow-up day after the end of the blanking period. The two rows of numbers at the bottom of the plot indicate the number of randomized subjects without a previous primary outcome event. These numbers exceed the number of patients who remain at risk for the primary endpoint in Figure 2 because they include patients who have discontinued follow-up assessments. The blue curves indicate the proportions of these subjects with at least one ECG reading in the 1-week period immediately preceding the follow-up day indicated by the horizontal axis. The red curves indicate the proportion of these same subjects who provided at least one ECG reading during the previous 30 days. The green curves indicate the proportions of these same subjects with at least one ECG reading any time after the blanking period prior to that day.

eFigure 3.- Kaplan Meier Curve for the Primary End Point by Fibrosis Stages <20% (A) and ≥20% (B)



Panel A



Panel B

The analysis was performed in the subgroups of the modified intent-to-treat population with baseline fibrosis $\leq 20\%$ (Panel A) and with baseline fibrosis $> 20\%$ (Panel B). Follow-up times are expressed in days following the end of the 90 day blanking period. Entries at the bottom indicate the number of patients remaining at risk at the indicated follow-up times without a prior AA-recurrence event.

Tables

eTable1.- Eligibility Criteria

<u>Inclusion Criteria</u>
Patients with persistent AF defined as 7 days or more of AF as evidenced by rhythm strips or written documentation
Undergoing first AF ablation as per recent HRS consensus document
Age \geq 18 years
<u>Exclusion Criteria</u>
Previous left atrial ablation or any type of valvular surgery
Contraindication for DE-MRI with a full dose of contrast agent
Contraindication to beta blockers, if necessary, for DE-MRI
Women currently pregnant
Mental or physical inability to take part in the study
Inability to be placed in MRI due to body mass or body habitus
Known terminally ill patients
Subjects without daily access to a smart phone compatible with the ECG Check application and ability to upload ECG tracings for the entire follow up period.

eTable 2.- Descriptive Statistics of Mean Fibrosis Covered/Encircled and Mean Fibrosis Targeted in Each Treatment Arm

Effect		PVI-Only	MRI Guided
Mean Fibrosis Covered/Encircled		(N=373)	(N=362)
Level 1 or more		373 (100%)	362 (100%)
Level 2 or more		151 (40.5%)	255 (70.4%)
Level 3 or more		58 (15.5%)	162 (44.8%)
Level 4 or more		16 (4.3%)	70 (19.3%)
Level 5		0 (0%)	2 (0.6%)
Mean Fibrosis Targeted			
		(N=305)	(N=335)
Level 1 or more		305 (100%)	335 (100%)
Level 2 or more		144 (47.2%)	324 (96.7%)
Level 3 or more		51 (16.7%)	271 (80.9%)
Level 4 or more		9 (3%)	179 (53.4%)
Level 5		0 (0%)	32 (9.6%)

Level 1: No or little fibrosis covered/encircled

Level 2: Some fibrosis covered/encircled

Level 3: About half of fibrosis covered/encircled

Level 4: Majority of fibrosis covered/encircled

Level 5: Nearly all or all fibrosis covered/encircled

eTable 3. – Sensitivity Analyses for Estimating the Hazard Ratio Comparing the Primary Atrial-Arrhythmia Recurrence Composite Outcome Between the MRI-Guided and PVI-Only Treatment Groups

Model	Hazard ratio and (95% confidence interval)
Prespecified primary analysis, stratifying only for Utah Stage	0.95 (0.77,1.17)
Post-hoc analysis, stratifying by Utah Stage and clinical center ^a	0.94 (0.76,1.17)
Post-hoc analysis, stratifying by Utah Stage with clinical center ^b as a random effect	0.94 (0.77,1.16)

- a. Cox proportional hazards regression comparing the MRI and PVI-only interventions with the baseline hazard stratified by 88 strata defined by the 88 = 44 x 2 combinations of the 44 clinical sites with the 2 baseline fibrosis stages.
- b. Cox proportional hazards regression comparing the MRI and PVI-only interventions with the baseline hazard stratified by the 2 baseline fibrosis stages, with a gamma frailty model to account for variation in the baseline hazard across the 44 clinical sites.

eTable 4A. - Effects of Randomized Interventions on Quality of Life Outcomes
Prespecified Analysis

	Baseline	Adjusted Mean Change from Baseline to 3 Months				Adjusted Mean Change from Baseline to 12 Months			
	Mean (SD)	MRI-Guided Mean (SE)	PVI Only Mean (SE)	Difference MRI-Guided vs. PVI Only Mean (95% CI)	P-Value	MRI-Guided Mean (SE)	PVI Only Mean (SE)	Difference MRI-Guided vs. PVI Only Mean (95% CI)	P-Value
Toronto Atrial Fibrillation Symptom Severity Score	12.29 (8.05)	-5.48 (0.37)	-6.17 (0.37)	0.69 (-0.19, 1.58)	0.12	-6.80 (0.37)	-6.42 (0.36)	-0.38 (-1.23, 0.47)	0.38
SF-36 Physical Health Composite	42.62 (10.18)	5.47 (0.47)	6.14 (0.47)	-0.67 (-1.88, 0.54)	0.28	6.30 (0.52)	6.29 (0.51)	0.00 (-1.33, 1.33)	0.99
SF-36 Mental Health Composite	45.24 (10.93)	4.55 (0.52)	5.12 (0.52)	-0.57 (-1.89, 0.76)	0.40	5.31 (0.54)	5.54 (0.53)	-0.23 (-1.61, 1.15)	0.74

