Atrial Fibrillation Ablation Outcome Is Predicted by Left Atrial Remodeling on MRI

Christopher McGann, Nazem Akoum, Amit Patel, Eugene Kholmovski, Patricia Revelo, Kavitha Damal, Brent Wilson, Josh Cates, Alexis Harrison, Ravi Ranjan, Nathan S. Burgon, Tom Greene, Dan Kim, Edward V.R. DiBella, Dennis Parker, Rob S. MacLeod and Nassir F. Marrouche

Circ Arrhythm Electrophysiol. published online December 20, 2013;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084

DOI: 10.1161/CIRCEP.113.000689

Atrial Fibrillation Ablation Outcome Is Predicted by Left Atrial Remodeling on MRI

Running title: *McGann et al.; AF Ablation Outcome Predicted by LGE-MRI*

Christopher McGann, MD[1,2,3]*; Nazem Akoum, MD[1,2]*; Amit Patel, MD[3]; Eugene Kholmovski, PhD[1,4]; Patricia Revelo, MD, PhD[6]; Kavitha Damal, PhD[1]; Brent Wilson, MD, PhD[1,2,3]; Josh Cates, PhD[1,5]; Alexis Harrison, MD[1,2]; Ravi Ranjan, MD[1,2]; Nathan S. Burgon BSc[1]; Tom Greene, PhD[7]; Dan Kim, PhD[1,4]; Edward V.R. DiBella, PhD[1,4]; Dennis Parker, PhD[1,4]; Rob S. MacLeod, PhD[1,5]; Nassir F. Marrouche, MD[1,2]

[1]Comprehensive Arrhythmia Research and Management Center (CARMA), [2]Division of Cardiology, [3]Department of Surgery, [4]Department of Radiology, [5]Scientific Computing and Imaging Institute, Bioengineering, [6]Department of Pathology, [7]Division of Epidemiology,University of Utah Health Sciences Center, Salt Lake City, UT
*contributed equally

Correspondence:
Christopher McGann, MD
Departments of Internal Medicine and Radiology
Comprehensive Arrhythmia Research and Management Center (CARMA)
University of Utah Health Sciences Center
30 North 1900 East
Salt Lake City, UT 84132
Tel: 801 585-2341
Fax: 801 587-5874
E-mail: chris.mcgann@hsc.utah.edu

Journal Subject Codes: [30] CT and MRI, [22] Ablation/ICD/surgery

DOI: 10.1161/CIRCEP.113.000689

Abstract:

Background - While catheter ablation therapy for atrial fibrillation (AF) is becoming more common, results vary widely and patient selection criteria remain poorly defined. We hypothesized that late gadolinium enhancement magnetic resonance imaging (LGE-MRI) can identify left atrial (LA) wall structural remodeling (SRM) and stratify patients who are likely or not to benefit from ablation therapy.

Methods and Results - LGE-MRI was performed on 426 consecutive AF patients without contraindications to MRI and before undergoing their first ablation procedure and on 21 non-AF control subjects. Patients were categorized by SRM stage (I-IV) based on percentage of LA wall enhancement for correlation with procedure outcomes. Histological validation of SRM was performed comparing LGE-MRI to surgical biopsy. A total of 386 patients (91%) with adequate LGE-MRI scans were included in the study. Post-ablation, 123 (31.9%) experienced recurrent atrial arrhythmias over one-year follow-up. Recurrent arrhythmias (failed ablations) occurred at higher SRM stages with 28/133 (21.0%) stage I, 40/140 (29.3%) stage II, 24/71 (33.8%) stage III, and 30/42 (71.4%) stage IV. In multi-variate analysis, ablation outcome was best predicted by advanced SRM stage (hazard ratio (HR) 4.89; $p<0.0001$) and diabetes (HR 1.64; $p=0.036$) while increased LA volume and persistent AF were not significant predictors. LA wall enhancement was significantly greater in AF patients vs. non-AF controls (16.6±11.2% vs. 3.1±1.9%, $p<0.0001$). Histological evidence of remodeling from surgical biopsy specimens correlated with SRM on LGE-MRI.

Conclusions - Atrial SRM is identified on LGE-MRI and extensive LGE (≥30% LA wall enhancement) predicts poor response to catheter ablation therapy for AF.

Key words: atrial fibrillation arrhythmia, catheter ablation, magnetic resonance imaging, remodeling, outcome

DOI: 10.1161/CIRCEP.113.000689

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice with its prevalence increasing along with the age of the population [1,2]. It occurs in 1-2% of the general population and the lifetime risk for development of AF in the Framingham cohort was 25% among those over 40 years of age [3]. The clinical consequences of AF are well known and include increased risk of heart failure, stroke, and death [4]. Increased risk for the development of AF has been associated with factors such as age, hypertension, and obesity [5-9] but more specific and early markers for disease could have important clinical impact.

Several large clinical trials have shown no significant benefits of rhythm control strategies using anti-arrhythmic medications over rate control alone in the treatment for AF [10-12]. As a result, the morbidity and mortality associated with AF remains largely unchanged along with the associated medical costs, which are estimated to be greater than 6 billion dollars annually in the United States and Europe alone. Given the limited utility of anti-arrhythmic medications, there has been growing interest in the treatment of AF with catheter ablation due to improvements in efficacy and outcomes [13-17]. However, reported success rates for AF ablation vary widely in the published literature ranging from 40-70% and suggest a need for better patient selection criteria [18].

Atrial structural remodeling with associated interstitial fibrosis is well described in patients with AF in histological studies [19-23]. Tissue examination of the LA has also confirmed the presence of fibrosis in regions of low voltage tissue [24]. Whether fibrotic transformation of atrial myocardium is a cause or consequence of AF in patients with cardiovascular disease remains unclear. Studies have demonstrated that AF is associated with electrical, contractile, and structural remodeling (SRM) in the LA that contributes to the persistence and sustainability

of the arrhythmia [25]. It has also been shown that the end result of this remodeling process is loss of atrial myocytes and increased collagen content and hence fibrosis of the LA wall. Previous small electrophysiology and imaging studies have shown low voltage and fibrotic LA tissue as independent predictors of procedure outcome and suggest that an accurate and reliable measure of LA fibrosis may improve clinical decision making [26-27]. Better patient selection criteria would be expected to improve procedure outcomes while reducing costs and avoiding potential complications in those unlikely to benefit from ablation.

In the current study, we tested the hypothesis that LGE-MRI can provide a measure of LA wall SRM in patients with AF and will stratify those patients who are likely or not to benefit from catheter ablation procedures.

Methods

Patients. The study population included 426 consecutive patients without contraindications to MRI who underwent their first AF ablation procedure, 21 control subjects, and 9 AF patients and 1 non-AF patient who had LA wall biopsies during cardiothoracic surgical procedures. The control group was comprised of a series of consecutive patients presenting for routine screening colonoscopy (21 patients), none of whom had a history of AF. The AF study population was recruited from the AF clinic from December 2006 to May 2009 with three-year follow-up. Statistical analysis of the data focuses on the 1-year follow-up when recurrences were based on routine, scheduled Holter monitoring in all patients (see details of follow-up below). The control and surgical groups were recruited from August 2010 to December 2011. Written informed consent was obtained on all patients and the protocol was approved by the Institutional Review Board at the University of Utah and was compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

DOI: 10.1161/CIRCEP.113.000689

Magnetic resonance imaging. All subjects underwent initial 3D LGE-MRI scanning to determine the degree of LA wall SRM regardless of the rhythm at the time of scanning. Adequate images for quantification of LA wall SRM was obtained in 386/426 patients in the AF ablation cohort (91%), all control subjects, and all surgical patients. High-resolution LGE images of LA were acquired approximately 15 minutes after injection of 0.1 mmol/kg gadolinium contrast (Multihance, Bracco Diagnostics Inc., Princeton, NJ) using a 3D respiratory navigated, inversion recovery prepared GRE pulse sequence with specific parameters published previously [27-29]. The specific parameters for MR scanning at 1.5T vs. 3T are provided in the supplemental materials. Briefly, for this 3D respiratory navigated, ECG-gated, inversion recovery prepared GRE pulse sequence, an inversion preparation was applied every heart beat and fat saturation was applied immediately before data acquisition. The voxel size = 1.25 x 1.25 x 2.5 mm on both 1.5T and 3T scanners.

