Left Atrial Volume and the Benefit of Cardiac Resynchronization Therapy
in the MADIT-CRT Trial
Kuperstein et al: Left Atrial Volume and CRT

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Abstract

Background—Left atrial volume (LAV) is an important marker of heart failure severity. We hypothesized that LAV independently correlates with clinical outcomes in patients who receive cardiac resynchronization therapy with a defibrillator (CRT-D) and can be used for improved risk assessment in this population.

Methods and Results—The benefit of CRT-D versus defibrillator-only therapy in reducing the risk of heart failure or death was assessed by LAV (dichotomized at the upper quartile of >52 ml/m²) among 1,785 patients enrolled in the MADIT-CRT study. Landmark analysis was employed to evaluate the relationship between LAV response to CRT-D and subsequent clinical outcomes. Multivariable analysis showed that patients with a higher baseline LAV experienced 69% (p<0.001) and 59% (p=0.02) increased hazard for heart failure or death and for all-cause mortality, respectively, independently of baseline left ventricular volume. CRT-D was associated with a significant reduction in LAV compared with defibrillator-only therapy (-28% versus -10%, respectively; p<0.001). Landmark analysis showed that following CRT-D implantation each 1% reduction in LAV was independently associated with a corresponding 4% reduction in the hazard of subsequent heart failure or death (p<0.001).

The assessment of LAV change following CRT implantation improved prediction of clinical response to the device compared with assessment of the corresponding changes in left ventricular volume.

Conclusions—LAV is an independent correlate of clinical outcomes in mildly symptomatic heart failure patients treated with CRT-D. CRT exerts pronounced reverse remodeling effects on the left atrium that independently correlate with improved clinical outcomes following device implantation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00180271.

Key Words: cardiac resynchronization therapy; heart failure; left atrial volume
Left atrial volume (LAV) has been shown to be a reliable predictor of cardiovascular outcomes in several conditions, including heart failure (HF) (1-3), initially by echocardiography and lately by magnetic resonance imaging (4). During ventricular diastole, the left atrium (LA) is exposed to pressures of the left ventricle (LV). Thus, LAV often reflects the cumulative effects of filling pressures over time (5-6), and may therefore provide a more sensitive morpho-physiologic expression of the severity of diastolic dysfunction than the LV.

During the past decade cardiac resynchronization therapy (CRT) has emerged as an important therapeutic modality for patients with moderate to severe refractory HF (7,8) and more recently for patients with symptoms of mild HF (9). The clinical benefits associated with CRT are related to the reverse remodeling effects of the device on the LV (10). In addition, treatment with CRT has been shown to be associated with reduction in mitral regurgitation severity (11) and improvement in diastolic function (11,12), and thus may also exert favorable reverse remodeling effects on LAV (13). However, the role of LAV as an independent correlate of clinical outcomes following CRT implantation has not been established.

The present study was carried out in a population of patients with mild symptoms of HF who were enrolled in the MADIT-CRT study, and was designed to evaluate: 1) the association of baseline LAV with the hazard of HF and death in mildly symptomatic HF patients; 2) the relationship between LAV and the clinical benefit of CRT; and 3) the association between the reverse remodeling effects of CRT on LAV and subsequent clinical outcomes.
Methods

Study population

The design and results of the MADIT-CRT study have been reported previously (10). Briefly, 1,820 patients either with ischemic cardiomyopathy and New York Heart Association (NYHA) class I-II or with non-ischemic cardiomyopathy and NYHA class II, QRS duration of ≥130 ms and an ejection fraction of ≤0.30, were randomized to receive either CRT with a defibrillator (CRT-D) or an implantable cardioverter defibrillator (ICD) in a 3:2 ratio. Exclusion criteria included: age <21 years, an existing indication for CRT, an implanted pacemaker, NYHA III or IV functional class during the past 90 days prior to enrollment, coronary artery bypass graft surgery, percutaneous coronary intervention or myocardial infarction during the past 90 days prior to enrollment. One hundred and ten hospital centers from North America and Europe participated in this international multicenter trial, which complied with the Declaration of Helsinki. Protocols of all enrollment sites were approved by the local institutional review board, and all patients provided signed informed consent before enrollment.

Data acquisition and follow-up

The MADIT-CRT study was conducted from 22 December, 2004 through 22 June, 2009. Following cessation of the study on the recommendation of the safety monitoring board, complete data collection and adjudication of clinical endpoints were continued through 31 December, 2009. The present study includes 1,785 patients (98%) who had LAV measurements in accordance with the study protocol.

