Supplementary Online Content

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Appendix.

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

Appendix

Study Design:

Clinical patient characteristics were collected for this study from clinic visits and chart reviews. Information such as age, gender, classic cardiovascular risk factors including diabetes, hypertension, hyperlipidemia, smoking history, previously diagnosed coronary artery disease, bypass surgery, mitral valve disease or surgery, etc. were entered into a database at baseline and at the last follow-up for final analyses. Data pertinent to the diagnosis of atrial fibrillation (AF) including date of first diagnosis, type of AF (paroxysmal, persistent, long-standing persistent or permanent), history of stroke and anti-coagulation, rate control drugs and anti-arrhythmic medications were collected. Sites were required to send the core center a copy of the patients' electrocardiograms or ambulatory monitor recordings/reports for the outcomes analysis. Here are the detailed inclusion and exclusion criteria:

Inclusion Criteria:

1. Patients who will undergo a first AF ablation as per recent Heart Rhythm Society (HRS) consensus document [15]
2. Patients who have had a DE-MRI pre-ablation.
3. Age ≥18 years.

Exclusion Criteria:

1. Contraindication for delayed-enhancement MRI (DE-MRI) with a full dose of Gadolinium-based contrast agent (with a GFR of not less than 30 ml/min).
2. Previous left atrial ablation or surgical procedure
3. Women currently pregnant, breastfeeding, or of childbearing age not currently taking or not willing to use a reliable form of contraception
4. Mental or physical inability to take part in the study
5. Uncontrolled hypertension

6. Morbid obesity (BMI > 35), or inability to be placed in MRI scanner due to body mass.

Atrial MR Image Acquisition:

The atrial imaging protocol included pulse sequences to evaluate anatomy of the left atrium and pulmonary veins (PVs) and to detect left atrial fibrosis. High-resolution three-dimensional (3D) DE-MR images of the left atrium were acquired about 15 minutes after contrast injection using a 3D ECG-gated, respiratory navigated, inversion recovery prepared gradient echo (GRE) pulse sequence. Inversion preparation was applied every heart beat and fat saturation was performed immediately before data acquisition. Data acquisition was limited to 15% of averaged cardiac cycle and was performed during left atrial diastole. The other scan parameters for DE-MRI of left atrium at 3 Tesla (T) scanner were: axial imaging volume with field of view (FOV)=400x400x110 mm, voxel size=1.25x1.25x2.5 mm, repetition time (TR)=3.1 ms, echo time (TE)=1.4 ms, flip angle of 14 degrees. Scan parameters for DE-MRI of left atrium at 1.5T scanner were: FOV=360x360x100 mm, voxel size=1.25x1.25x2.5, TR/TE=5.2/2.4 ms, flip angle of 20 degrees. Depending on patient respiration, typical scan time for DE-MRI study was 6-12 minutes at 1.5T and 5-9 minutes at 3T scanners. Each of the participating centers followed their regular clinical protocol for contrast injection for cardiac MRI. Table A1 below shows the contrast agents and their respective doses used at the various centers participating in the DECAAF study.

Left Atrium Image Segmentation:

Left atrial wall volumes were manually segmented by expert observers from

the DE-MRI images using the Corview image processing software (MARREK, Salt Lake City, UT). Briefly, the protocol for segmentation proceeded as follows: first, the endocardial border of the left atrium was defined, including the PV extensions, by manually tracing the left atrium-PV blood pool in each slice of the DE-MRI volume. Next, the endocardial segmentation was morphologically dilated and then manually adjusted to create an assessment of the boundary of the epicardial left atrium surface. Finally, the endocardial segmentation was subtracted from the epicardial segmentation to define a wall segmentation, which was manually edited to exclude the mitral valve and PVs. Thus, the resulting left atrial wall segmentation included the 3D extent of both the left atrial wall and the antral regions of the PVs. Images that could not be segmented or quantified due to poor contrast, blurred left atrial boundaries, and presence of artifacts in left atrial region were defined as poor quality.

e**Table 1.** Type of contrast agent and dosage in DECAAF participating sites

Contrast agent	Number of centers	Dose (mmol/kg)
Dotarem	2	0.2
Gadovist	3	0.15, 0.15, 0.2
Magnevist	5*	0.1, 0.2, 0.2, 0.2, 0.2
Multihance	5*	0.1
Omniscan	1	0.2

*One center switched from Magnevist to Mutihance during the study.

eTable 2. Distribution of ablation procedures in the patient cohort

Ablation Type	Number (%)
PVI Only	177 (68.1%)
PVI/CTI	43 (16.5%)
CTI/CFAE	17 (6.5%)
PVI/CFAE	14 (5.4%)
PVI/PWD	3 (1.1%)
PVI/PWD/CTI	1 (0.4%)
PVI/PWD/CFAE/CTI	1 (0.4%)
PVI/CTI/CFAE	2 (0.8%)
PWD	2 (0.8%)