Though pre-scan ECG's were not routinely obtained, the rhythm status is always clarified at the time of MRI scanning by the technologist and reading physician by use of the ECG gating from the scanner and if necessary by evaluating the cine images. By these criteria, 67% of the study patients appeared in sinus rhythm at the time of scanning. Of the 40 patients with inadequate scans, artifacts due to patient motion, marked arrhythmias, or gating problems were the main contributing factors. Scanning was performed on a 1.5 Tesla Avanto (286 patients) or a 3 Tesla Verio (100 patients) MR scanner (Siemens Healthcare, Erlangen, Germany).

LGE-MRI assessment of LA structural remodeling. LA wall volumes were manually segmented by three trained observers from the LGE-MRI images using the Corview image processing software (MARREK Inc., Salt Lake City, UT). The MRI scans were de-identified and observers were blinded to whether scans were performed on control subjects, AF patients, or

surgical patients. The protocol for segmentation proceeded as follows. First, the endocardial border of the LA was defined, including an extent of pulmonary vein (PV) sleeves, by manually tracing the LA-PV blood pool in each slice of the LGE-MRI volume. Next, the endocardial segmentation was morphologically dilated and then manually adjusted to create an assessment of the boundary of the epicardial LA 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 LA wall segmentation included the 3D extent of both the LA wall and the antral regions of the PVs **(Figure 1)**.

Quantification of LA remodeling was obtained using the methods previously described with the addition of software implemented in Corview to improve determination of MRI intensity values[29]. Typically, enhancement values are found to be in the range of 2-4 standard deviations from the mean value. Once the threshold has been determined, the percentage of enhancement is calculated as the number of voxels in the LA wall segmentation with values above the threshold divided by the total number of voxels in the LA wall segmentation. The study patients were then assigned to one of 4 SRM categories based on LA wall enhancement as a percentage of the total LA wall volume with stage I defined as <10%, stage II ≥10-20%, stage III ≥20-30%, and stage IV ≥30%. Additional details for methods for quantification of LA remodeling are provided in the supplemental materials.

Ablation procedure and follow-up. The details of the PV isolation in addition to posterior wall and septal debulking has been described elsewhere [30]. A 10-pole circular mapping Lasso catheter and a 3.5 mm Thermocool ablation catheter (Biosense Webster, Diamond Bar, CA) were used and radiofrequency energy was delivered with 50 Watts at a catheter tip temperature of 50 °C for 5 seconds, guided by electrogram abolition recordings. Post-ablation, recurrences in year one

were determined by 8 day Holter monitoring performed on patients at 3, 6, and 12 months, patient reporting, and all ECG data. In years 2-3, follow-up was based on symptom-guided Holter monitoring and ECG data during clinic follow-up. Atrial arrhythmia recurrence following ablation was defined using the Heart Rhythm Society consensus document on catheter and surgical ablation of AF[18,31], and required the presence of 30 seconds of atrial arrhythmia following a 90-day blanking period. Additional details are provided in the supplemental materials.

Surgical biopsies and histochemical stains. Myocardial tissue was obtained from the LA at the time of cardiac surgery in 9 patients with AF and one non-AF patient. All patients underwent cardiac MRI/MRA scans prior to surgery. The surgeon obtaining the biopsy specimens marked the biopsy location on an interactive 3D MRA of the LA for each subject, which was then overlaid on the 3D LGE-MRI to correlate the surgical biopsy site with LA wall tissue on MRI. The LA biopsy tissue was formalin-fixed and paraffin embedded. Evaluation for collagen content was performed using Masson's trichrome stain. Details of whole-field digital microscopy[32] is provided in the supplemental materials.

Statistics. Statistical analysis was performed using STATA12 (Statacorp, College Station, Tx). LA wall SRM was reported as a continuous variable with a mean +/- standard deviation. Other continuous variables included age, LA volume and left ventricular ejection fraction. Categorical variables included gender, and medical comorbidities. An unpaired two-sided Student's t-test assuming unequal variences was used to compare means between controls and AF patients and ANOVA with the Bonferroni correction was used for multiple means comparison between SRM groups. A Chi-squared test was used to evaluate differences in categorical variables across different stages. A Fisher's exact test was used to evaluate differences between the AF group and

the control group. Survival analysis using Cox proportional hazards model was used to identify uni-variate, multi-variate recurrence predictors. Statistical interaction was examined by including interaction terms, specifically for clinical variables correlated with atrial SRM. The interaction terms did not alter the results of statistical association and are not displayed. A p-value less than 0.05 was considered statistically significant. Interobserver variability was calculated using Pearson's correlation coefficient.

Results

Study patients and association with SRM stages. A comparison of baseline characteristics of AF patients across SRM stages is provided in **Table 1**. AF patients distributed into the four SRM categories based on the percentage of LA wall enhancement on LGE-MRI as follows: 133 (34.5%) stage I, 140 (36.3%) stage II, 71 (18.4%) stage III, and 42 (10.9%) stage IV. Advanced SRM stage was associated with increased LA volume index. When comparing SRM stage versus classification according to AF clinical phenotypes, the prevalence of persistent AF increased with higher SRM stage while the prevalence of paroxysmal AF decreased. However, for any individual patient, SRM stage was not predicted by clinical phenotype alone as each stage showed a heterogeneous mix of phenotypes. Also noteworthy, within our study population, we found 13 patients with long standing persistent AF of great than 1 year. The average fibrosis for patients categorized this way was 19.5 ±21.6 vs. 18.7 ±11.5 for persistent AF (p=0.9). However, there were simply not enough patients in the long-standing persistent group to deduce any relevance between these two groups. **Figure 2** shows representative examples of patients from each SRM stage on LGE-MRI.

Study patients compared to control groups. The AF study patients were compared to a control group, without history of AF, consisting of a series of consecutive patients presenting for routine

screening colonoscopy. LA SRM with percent wall enhancement on LGE-MRI was significantly greater in the AF patient group when compared to the control group (16.6±11.2% vs. 3.1±1.9%, p<0.0001). While the AF patients were dispersed across all SRM stages (as noted above), all control patients were categorized in stage I. Comparisons of other characteristics between AF patients and controls showed that LA volume was significantly increased in the AF group compared to the control group (103±41 ml vs. 62±21 ml; p<0.0001). AF patients were also significantly older and had a higher prevalence of hypertension. A detailed summary of baseline characteristics of these groups is provided in **Table 2**.

Predictors of AF ablation outcome. All 386 patients underwent a single ablation procedure for treatment of AF and 123 (31.9%) experienced recurrent atrial arrhythmias at one-year follow-up. Kaplan Meier analysis showed recurrent arrhythmias (failed ablations) occurred in patients with higher SRM scores with 28/133 (21.0%) in stage I, 41/140 (29.3%) in stage II, 24/71 (33.8%) in stage III, and 30/42 (71.4%) in stage IV. For those who experienced recurrent arrhythmia within the first year of follow-up, the median time to recurrence was 142 days. The strong association between atrial SRM stage and arrhythmia recurrence following ablation therapy is shown graphically in **Figure 3**.