Echocardiographic methods

Echocardiograms were obtained according to a study-specific protocol at baseline prior to device implantation, and at one year (n = 626 in ICD group; n = 752 in CRT-D group). Paired echocardiograms from baseline and at 12 months with the device turned on were
available in 1372 patients. Echocardiography investigators, sonographers were qualified to perform echocardiography studies according to the approved echocardiography protocol. Recordings were analyzed off-line at the Brigham and Women's Hospital, Boston, MA, USA which was recognized as an independent echocardiographic core laboratory.

Echocardiography investigators analyzing the images were blinded to treatment assignment and clinical outcome.

Left ventricular and atrial volumes were measured by Simpson’s disk method in the apical 4- and 2-chamber views. The coefficients of variation for end-diastolic volume, end-systolic volume and left ventricular ejection fraction were 5.2%, 6.2%, and 5.5%, respectively, as reported previously (10).

**Definitions and outcome measures**

LAV was indexed to body surface area and categorized as high ($\geq$ upper quartile LAV index (LAVi)) or low (< upper quartile LAVi). The reverse remodeling effects of the CRT-D on the LA and LV were calculated as the difference between the 1-year and baseline LAV and LV end-systolic volume, divided by baseline LAV and LV end-systolic volume, respectively (i.e. percent change in LAV and LV end-systolic volume).

The primary endpoints of the present study were defined as time to the occurrence of hospitalization for HF or death, whichever occurred first, and the separate occurrence of all-cause mortality. Endpoints occurrence were assessed by baseline LAV from enrollment. In a landmark analysis we also assessed the risk of HF or death in the CRT-D group subsequent to the 1-year echocardiogram by LAV change at one-year (assessed both as a continuous measure and categorized into approximate quartiles).

**Statistical analysis**

Baseline characteristics by LAV groups (dichotomized at the upper quartile) were compared with the Mann-Whitney U tests for continuous variables, and with chi-square
test for categorical variables. The cumulative probabilities of HF or death and the separate occurrence of all-cause mortality were assessed according to the Kaplan-Meier method, with comparison of cumulative events by the log-rank test. Cumulative event rates were compared by baseline LAV, by treatment arm within each baseline LAV group, and by LAV response to the CRT-D at 1-year compared with ICD-only patients. Multivariable analysis for HF or death and all-cause mortality endpoints was carried out using Cox proportional hazards regression modeling. Among patients who underwent CRT-D implantation we also assessed the relationship between echocardiographic changes from baseline to follow-up and endpoint occurrence subsequent to the 1-year echocardiogram (landmark-type analysis). Covariables included in the multivariable models were identified using a best subset procedure among candidate covariates listed in Table 1. In the landmark analyses the fit of the multivariable model which incorporated change in LAV was compared to the model in which change in LV end-systolic volume was employed in order to assess which echocardiographic measure of reverse remodeling was associated with improved prediction of clinical response to CRT-D.

All p values were two-sided, and a p value ≤0.05 was considered significant. Analyses were conducted with SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Study patients had a mean LAV value of 94 ml (SD 22) and a median of 91 ml (IQR 26). The mean LAV indexed value (LAVi calculated as LAV/BSA) was 47 ml/m² (SD 29) and the median of 46 ml/m² (IQR 39 ml/m²). Thus, the upper quartile used to define patients with enlarged LAV was > 52 ml/m². The mean LVESi value was 88 ml/m² (SD
23) and the median 84 ml/m² (IQR-26).

The baseline clinical, ECG, and echocardiographic characteristics of study patients by the LAVi groups are shown in Table 1. The majority of demographic and clinical parameters were similar between the two groups, including age, gender, HF etiology, NYHA class, diabetes, hypertension and prior myocardial infarction. However, patients with LAVi >52 ml/m² displayed several important differences from those with LAVi in the lower quartiles, including lower blood pressure levels, a higher frequency of prior atrial arrhythmias, a more prolonged QRS, and a higher frequency of left bundle branch block on the baseline ECG (Table 1). Baseline echocardiography showed that patients with a higher baseline LAV also had higher baseline left ventricular volumes and a lower left and right ventricular function.