PVI=Pulmonary Vein Isolation; CTI= Cavo-tricuspid Isthmus; CFAE=Complex Fractionated Electrogram; PWD=Posterior Wall Debulking

e**Table 3.** Baseline characteristics for different stages of fibrosis

	Stage I (N = 49)	**Stage II (N = 107)**	**Stage III (N = 80)**	**Stage IV (N = 24)**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age at ablation	57.7 (13.2)	59.2 (10.2)	59.4 (10.3)	59.1(10.7)
Initial BMI (kg/m)	26.9 (4.4)	28.1 (5.7)	27.8 (4.3)	28.4 (4.9)
$CHADS_2$ score[a]	0.67 (0.77)	0.93 (1.05)	0.94 (0.89)	0.88 (0.68)
LVEF (%)	57.9 (9.7)	58.7 (10.0)	58.8 (7.3)	58.5(8.5)
Left Atrial Volume (ml)	101.3 (50.9)	104.4 (38.3)	100.9 (35.1)	99.9(33.3)
Left Atrial Fibrosis (%)	7.7 (1.9)	14.4 (2.9)	24.1 (2.7)	35.6 (4.2)

[a]The $CHADS_2$ score is a validated clinical prediction tool commonly used to estimate the risk of stroke in AF. The score is derived from the sum of point values of the five individual stroke risk factors listed in the table.

e**Table 4.** Mean differences in structural remodeling (% SRM) associated with individual clinical and demographic factors

Factor	Estimate	95% CI	p-value
Female gender	-0.907	(-3.148 – 1.334)	0.43
Age at ablation (per 10 years)	0.353	(-0.619 – 1.325)	0.48
AF type Persistent/Permanent vs. paroxysmal	-0.829	(-3.163 – 1.505)	0.49
Initial BMI (per kg/m^2)	0.056	(-0.154 – 0.266)	0.60
History of CAD	2.316	(-1.148 – 5.779)	0.19
History of CHF	1.201	(-3.415 – 5.817)	0.61
History of Diabetes	1.468	(-1.838 – 4.775)	0.38
History of Smoking	0.417	(-3.254 – 4.088)	0.82
History of Mitral Valve Disease	3.572	(-1.026 – 8.170)	0.13
History of Hyperlipidemia	1.366	(-0.903 – 3.635)	0.24
History of Stroke	-4.190	(-9.132 – 0.752)	0.10
CHADS2 score=1 vs. 0	1.562	(-0.558 – 3.681)	0.15
CHADS2 score=2 vs. 0	1.512	(-1.372 – 4.395)	0.31
CHADS2 score=3 vs. 0	-3.200	(-9.629 – 3.229)	0.33
CHADS2 score=4 vs. 0	-0.360	(-7.303 – 6.583)	0.92
Congestive Heart Failure	-1.420	(-5.888 – 3.047)	0.53
Age more than 75 years	-3.231	(-7.998 – 1.536)	0.19
Hypertension more than 160 mm Hg	3.264	(1.207 – 5.321)	0.002
Diabetes Mellitus	2.031	(-1.133 – 5.194)	0.21
Prior Stroke or TIA	-3.283	(-8.049 – 1.483)	0.18
Antiarrhythmic drug therapy	-0.878	(-3.045 – 1.290)	0.43
Left Atrial Volume (per 10 ml)	-0.021	(-0.285 – 0.244)	0.88
LVEF (per 1 %)	0.011	(-0.106 – 0.127)	0.86

Shown are estimated mean differences in % fibrosis associated with each of the indicated demographic and clinical factors based on separate univariable linear regression analyses.

[BMI=body mass index, CAD=coronary artery disease, CHF=congestive heart failure, TIA=transient ischemic attack, LVEF=left ventricular ejection fraction]

e**Table 5.** Association of recurrence of atrial fibrillation with percentage fibrosis censored at follow-up of 325 days from the blanking period

Model	HR (per 1%)	Lower confidence Interval	Higher confidence interval	p-value
Model 1	1.056	1.033	1.081	<0.0001
Model 2	1.056	1.032	1.081	<0.0001
Model 3	1.056	1.033	1.082	<0.0001
Model 4	1.053	1.029	1.079	<0.0001
Model 5	1.058	1.033	1.085	<0.0001

Shown are the overall hazard ratios relating time of atrial fibrillation recurrence to % fibrosis after adjustment for the following sets of covariates:
Model 1: Unadjusted
Model 2: Adjusted for participating center
Model 3: Adjusted for age, gender and participating center
Model 4: Adjusted for age, gender, hypertension, congestive heart failure, mitral valve disease, diabetes and participating center
Model 5: Adjusted for age, gender, hypertension, congestive heart failure, mitral valve disease, diabetes, paroxysmal/persistent atrial fibrillation, left atrial volume, left ventricular ejection fraction and participating center.
Follow-up time was censored at day 325 after completion of the blanking period.