We performed univariate and multivariate analysis to identify significant predictors of arrhythmia recurrence. In the univariate analysis, LA volume increase for each 10 ml/m2 (HR 1.16;p=0.0001), age for each 10-year increase (HR 1.22, p=0.011), hypertension (HR 1.61; p=0.016), diabetes (HR 1.80; p=0.006), and persistent AF (HR 1.47; p=0.014) were associated with arrhythmia recurrence. Compared to patients with stage I SRM, stage IV patients had the highest risk of arrhythmia recurrence (HR 5.47; p<0.0001) followed by stage III (HR 1.65; p=0.069). In the multivariate model, SRM stage IV was associated with the highest risk of

recurrence (HR 4.89 compared to SRM stage I; p<0.0001). Diabetes was another significant predictor of arrhythmia recurrence (HR 1.64; p=0.036). The results of the univariate and multivariate Cox regressions are summarized in **Table 3**.

After the first year, arrhythmia recurrence was diagnosed based on patient symptom-guided Holter monitoring and ECG data during clinic follow-up for two additional years. When we analyze the data over the 3 year period (mean follow-up of 746±428 days), we found that 169 patients (43.8%) experienced recurrent atrial arrhythmias . Similar to the one-year outcomes, recurrent arrhythmias occurred in patients with higher SRM scores with 44/133 (33.1%) in stage I, 58/140 (41.4%) in stage II, 34/71 (47.9%) in stage III, and 33/42 (78.6%) in stage IV.

Histologic basis for LA wall fibrosis. Tissue characterization of the LA wall on LGE-MRI correlated with histology from surgical biopsy specimens. A total of 14 biopsies were taken from the 10 surgical patients with histories of AF. Nine biopsy locations showed evidence of significant interstitial fibrosis on Masson's trichrome staining and 5 locations showing normal LA wall tissue or minimal collagen staining. LA wall biopsies demonstrating tissue fibrosis matched with regions of LA wall enhancement on MRI, while normal biopsy tissue corresponded with non-enhanced regions on MRI. Furthermore, in a surgical patient without AF and with normal sized LA, no significant atrial wall enhancement was seen on LGE-MRI and biopsy confirmed tissue without significant interstitial fibrosis (**Figure 4**).

Interobserver reproducibility. Atrial fibrosis on MRI scans was analyzed and quantified by three blinded observers on a subset of 170 patients randomly selected from the entire cohort. The calculated mean fibrosis values between the three observers were not significantly different and the correlation coefficients ranged from 0.79 to 0.97, indicating a high degree of reproducibility. The high degree of correlation reflects the good scan quality visualization of the LA wall as well

as the experience of the operators in our lab who perform these tracings on a regular basis with the aid of computer processing tools.

Discussion

We report that LGE-MRI can detect SRM in patients with AF as healthy atrial myocardium becomes fibrotic. For catheter ablation of AF, restoration of sinus rhythm is shown significantly less likely as the remodeling process advances. These findings suggest that MRI can improve the selection process and outcome for patients being considered for AF ablation procedures.

The results here build on previous work showing LGE-MRI an important tool in the evaluation of LA fibrosis [26,27,29,33]. Though LGE-MRI is a well-established method for characterizing fibrosis and tissue remodeling in the ventricle [34-36], limitations in spatial resolution have made imaging the LA wall more challenging. Recent advancements in navigated 3D MR imaging now yield greater signal and improved resolution with the ability to locate and quantify atrial remodeling. Data here lend validation of the LA remodeling process on LGE-MRI with clear distinctions between control and AF patients. Specifically, the AF patient cohort demonstrated a greater than four fold increase in percentage of LA wall enhancement than the control group. Furthermore, we show that LA wall biopsy specimens with varying degrees of interstitial fibrosis correlate with findings on LGE-MRI in AF patients. While previous surgical studies have demonstrated LA SRM on histological examination of biopsies from AF patients [23,37-38], we report that tissue enhancement on LGE-MRI reflects SRM changes. These results support the use of MRI for non-invasive assessment of the remodeling process.

The amount of LA wall fibrosis on LGE-MRI strongly correlates with AF ablation outcome, which is the central finding in this study. Arrhythmia recurrence is significantly higher when ≥30% fibrosis (IV patients) is present on pre-procedure MRI scans. Scores below 30%

identify patients far more likely to benefit from catheter ablation procedures. In multivariate analysis, SRM stage was clearly the strongest predictor of ablation outcomes. Patients with ≥30% enhancement on MRI (SRM stage IV) demonstrated poor procedure outcomes with a greater than 70% failure rate. These data support prior studies showing pre-existing low voltage tissue and scarring in the LA determined invasively during electrophysiology studies are independent predictors of ablation procedure failure and arrhythmia recurrence[39]. The presence of low voltage, fibrotic tissue appears to result in abnormal atrial activation, which may underlie the initiation and maintenance of fibrillation [20]. Indeed, both animal and human studies have repeatedly shown that atrial fibrosis can lead to AF though mechanisms that cause alterations in fibrillatory dynamics [40-42]. By altering the LA substrate, fibrotic change and SRM probably aid in the formation of circuits needed for reentry, thus perpetuating the atrial arrhythmia. As the fibrotic process becomes more advanced, our data supports the notion that that the fibrillatory circuits increase and become more extensive thereby making it increasingly difficult to restore sinus rhythm. Interrupting the fibrillatory pathways in the early stages of fibrosis appears to be important for success of ablation procedures as patients in the earliest remodeling stages (stages I and II) showed higher success rates of 66.9% and 58.6% respectively.

The hallmark of SRM is atrial fibrosis, a factor leading to persistence of AF. However, whether fibrosis is a cause or result of AF remains a subject of debate. Data here show significant SRM changes on LGE-MRI in AF patients but not in control populations without AF. In addition, the fibrosis stage correlates with AF clinical phenotype with more advanced remodeling seen in persistent forms of AF. These findings support previous studies showing that increasing AF burden leads to structural and functional remodeling [43]. Progressive structural changes in the atria are seen as paroxysmal AF eventually becomes persistent or permanent AF

and conversion to sinus rhythm can lead to reversal of these changes [44-46]. These data support a mechanism for atrial fibrosis that results from AF and the notion that AF begets AF [47].

On the other hand, atrial SRM can result from other disease processes such as valvular heart disease (e.g. mitral stenosis) or heart failure[48-50]. In such cases, the fibrotic process appears to precede the development of AF. In order to better understand the fundamental association between fibrosis and AF, surveillance imaging of the LA in populations with and without AF could help enhance our understanding of the fibrotic process and its consequences in cardiovascular disease states. Our best understanding of the current available literature points to more than one mechanism including accelerated LA fibrosis resulting from AF or alternatively from fibrotic processes (e.g. structural disease) leading to AF.

Our study is limited as it is a single center, observational study. In addition, in order to perform quality 3D LGE-MRI studies routinely in patients requires a high level of expertise in MRI and support during the studies by expert MR imagers and technologists. Processing of the MR images is laborious and requires experienced observers to perform the LA wall tracings and to select the threshold levels. Improvements in image processing and automization of the process is possible and is expected to simplify and help further standardize the image processing. In addition, the operators performing the AF ablation procedures were not blinded to the results of the MRI scan. Knowledge of the fibrosis score could have lead to biases in their approach to the ablation procedure.

Non-invasive evaluation of myocardial tissue using LGE-MRI is a powerful tool for detecting and quantifying atrial tissue disease and changes that result from the SRM process. In patients with AF, the degree of LA wall SRM predicts response to catheter ablation therapy with restoration of sinus rhythm highly unlikely in patients with advanced remodeling stage.

Currently, the selection process for ablation procedures remains somewhat subjective with failed anti-arrhythmic drug therapy, clinical phenotype, and patient treatment preferences all taken into consideration. With better and more stringent selection criteria, we can improve outcomes and cost effectiveness by avoiding ablation procedures unlikely to benefit patients with AF.

Conflict of Interest Disclosures: None

References:

1. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huezey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS, Smith SC Jr, Priori SG, Estes NA 3rd, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Jacobs AK, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson WG, Tarkington LG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011;123:e269–e367.