**Clinical outcomes by baseline left atrial volume**

Patients with enlarged LAV (in the upper quartile range) had worse outcomes, showing a significant increase in the rate of all-cause mortality (Figure 1A) and the rate of HF or death (Figure 1B). Furthermore, when the rate of HF or death was assessed by each LAVi quartile, patients with LAVi in the range of Q1-3 were shown to have a similar cumulative probability of HF or death (in the range of 10%-14% at 2-years of follow-up; p = 0.45 for the difference among the 3 groups), whereas patients with upper quartile LAVi showed a pronounced increased in event rate (23% at 2-years of follow-up; p<0.001 for the overall difference among the 4 groups during follow-up, Figure 2).

Consistent with these findings, multivariable analysis (Table 2) showed that patients with upper quartile LAVi experienced a 69% increased hazard for HF or death (p<0.001) and a 59% (p=0.02) increase in the hazard of death compared with those who had a lower baseline LAVi. Furthermore, when LAVi was assessed as a continuous measure, each 1 ml/m² increase in LAV was associated with a corresponding 3%
(p<0.001) increase in the hazard of HF or death, and with a 2% (p=0.03) increase in the rate of all-cause mortality (Table 2). Additional covariables shown to be significantly associated with outcomes included treatment assignment, QRS duration ≥150 ms, NYHA >class II at 90 days or more prior to randomization, ischemic etiology, left bundle branch block, atrial arrhythmias, blood urea nitrogen ≥25 mg/dl, LV end-systolic volume indexed to body surface area at baseline, and left ventricular ejection fraction, (Table 2), whereas other factors listed in Table 1 were not included in the final model due to lack of a statistically significant association with the study end points.

Notably, the hazard of HF or death associated with LAV remained independent after adjustment for LV end-systolic volume. In contrast, the hazard associated with LV end-systolic volume was not statistically significant after adjustment for LAV (HR=1.00 [95% CI 0.99-1.00]), suggesting that the LA is a more important prognostic correlate than the LV in the MADIT-CRT population. Introduction of treatment-by-LAVi interaction terms to the multivariable models for the endpoints of HF or death and of all-cause mortality was not found to be statistically significant (p= 0.91 and 0.78, respectively), suggesting that the effect of LAVi on clinical outcomes is independent of treatment effect.

Effect of CRT-D on left atrial remodeling and its relationship to subsequent outcomes

CRT-D was associated with a significant percent reduction in LAV compared with ICD-only therapy (28% and 10% reduction, respectively; p < 0.001). Among patients treated with CRT-D, echocardiographic baseline LAVi was inversely correlated with a change in left atrial and ventricular volumes at 1 year (Figure 3).

Kaplan-Meier survival analysis among CRT-D patients showed that, subsequent to the 1-year echocardiographic assessment of LAV change, the cumulative probability
of HF or death was inversely correlated with the degree of the reverse remodeling effects of CRT-D on LAV (Figure 4). Notably, the highest rate of clinical events during follow-up was observed among patients in whom the CRT-D was associated with the lowest reductions in LAV (Q1: <20%), whereas CRT-D patients with greater reductions in LAV experienced a significantly lower rate of clinical events during subsequent follow-up (Figure 4).

Consistent with the univariable findings, multivariable analysis, after further adjustment for clinical and echocardiographic covariables (Table 3), showed that among patients treated with CRT each 1% reduction in LAV at 1 year was independently associated with a corresponding 4% (p<0.001) reduction in the hazard of subsequent HF or death. Similar results were obtained in the multivariable models in which percent reductions in LAV with CRT-D were categorized into approximate quartiles: compared with patients who experienced <1st quartile reduction in LAV at 1 year (<20%) with CRT, those who exhibited greater reverse remodeling effects following device implantation experienced a distinctly (in the range of 50% to 70%) lower hazard of subsequent HF or death (Table 3).

Notably, the association between LAV change and subsequent outcome in CRT-D patients remained independent after further adjustment for changes in LV. Furthermore, the fit of the model incorporating percent change in LAV was improved when compared with the corresponding model in which percent change in LV end-systolic volume was employed, suggesting that assessment of the reverse remodeling effects of CRT on the LA may provide incremental prognostic information compared with assessment of the effects of the device on the LV.
Discussion

In the present study we evaluated the prognostic implications of baseline and follow-up LAV on the outcome of patients who receive cardiac resynchronization therapy. We have shown that LAV is a strong correlate of subsequent clinical outcomes in mild HF patients treated with CRT, and that these outcomes are independent of left ventricular size and function. Furthermore, our data suggest that CRT exerts profound remodeling effects on the left atrium that provide incremental prognostic information in this population compared with sole assessment of the effects of the device on the left ventricle.