The Toronto Atrial Fibrillation Severity Score was measured for 821, 739 and 700 randomized subjects who received ablation at baseline, 3 months and 12 months, respectively. The SF-36 was administered for 831, 811, and 786 subjects at baseline, 3 months and 12 months. Baseline means and SD were computed without adjustment from all available baseline data. Adjusted mean changes from baseline to 3 and 12 months were estimated within each treatment group and compared between treatment groups using a constrained mixed effects model in which baseline means were assumed equal between the randomized groups with adjustment for baseline fibrosis stratum and with an unstructured covariance matrix to account for serial correlation.

***eTable 4B. - Effects of Randomized Interventions on Quality of Life Outcomes
Post-hoc Sensitivity Analysis Including Site as a Random Effect***

	Baseline	Adjusted Mean Change from Baseline to 3 Months				Adjusted Mean Change from Baseline to 12 Months			
	Mean (SD)	MRI-Guided Mean (SE)	PVI Only Mean (SE)	Difference MRI-Guided vs. PVI Only Mean (95% CI)	P-Value	MRI-Guided Mean (SE)	PVI Only Mean (SE)	Difference MRI-Guided vs. PVI Only Mean (95% CI)	P-Value
Toronto Atrial Fibrillation Symptom Severity Score	12.29 (8.05)	-5.44 (0.37)	-6.16 (0.37)	0.72 (-0.15, 1.59)	0.11	-6.78 (0.36)	-6.42 (0.36)	-0.36 (-1.20, 0.48)	0.40
SF-36 Physical Health Composite	42.62 (10.18)	5.45 (0.47)	6.14 (0.47)	-0.69 (-1.88, 0.51)	0.26	6.30 (0.51)	6.31 (0.51)	-0.01 (-1.31, 1.30)	0.99
SF-36 Mental Health Composite	45.24 (10.93)	4.53 (0.52)	5.12 (0.52)	-0.59 (-1.91, 0.73)	0.38	5.29 (0.54)	5.55 (0.53)	-0.25 (-1.63, 1.12)	0.72

The Toronto Atrial Fibrillation Severity Score was measured for 821, 739 and 700 randomized subjects who received ablation at baseline, 3 months and 12 months, respectively. The SF-36 was administered for 831, 811, and 786 subjects at baseline, 3 months and 12 months. Baseline means and SD were computed without adjustment from all available baseline data. Adjusted mean changes from baseline to 3 and 12 months were estimated within each treatment group and compared between treatment groups using a constrained mixed effects models in which baseline means were assumed equal between the randomized groups with adjustment for baseline fibrosis stratum, inclusion of clinical site as a random effect, and with an unstructured covariance matrix to account for serial correlation.

eTable 5. - Efficacy Outcomes by Fibrosis Stages: A <20% and B ≥20%^a

A. Baseline fibrosis < 20%

	MRI-guided N=237	PVI Only N=236	Risk difference (95% Confidence Interval) ^b	Hazard Ratio (95% Confidence Interval) ^c	P-value ^d
	N (%)	N (%)			
Primary Outcome					
Atrial arrhythmia recurrence or repeat ablation ^e	97 (40.9)	109 (46.2)	-0.037 (-0.117,0.042)	0.88 (0.67, 1.16)	0.37
Components of the Primary Outcome (Atrial arrhythmia types) ^f					
Atrial fibrillation	75 (31.6)	80 (33.9)	-0.018 (-0.096,0.062)	0.93 (0.68, 1.28)	0.66
Atrial flutter	15 (6.3)	19 (8.1)	-0.020 (-0.076,0.034)	0.78 (0.40, 1.54)	0.47
Atrial tachycardia	4 (1.7)	4 (1.7)	-0.000 (-0.028,0.030)	0.98 (0.25, 3.91)	0.98
Secondary Outcomes					
Atrial arrhythmia, repeat ablation, or new atrial arrhythmia medication ^{e,g}	99 (41.8)	116 (49.2)	-0.058 (-0.139,0.025)	0.83 (0.64, 1.09)	0.17
Repeat Ablation ^h	30 (12.7)	41 (17.4)	-0.035 (-0.091,0.014)	0.73 (0.46, 1.17)	0.20
Post-hoc Outcome					
Atrial arrhythmia recurrence, repeat ablation, new atrial arrhythmia medication or cardioversion ^{e,g}	101 (42.6)	118 (50)	-0.060 (-0.142,0.025)	0.83 (0.63, 1.08)	0.16