2. Go AS, Hylek EM, Phillips KA, Chang Y, Henault L, Selby J, SingerD. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-2375.

3. Lloyd-Jones DM, Wang TJ, Leip EP, Larson M, Levy D, Vasan R, D'Agostino R, Massaro J, Beiser A, Wolf P, Benjamin E. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042-1046.

4. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113:359-364.

5. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271:840-844.

6. Psaty BM, Manolio TA, Kuller LH, Kronmal R, Cushman M, Fried L, White R, Furberg C, Rautaharju P. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455-2461.

7. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Med*. 2005;118:489-495.

8. Wang TJ, Parise H, Levy D, D.Agostino R, Wolf P, Vasan R, Benjamin E. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471-2477.

9. Dublin S, French B, Glazer NL, Wiggins K, Lumley T, Psaty B, Smith N, Heckbert S. Risk of new-onset atrial fibrillation in relation to body mass index. *Arch Intern Med*. 2006;166:2322-2328.

10. Van Gelder IC, Hagens VE, Bosker HA, Kingma A, Kamp O, Kingma T, Said S, Darmanata J, Timmermans A, Tijssen J, Crijns H. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834-1840.

11. Roy D, Talajic M, Nattel S, Wyse G, Dorian P, Lee K, Bourassa M, Arnold J, Buxton A, Camm A, Connoly S, Dubuc M, Ducharme A, Guerra P, Hohnloser S, Lambert J, Heuzey J, O'Hara G, Pedersen O, Rouleau J, Singh B, Stevenson L, Stevenson W, Thibault B, Waldo A. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667-2677.

12. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga Y, Tijssen J, Alings A, Hillege H, Bergsma-Kadijk J, Cornel J, Kamp O, Tukkie R, Bosker H, Van Veldhuisen D, Van den Berg M. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363-1373.

13. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659-666.

14. Haissaguerre M, Jais P, Shah DC, Garrigue S, Takahashi A, Lavergne T, Hocini M, Peng J, Roudaut R, Clementy J. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. *Circulation*. 2000;101:1409-1417.

15. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Calabro M, Mazzone P, Ficarra E, Di Gioia C, Gulletta S, Nardi S, Santinelli V, Benussi S, Alfieri O. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation*. 2001;104:2539-2544

16. Oral H, Knight BP, Tada H, Ozaydin M, Chuch A, Hassan S, Scharf C, Lai S, Greenstein R, Pelosi F, Strickberger A, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation*. 2002;105:1077-1081.

17. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sancher F, Takahasi Y, Rotter M, Pasquie J, Scavee C, Bordachar P, Clementy J, Haissaguerre. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373-2383.

18. Calkins H, Kuck KH, Cappato R, Brugada J, Camm A, Chen S, Crijns H, Damiano R, Davies D, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz M, Haines D, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim Y, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay B, Mansour M, Marchlinski F, McCarthy P, Mont J, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer D, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin J, Shemin R, Tsao H, Wilber D. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. *Heart Rhythm*. 2012;9:632-696 e21.

19. Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. *Pacing Clin Electrophysiol*. 1997;20:397-413.

20. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation*. 1999;100:87-95.

21. Chen MC, Chang JP, Liu WH, Yang CH, Tsai TH, Wang YH, Pan KL. Increased inflammatory cell infiltration in the atrial myocardium of patients with atrial fibrillation. *Am J Cardiol*. 2008;102:861-865.

22. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. *J Am Coll Cardiol*. 2011;58:2225-2232.

23. Kainuma S, Masai T, Yoshitatsu M, Miyagawa S, Yamauchi T, Takeda K, Moii E, Sawa Y. Advanced left-atrial fibrosis is associated with unsuccessful maze operation for valvular atrial fibrillation. *Eur J Cardiothorac Surg*. 2011;40:61-69.

24. Boldt A, Wetzel U, Lauschke J, Weigl J, Gummert J, Hindricks G, Kottamp H, Dhein S. Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. *Heart*. 2004;90:400-405.

25. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res*. 2002;54:230-246.

26. Mahnkopf C, Badger TJ, Burgon NS, Daccarett M, Haslam TS, Badger CT, McGann CJ, Akoum N, Kholmovski E, Macleod RS, Marrouche NF. Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: implications for disease progression and response to catheter ablation. *Heart Rhythm*. 2010;7:1475-1481.

27. Akoum N, Daccarett M, McGann C, Segerson N, Vergara G, Kuppahally SS, Badger TJ, Burgon N, Haslem TS, Kholmovski EG, Macleod R, Marrouche NF. Atrial fibrosis helps select

the appropriate patient and strategy in catheter ablation of atrial fibrillation: a DE-MRI guided approach. *J Cardiovasc Electrophysiol*. 2011;22:16-22.

28. McGann C, Kholmovski E, Blauer J, Vijayakumar S, Haslam T, Cates J, DiBella E, Burgon NS, Wilson B, Alexander A, Prastawa M, Daccarett M, Vergara G, Akoum N, Parker D, MacLeod RS, Marrouche NF. Dark regions of no-reflow on late gadolinium enhancement magnetic resonance imaging result in scar formation after atrial fibrillation ablation. *J Am Coll Cardiol*. 2011;58:177-185.

29. Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, Blauer JJE, Rao SN, DiBella EVR, Segerson NM, Daccarett M, Windfelder J, McGann CJ, Parker D, MacLeod RS, Marrouche NF. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation*. 2009;119:1758-1767.

30. Segerson NM, Daccarett M, Badger TJ, Shabaan A, Akoum N, Fish EN, Rao S, Burgon NS, Adjei-Poku Y, Kholmovski E, Vijayakumar S, DiBella EV, MacLeod RS, Marrouche NF. Magnetic resonance imaging-confirmed ablative debulking of the left atrial posterior wall and septum for treatment of persistent atrial fibrillation: rationale and initial experience. *J Cardiovasc Electrophysiol*. 2010;21:126-132.

31. Calkins H, Kuck KH, Cappato R, Brugada J, Camm A, Chen S, Crijns H, Damiano R, Davies D, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz M, Haines D, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim Y, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay B, Mansour M, Marchlinski F, McCarthy P, Mont J, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer D, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin J, Shemin R, Tsao H, Wilber D. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace*. 2012;14:528-606.

32. Ho J, Parwani AV, Jukic DM, Yagi Y, Anthony L, Gilbertson JR. Use of whole slide imaging in surgical pathology quality assurance: design and pilot validation studies. *Hum Pathol*. 2006;37:322-331.

33. Peters DC WJ, Hauser TH, Kissinger KV, Botnar RM, Essebag V, Josephson, ME, and Manning, WJ. Detection of pulmonary vein and left atrial scar after catheter ablation with three-dimensional navigator-gated delayed enhancement MR imaging: initial experience. *Radiology*. 2007;243:690-695.

34. Judd RM, Lugo-Olivieri CH, Arai M, Kondo T, Croisille P, Lima J, Mohan V, Becker L, Zerhouni E. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. *Circulation*. 1995;92:1902-1910.

35. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen E, Simonetti O, Bundy J, Finn J, Klocke F, Judd R. Relationship of MRI Delayed Contrast Enhancement to Irreversible Injury, Infarct Age, and Contractile Function. *Circulation*. 1999;100:1992-2002.

36. Lima JAC, Judd RM, Bazille A, Schulman SP, Atalar E, Zerhouni EA. Regional Heterogeneity of Human Myocardial Infarcts Demonstrated by Contrast-Enhanced MRI : Potential Mechanisms. *Circulation*. 1995;92:1117-1125.

37. Kostin S, Klein G, Szalay Z, Hein S, Bauer EP, Schaper J. Structural correlate of atrial fibrillation in human patients. *Cardiovasc Res*. 2002;54:361-379.