Left atrial volume and prognosis

Observational studies, including 6,657 patients without a baseline history of atrial fibrillation and significant valvular heart disease, have shown that increased LAV is an independent predictor of death, HF, atrial fibrillation, and ischemic stroke (14). In echocardographic studies of HF patients, LAV was shown to independently predict mortality among patients with both ischemic and non-ischemic cardiomyopathy (2,3). In accordance, in a recently published report of 483 consecutive patients assessed by cardiovascular magnetic resonance imaging left atrial volume was also shown to be an independent predictor of transplant free survival and heart failure outcomes in patients with dilated cardiomyopathy (4).

Our present findings from the MADIT-CRT trial extend these prior findings regarding the prognostic implications of the LA to mildly symptomatic HF patients. We have shown that LAV is a strong correlate of mortality and adverse clinical outcomes in this population and that each increase of 1ml/m^2 on LAVi is independently associated with a corresponding 3% increase in the hazard of HF or death, and a 2% hazard increase in the separate occurrence of all-cause mortality. Notably, the association
between LAV and clinical outcomes was maintained after adjustment for LV end-
systolic volume, whereas the latter parameter was not shown to be significantly
associated with HF or death after adjustment for LAVi, suggesting that the LA may be a
more important prognostic indicator than the LV in this population. These findings are
in accordance with a recently published echocardiographic heart failure score by
Carluccio et al. in which measurements of LAV were the strongest predictors of
mortality in 747 patients with heart failure followed for almost 3 years (15).

**CRT-induced left atrial remodeling and prognosis**

Only a few studies have investigated the effects of CRT on left atrial function and
remodeling in patients with advanced HF, focusing mainly on the association with the
development of atrial tachyarrhythmia (16-19). In a recent analysis of the MADIT-CRT
cohort we have shown that CRT-induced left atrial remodeling effects are associated
with a significant reduction in the risk for the development of atrial tachyarrhythmia,
including atrial fibrillation or flutter (13). The results of the present study add to current
knowledge by demonstrating the independent prognostic implications of LAV in HF
patients who receive CRT. Furthermore, we have shown that the left atrial remodeling
effects of the device are also independently associated with a distinctly lower hazard of
subsequent HF and mortality in this population.

Possible mechanisms explaining the independent association of CRT-D-induced
reverse remodeling effects on the LA and subsequent clinical outcomes, may relate to
the effects of the device on diastolic function. In subjects with congestive HF,
increased LAV usually reflects elevated ventricular filling pressures. During ventricular
diastole, the LA is exposed to the pressures of the LV. With increased stiffness or non-
compliance of the LV, LA pressure rises to maintain adequate LV filling (5), and the
increased atrial wall tension leads to chamber dilatation and stretching of the atrial
myocardium. Thus, LAV increases with severity of diastolic dysfunction (6,20). Deteriorating LV diastolic dysfunction further causes the stretching of myocytes, leading to LV remodeling and intense neuro-hormonal activity. The structural changes of the LA express the chronicity of exposure to abnormal filling pressures (6) and reflect an average effect of LV filling pressures over time, rather than an instantaneous measurement at the time of the study. These factors contribute to adverse outcomes, which may be reduced through improved diastolic function and the associated reverse remodeling of LAV following CRT implantation.

Considering that the MADIT-CRT cohort included patients with less severe symptoms and a lower hemodynamic burden to the LA compared to patients with more advanced stages of the disease, our results concur with a recent study by Verbrugge et al. (21), which suggests that early initiation of CRT for HF postpones the deleterious effects of chronic left atrial pressure overload and improves prognosis in this population.

Limitations

The lack of more advanced echocardiographic measures of diastolic dysfunction in this study did not affect our conclusions, since diastolic function assessment by Doppler velocities and time intervals are highly variable and related to the hemodynamic status of the patient at the time of the examination. Conversely, LAV measurements are highly feasible and reliable, often reflecting the cumulative effects of filling pressures over time (22). As only 2% of the patients in MADIT-CRT trial had severe mitral regurgitation at baseline, the effect of LAV on outcome was not adjusted for this factor in the present study. Another potential limitation regards the effects of LV mass on LA volumes which was not available in MADIT-CRT. It should be noted that all our analysis in the present study (LAVi assessed as a continuous measure or quartile
analysis) were prespecified, whereas the statistical significance of selecting a cutoff after an ROC analysis may be criticized due to multiple testing.