eTable 5 (continued). Efficacy Outcomes by Fibrosis Stages: <20% and ≥20%

B. Baseline fibrosis ≥ 20%

	MRI-guided N=170	PVI Only N=172	Risk difference (95% Confidence Interval) ^b	Hazard Ratio (95% Confidence Interval) ^c	P-value ^d	Interaction P-value ⁱ
	N (%)	N (%)				
Primary Outcome						
Atrial arrhythmia recurrence or repeat ablation ^e	78 (45.9)	79(45.9)	0.027 (-0.073,0.105)	1.09 (0.80- 1.50)	0.59	0.32
Components of the Primary Outcome (Atrial arrhythmia types) ^f						
Atrial fibrillation	54 (31.8)	67(39.0)	-0.031 (-0.130,0.065)	0.90 (0.62, 1.29)	0.55	0.87
Atrial flutter	18 (10.6)	7(4.1)	0.080 (0.012,0.150)	2.82 (1.17, 6.80)	0.02	0.02
Atrial tachycardia	3 (1.8)	2(1.2)	0.011 (-0.021,0.043)	1.80 (0.29, 11.00)	0.53	0.60
Secondary Outcomes						
Atrial arrhythmia, repeat ablation, or new atrial arrhythmia medication ^{e, g}	84 (49.4)	80 (46.5)	0.057 (-0.041,0.157)	1.19 (0.87, 1.62)	0.27	0.09
Repeat Ablation ^h	27 (15.9)	31 (18.0)	-0.015 (-0.082,0.052)	0.90 (0.53- 1.50)	0.68	0.57
Post-hoc Outcome						
Atrial arrhythmia recurrence, repeat ablation, new atrial arrhythmia medication or cardioversion ^{e, g}	86 (50.6)	80 (46.5)	0.068 (-0.031,0.170)	1.23 (0.90- 1.67)	0.19	0.06

eTable 5 (continued). Efficacy Outcomes by Fibrosis Stages: <20% and ≥20%

- a. Efficacy outcomes were evaluated in randomized patients who remained in follow-up after the 90 day blanking period.
- b. Risk differences calculated as the difference in risk of the outcome in the MRI guided group and the risk of the outcome in the PVI guided group by day 275 after the start of the blanking period. 95% CI are percentile confidence intervals from 2000 bootstrap samples.
- c. Hazard ratios were computed using Cox regression with baseline hazards stratified by baseline fibrosis stratum.
- d. P-values were computed from the log-rank test stratified by baseline fibrosis stratum.
- e. The analysis evaluates the listed events as a composite outcome, with the first occurrence of any of the listed events counted as the composite event for the analysis.
- f. Atrial arrhythmia type for atrial arrhythmia recurrences designating the primary outcome
- g. Only new initiations of atrial arrhythmia medications are included in the atrial arrhythmia medication component of this composite outcome.
- h. Repeat ablation is counted as an outcome even if there was an atrial arrhythmia recurrence, cardioversion or start of atrial arrhythmia medications prior to the repeat ablation date
- i. Interaction p-values compare hazard ratios for the MRI-guided vs. PVI only groups between the two baseline fibrosis strata (<20% vs. ≥20%).

Abbreviations: MRI *Magnetic Resonance Imaging*, PVI *Pulmonary Vein Isolation*

eTable 6. – Details of Strokes in First 30 Days

	Age (years)	Sex	Stroke event	Day post-ablation	Baseline Fibrosis	Anticoagulation resumed post-ablation
Patient 1	72	Male	Left vision defect	1	17.5	Yes
Patient 2	62	Male	Vision and speech disturbances	3	26.9	Yes
Patient 3	67	Male	Expressive dysphasia	0	23.3	Yes
Patient 4	67	Male	Left vision defect	1	25.6	Yes
Patient 5	45	Male	Left facial droop	0	7.9	Yes
Patient 6	72	Male	In the context of Ventricular Fibrillation	26	31.7	Yes

eTable 7.- Safety Outcomes by Fibrosis Stages ^a

	Baseline fibrosis < 20%		Baseline fibrosis ≥ 20%	
	MRI Guided ^b (N = 234)	PVI Only ^b (N = 250)	MRI Guided ^b (N = 169)	PVI Only ^b (N = 178)
Bleeding requiring transfusion	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Heart Failure	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Pulmonary Vein Stenosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stroke/TIA	2 (0.9%)	0 (0%)	4 (2.4%)	0 (0%)
Death	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Primary Composite Safety Outcome, defined as at least one of the above events	4 (1.7%)	0 (0%)	5 (3.0%)	0 (0%)
Esophageal Injury ^c	2 (0.9%)	1 (0.4%)	3 (1.8%)	0 (0%)
Perforation/Tamponade ^c	2 (0.9%)	4 (1.6%)	3 (1.8%)	1 (0.6%)

- a. The safety outcomes were evaluated in the two baseline fibrosis subgroups of the safety population for the 30 day period following ablation.
- b. The safety outcomes were evaluated according to the received treatment intervention.
- c. Esophageal injury and perforation/tamponade were initially identified by clinical sites and reviewed by the trial’s medical monitor. Final classifications were made by a Safety Outcome Review Committee.

Abbreviations: TIA *Transient Ischemic Attack*, MRI *Magnetic Resonance Imaging*, PVI *Pulmonary Vein Isolation*