38. Nakai T, Chandy J, Nakai K, Bellows WH, Flachsbart K, Lee RJ, Leung JM. Histologic assessment of right atrial appendage myocardium in patients with atrial fibrillation after coronary artery bypass graft surgery. *Cardiology*. 2007;108:90-96.

39. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, Schweikert RA, Saliba W, Cummings J, Burkhardt JD, Bhargava M, Belden WA, Abdul-Karim A, Natale A. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *J Am Coll Cardiol*. 2005;45:285-292.

40. Verheule S, Sato T, Everett Tt, Engle SK, Otten D, Rubart-von der Lohe M, Nakajima HO, Nakajima H, Field LJ, Olgin JE. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. *Circ Res*. 2004;94:1458-1465.

41. Tang M, Zhang S, Sun Q, Huang C. Alterations in electrophysiology and tissue structure of the left atrial posterior wall in a canine model of atrial fibrillation caused by chronic atrial dilatation. *Circ J*. 2007;71:1636-1642.

42. Hayashi H, Wang C, Miyauchi Y, Omichi C, Pak HN, Zhou S, Ohara T, Mandel WJ, Lin SF, Fishbein MC, Chen PS, Karagueuzian HS. Aging-related increase to inducible atrial fibrillation in the rat model. *J Cardiovasc Electrophysiol*. 2002;13:801-808.

43. Allessie MA. Atrial electrophysiologic remodeling: another vicious circle? *J Cardiovasc Electrophysiol*. 1998;9:1378-1393.

44. Nishino M, Hoshida S, Tanouchi J, Ito T, Kato J, Iwai K, Tanahashi H, Hori M, Yamada Y, Kamada T. Time to recover from atrial hormonal, mechanical, and electrical dysfunction after successful electrical cardioversion of persistent atrial fibrillation. *Am J Cardiol*. 2000;85:1451-1454.

45. Therkelsen SK, Groenning BA, Svendsen JH, Jensen GB. Atrial and ventricular volume and function evaluated by magnetic resonance imaging in patients with persistent atrial fibrillation before and after cardioversion. *Am J Cardiol*. 2006;97:1213-1219.

46. Wozakowska-Kaplon B, Opolski G. Concomitant recovery of atrial mechanical and endocrine function after cardioversion in patients with persistent atrial fibrillation. *J Am Coll Cardiol*. 2003;41:1716-1720.

47. Wijffels M, Kirchhof C, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995;92:1954-1968.

48. Goldsmith I, Kumar P, Carter P, Blann A, Patel RL, Lip G. Atrial endocardial changes in mitral valve disease: A scanning electron microscopy study. *Am Heart J*. 2000;140:777-784.

49. Corradi D, Callegari S, Maestri R, Ferrara D, Mangieri D, Alinovi R, Mozzoni P, Pinelli S, Goldoni M, Privitera YA, Bartoli V, Astorri E, Macchi E, Vaglio A, Benussi S, Alfieri O. Differential structural remodeling of the left-atrial posterior wall in patients affected by mitral regurgitation with or without persistent atrial fibrillation: a morphological and molecular study. *J Cardiovasc Electrophysiol*. 2012;23:271-279

50. Boixel C, Fontaine V, Rücker-Martin C, Milliez P, Louedec L, Michel JB, Jacob MP, Hatem SN. Fibrosis of the left atria during progression of heart failure is associated with increased matrix metalloproteinases in the rat. *J Am Coll Cardiol*. 2003;42:336-44.

DOI: 10.1161/CIRCEP.113.000689

Table 1. Comparison of baseline characteristics across structural remodeling stages in the AF group

	Stage -I- (n=133)	**Stage -II- (n=140)**	**Stage -III- (n=71)**	**Stage -IV- (n=42)**	**P value**
Age (yrs)	63±13	65±11	66±13	67±12	0.17
Female (%)	33.8	30.7	42.3	47.6	0.06
Hypertension (%)	62.9	61.4	57.8	66.7	0.81
Diabetes (%)	11.4	12.9	21.1	21.4	0.08
Coronary Disease (%)	13.6	12.5	24.4	14.3	0.10
Congestive Heart Failure (%)	6.1	13.0	12.7	7.1	0.41
LV ejection fraction (%)	58±12	59±10	57±12	56±13	0.16
CVA/TIA (%)	6.1	7.9	11.3	16.7	0.03
Paroxysmal AF (%)	61.7	46.4	49.3	26.2	0.002
Persistent AF (%)	38.4	53.6	50.7	73.8	0.002
Prior AAD use (%)	22.6	12.9	18.5	15.0	0.11
Atrial volume/BSA (ml/m^2)	48±18	51±18	52±21	64±24	<0.0001
LA fibrosis (%)	6.7±2.0	15.2±2.9	23.3±2.8	40.9±10.4	<0.0001

DOI: 10.1161/CIRCEP.113.000689

Table 2. Comparison of baseline characteristics of AF patients and a non-AF control group

	AF group (n=386)	**Non-AF group (n=21)**	**P value**
Age (yrs)	64±12	54±17	0.01
Female (%)	36	38	0.47
Hypertension (%)	62.0	4.7	<0.0001
Diabetes (%)	15.2	19.0	0.64
Coronary Disease (%)	16.0	14.3	0.84
Congestive Heart Failure (%)	9.8	0	0.13
LV ejection fraction (%)	58±11	61±10	0.22
CVA/TIA (%)	8.8	0	0.16
Left atrial fibrosis (%)	16.6±11.2	3.5±2.3	<0.0001
Atrial volume/BSA (ml/m^2)	51±20	31±10	<0.0001

DOI: 10.1161/CIRCEP.113.000689

Table 3. Univariate and multivariate predictors of arrhythmia recurrence following catheter ablation: 1 year follow-up

	Univariate analysis			**Multivariate analysis**		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age (per 10 yr. increase)	1.22	1.05-1.43	0.011	1.12	0.94-1.34	0.192
Female	1.09	0.75-1.57	0.636	0.84	0.56-1.25	0.393
Hypertension	1.61	1.09-2.38	0.016	1.33	0.86-2.04	0.195
Diabetes	1.80	1.18-2.75	0.006	1.64	1.03-2.61	0.036
Coronary Disease	1.19	0.75-1.88	0.465	0.75	0.45-1.24	0.260
Congestive heart failure	1.19	0.68-2.07	0.543	1.17	0.65-2.09	0.607
Persistent AF	1.47	1.08-1.99	0.014	1.09	0.76-1.55	0.648
SRM Stage						
Stage I	Referent			Referent		
Stage II	1.47	0.91-2.38	0.116	1.29	0.81-1.82	0.303
Stage III	1.65	0.96-2.86	0.069	1.49	0.92-2.32	0.166
Stage IV	5.47	3.26-9.2	<0.0001	4.89	2.37-6.28	<0.0001
LA volume index (10 ml/m^2)	1.16	1.07-1.26	<0.0001	1.05	0.96-1.17	0.279

DOI: 10.1161/CIRCEP.113.000689

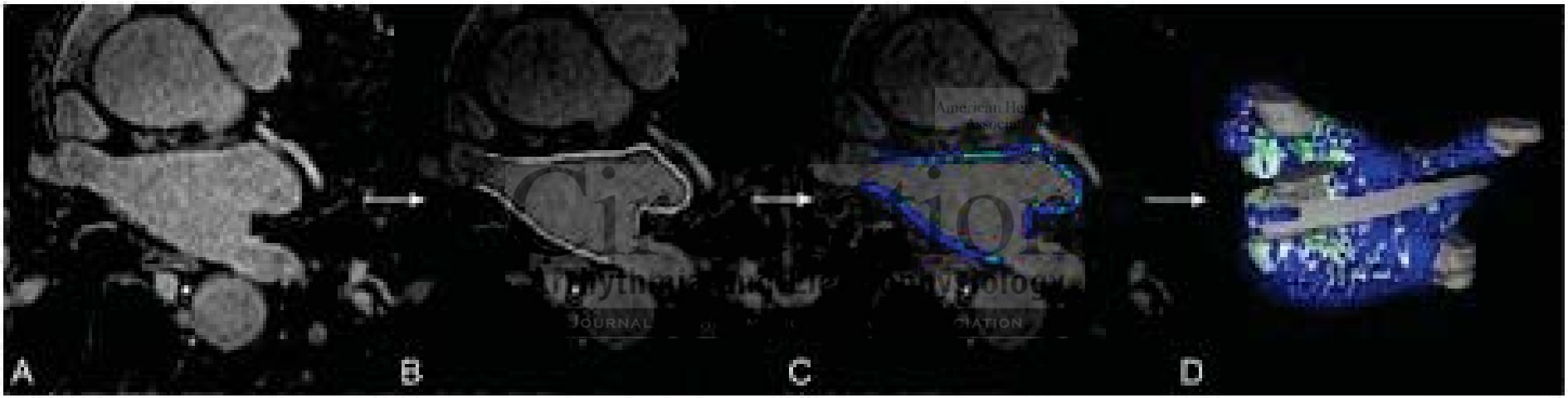
Figure Legends:

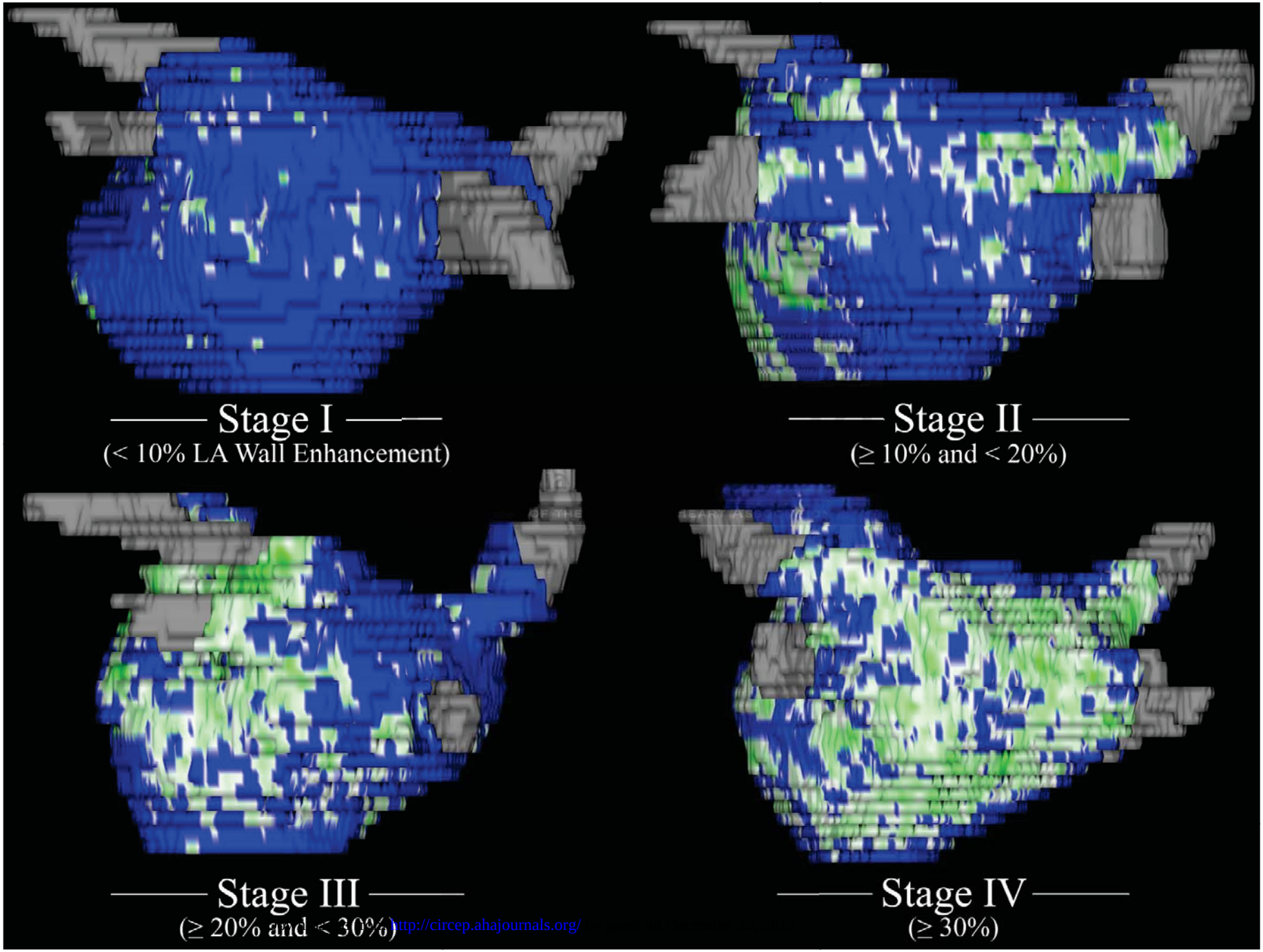
Figure 1. Segmentation process used for quantification of LA wall fibrosis. Panel A shows single slice level from 3D late gadolinium enhancement data set pre-ablation. Panel B shows endo and epi contours of the LA wall used for determining degree of fibrosis. Panel C shows abnormal, fibrotic regions in green and normal, non-fibrotic tissue in blue. Panel D shows 3D reconstruction of the entire data set separated to highlight the specific slice level in this example.

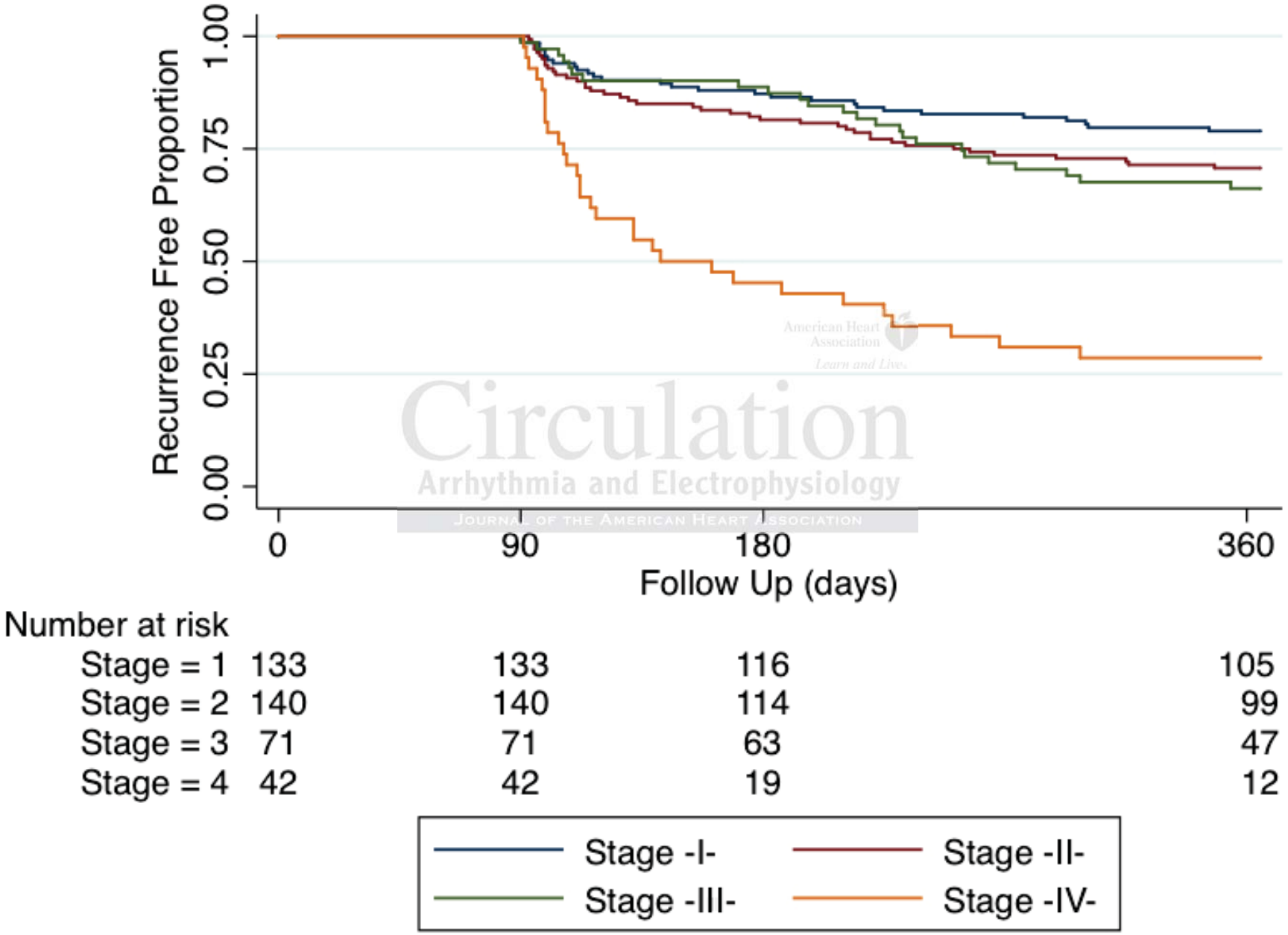
Figure 2. Four stages of LA structural remodeling (SRM) based on 3D late gadolinium enhancement (LGE) MRI scans. Representative examples from patients in each stage of LA remodeling in PA views (above examples of stages I-IV are 3%, 13%, 26%, and 56%, respectively). Normal LA wall displayed in blue with SRM changes in green. The pulmonary veins are shown in grey.

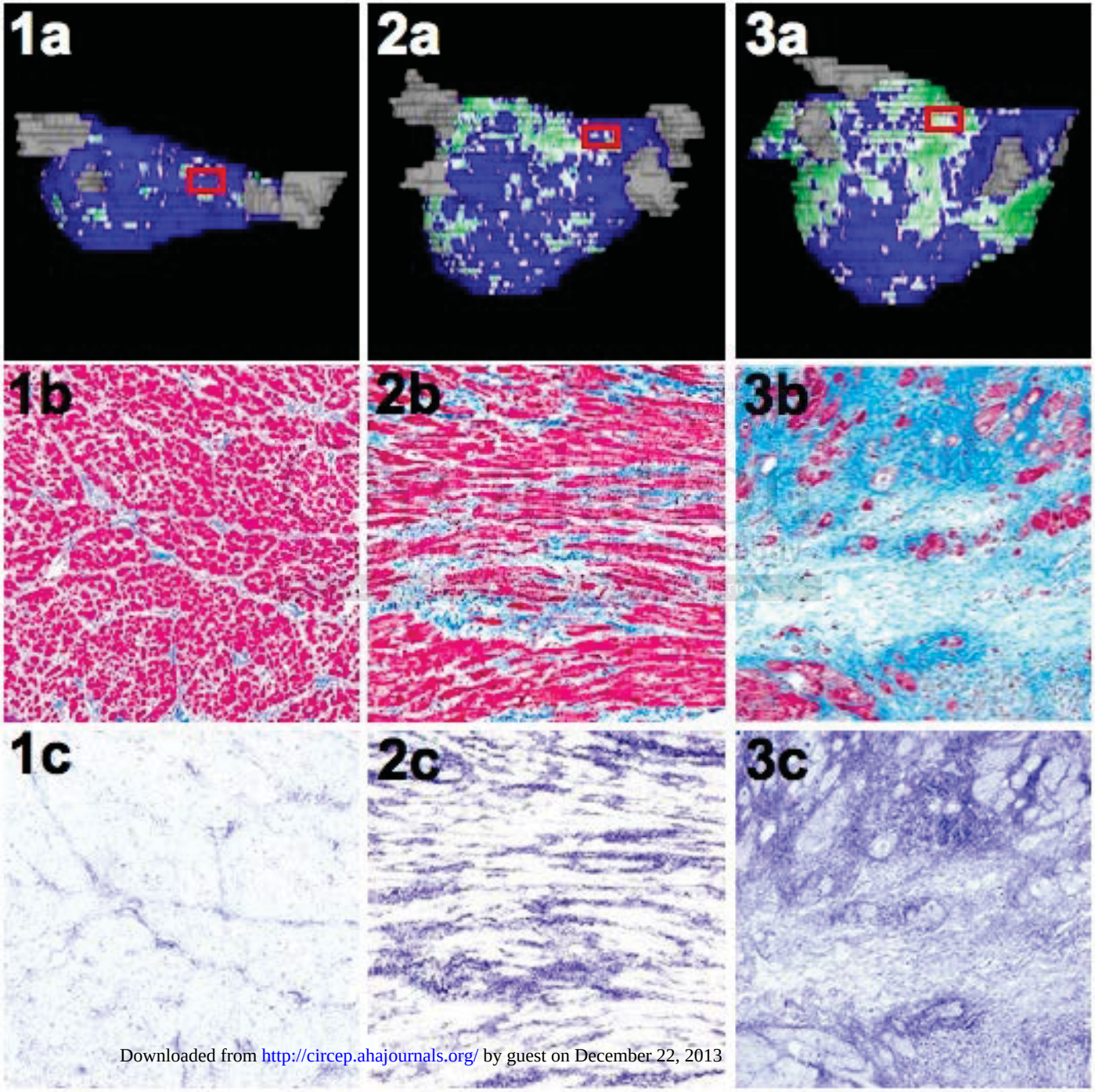
Figure 3. Kaplan-Meier rates of AF recurrence. Post AF ablation recurrences according to four stages of atrial structural remodeling over 1-year follow-up period.

Figure 4. LA wall structural remodeling on LGE-MRI correlates with surgical biopsy specimens. Examples from 3 surgical patients who underwent both 3D LGE-MRI scanning and biopsy of the LA wall. "Control' patient without AF shown left (1a-1c), AF patient with moderate amount of SRM in center (2a-2c), and AF patient with advanced SRM on right (3a-3c). 3D LGE-MRI renderings show fibrosis/structural remodeling (SRM) in green with normal tissue in blue (*top panels)*. Masson's trichrome stains collagen blue and LA myocytes red (*middle panels* standard staining, *bottom panels* are subtraction images). Red box shows biopsy location.









SUPPLEMENTAL MATERIAL

Methods

Magnetic resonance imaging. Details for the 3D LGE-MRI imaging for left atrial fibrosis at 1.5T and 3T are as follows: for the patient in sinus rhythm, data acquisition was performed during LA diastole. Specifically, data acquisition window was 15% of averaged cardiac cycle (aRR) and it was positioned from 65% to 80% of aRR (0% corresponds to peak of R-wave). For AF patients with non-regular heart rate during the imaging session, the duration of data acquisition window was reduced to 12% of aRR and it was shifted closer to the R-wave and positioned from 47% to 59% of aRR. Other scan parameters for LGE of LA at 3T scanner were: axial imaging volume, FOV=400x400x110 mm, voxel size=1.25x1.25x2.5 mm, TR/TE=3.1/1.4 ms, flip angle of 14 degrees. Scan parameters for LGE of LA at 1.5T scanner were: axial image volume, FOV=360x360x100 mm, voxel size=1.25x1.25x2.5 mm, TR/TE=5.2/2.4 ms, flip angle of 20 degrees. Typical scan time for LGE study was 6-12 minutes at 1.5 and 5-9 minutes 3T scanner depending on patient respiration.

LGE-MRI assessment of left atrial structural remodeling. As noted in the manuscript, quantification of LA remodeling was obtained using the methods previously described with the addition of software implemented in Corview to improve determination of MRI intensity values[29]. Some important details are as follows. After segmentation of the LA wall (see methods in manuscript and **Figure 1**), next we estimate an intensity threshold

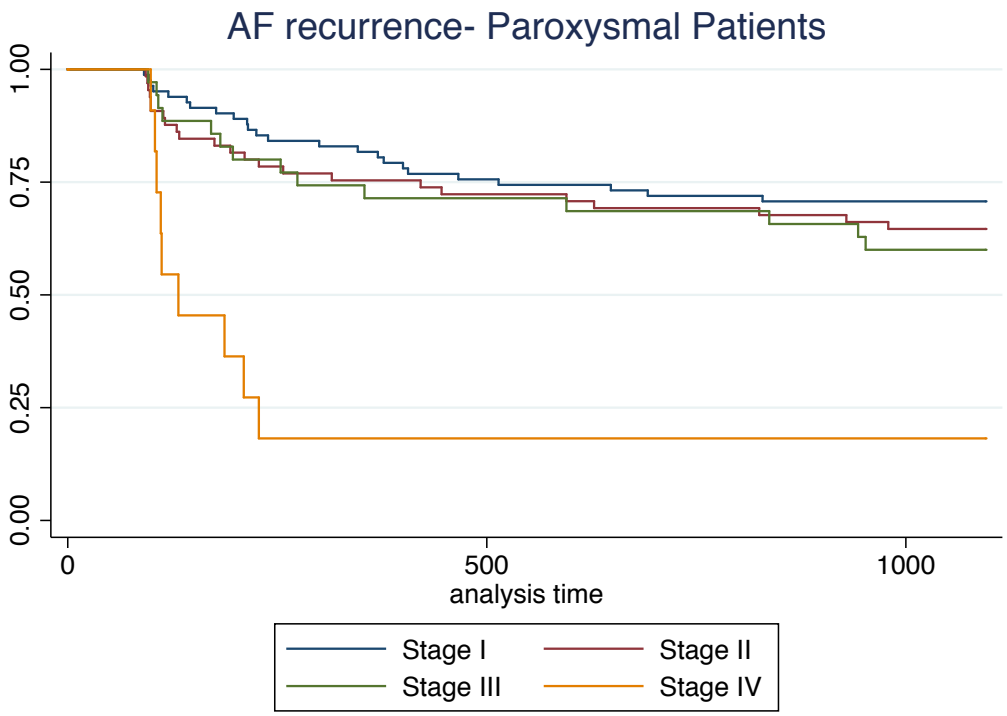
for enhancement (fibrosis) by inspection with an interactive intensity thresholding tool within Corview. The thresholding tool displays the mean and standard deviations of the MRI voxel values in the LA wall on top of a histogram of the wall intensity values. The user then selects a threshold value for enhancement using a slider. As the threshold slider is moved, the user can see which pixels are being selected in the both a 2D display of the MRI image stack and a 3D volume rendering of the MRI. Typically, enhancement values are found to be in the range of 2-4 standard deviations from the mean value. Once the threshold has been determined, the percentage of enhancement is calculated as the number of voxels in the LA wall segmentation with values above the threshold divided by the total number of voxels in the LA wall segmentation.

Ablation procedure and follow up. The LA was accessed through two trans-septal punctures under intracardiac echo guidance using a phased array catheter (Acunav, Siemens Medical Solutions USA, Inc, Mountain View, CA). A 10-pole circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA) and a 3.5 mm Thermocool ablation catheter (Biosense Webster, Diamond Bar, CA) were advanced into the LA for mapping and ablation. A 14-pole catheter (TZ medical, Portland, OR; Biosense Webster, Diamond Bar, CA) was used to record right atrial and coronary sinus electrograms and was used as the reference catheter for 3D electro-anatomical mapping with CARTO (Biosense Webster, Diamond Bar, CA). Radiofrequency energy was delivered with 50 Watts at a catheter tip temperature of 50 °C for 5 seconds, guided by electrogram abolition recorded on the Lasso catheter. Ablation lesions were placed in a circular fashion in the pulmonary vein antral region until electrical isolation of the pulmonary

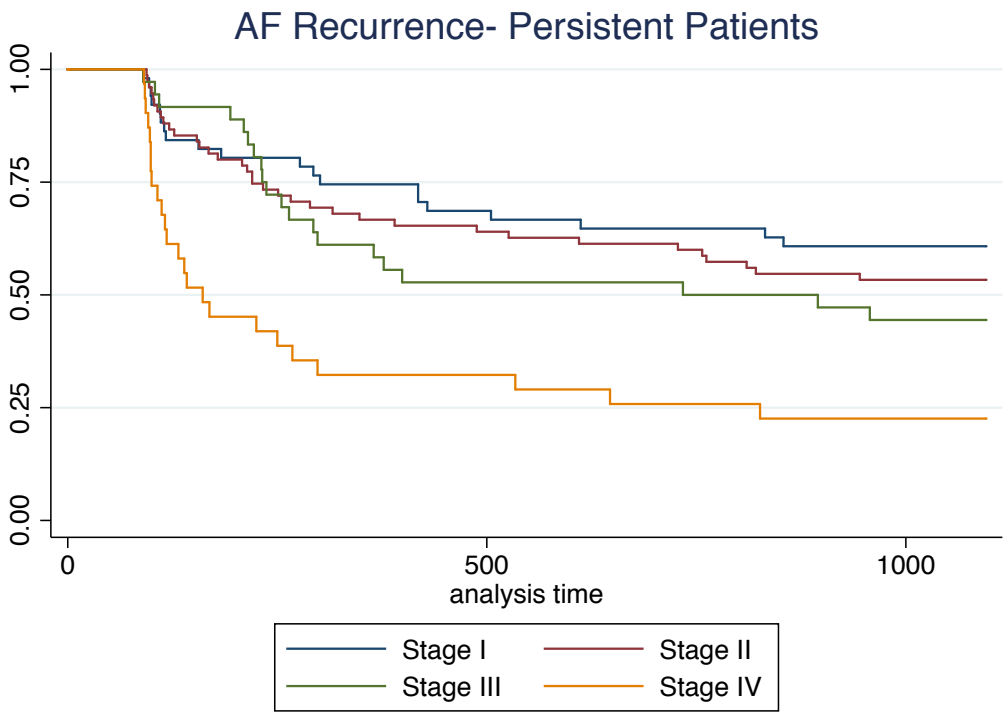
veins was achieved. Additional lesions were placed along the LA posterior wall and septum at the discretion of the operator.

Surgical biopsies and histochemical stains. *Whole-field digital microscopy:* Advanced digital microscopy allowed examination of the entire heart tissue areas from the epicardium to the endocardium. Whole-slide images were analyzed with the ScanScope XT system equipped with the ImageScope 10.0 image analysis algorithms (Aperio Technologies, Vista, CA) [31]. *Collagen content evaluation:* we set the staining color threshold of the ImageScope 10.0 Color deconvolution analysis algorithm to accurately identify collagen based on its blue color. Subsequently, myocardial collagen content was determined by running the algorithm on the stained myocardial tissue. "Interstitial Fibrosis" was defined as the collagen content determined in the interstitial spaces and endomysial/perimysial spaces including the collagen content around capillaries and small vessels found within those spaces.

Tables.



Kaplan-meier rates of recurrence in paroxysmal AF patients. Percentages of paroxysmal AF patients in each stage are as follows: 61.7 Stage I, 46.4 Stage II, 49.3 Stage III, and 26.2 Stage IV.



Kaplan-meier rates of recurrence in persistent AF patients. Percentages of persistent AF patients in each stage are as follows: 38.4 Stage I, 53.6 Stage II, 50.7 Stage III, and 73.8 Stage IV.