Conclusions and clinical implications

LAV, a marker of diastolic dysfunction severity, is an independent prognostic correlate in patients with mild HF receiving CRT. CRT exerts pronounced reverse remodeling effects on the LA, which may provide improved clinical assessment response to CRT. These findings suggest that baseline and follow-up measures of the LA should be routinely employed and considered in the assessment of patients who undergo CRT-D implantation.

Disclosures

Drs. Moss, Solomon, and Zareba have received research support for the conduct of the MADIT-CRT trial from Boston Scientific through a grant to the University of Rochester. Dr. Goldenberg receives research grant support from Boston Scientific and the Mirowski Foundation.

References

16. Fung JW, Yip GW, Zhang Q, Fang F, Chan JY, Li CM, Wu LW, Chan GC, Chan HC, Yu CM. Improvement of left atrial function is associated with
Table 1. Baseline characteristics of the two patients groups as defined by LAVi

<table>
<thead>
<tr>
<th></th>
<th>LAVi Q1-Q3</th>
<th>LAVi Q4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>64 ± 11</td>
<td>65 ± 11</td>
<td>0.52</td>
</tr>
<tr>
<td>Age &gt; 65(%)</td>
<td>49</td>
<td>50</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Cardiac history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic NYHA class I(%)</td>
<td>15</td>
<td>14</td>
<td>0.70</td>
</tr>
<tr>
<td>Ischemic NYHA class II(%)</td>
<td>40</td>
<td>42</td>
<td>0.48</td>
</tr>
<tr>
<td>Diabetes mellitus(%)</td>
<td>31</td>
<td>29</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension(%)</td>
<td>65</td>
<td>60</td>
<td>0.05</td>
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<tr>
<td>Prior myocardial infarction(%)</td>
<td>43</td>
<td>44</td>
<td>0.81</td>
</tr>
<tr>
<td>Prior revascularization(%)</td>
<td>29</td>
<td>23</td>
<td>0.01</td>
</tr>
<tr>
<td>Prior atrial arrhythmias(%)</td>
<td>10</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior ventricular arrhythmias(%)</td>
<td>7</td>
<td>9</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>SBP, mm Hg</strong></td>
<td>123 ± 17</td>
<td>120 ± 18</td>
<td>0.001</td>
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<tr>
<td><strong>DBP, mm Hg</strong></td>
<td>72 ± 10</td>
<td>70 ± 10</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>BMI &gt;=30 kg/m²</strong></td>
<td>37</td>
<td>30</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
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<td>BUN, mg/dl</td>
<td>21 ± 9</td>
<td>22 ± 9</td>
<td>0.08</td>
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<td>BUN &gt;25 mg/dl</td>
<td>24</td>
<td>25</td>
<td>0.6</td>
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<tr>
<td>Creatinine, mg/dl</td>
<td>1.2 ± 0.4</td>
<td>1.2±0.3</td>
<td>0.58</td>
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<tr>
<td>BNP level (pg/dl)</td>
<td>108 ± 136</td>
<td>178 ± 216</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Electrocardiographic findings at enrollment</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>QRS (ms)</td>
<td>157 ± 19</td>
<td>162 ± 22</td>
<td>&lt;0.001</td>
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<tr>
<td>QRS &gt; 150 ms(%)</td>
<td>63</td>
<td>68</td>
<td>0.07</td>
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<tr>
<td>LBBB(%)</td>
<td>69</td>
<td>74</td>
<td>0.05</td>
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<tr>
<td><strong>Echocardiographic findings at enrollment</strong></td>
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<tr>
<td>LVEDV indexed by BSA</td>
<td>116 ± 21</td>
<td>145 ± 36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV indexed by BSA</td>
<td>89 ± 16</td>
<td>107 ± 29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF %</td>
<td>30 ± 3</td>
<td>27 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAV indexed by BSA*, ml/m²</td>
<td>42 ± 6</td>
<td>60 ± 7</td>
<td></td>
</tr>
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<td><strong>Medications at baseline</strong></td>
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<tr>
<td>ACEIs or ARBs(%)</td>
<td>96</td>
<td>96</td>
<td>0.8</td>
</tr>
<tr>
<td>Beta-blockers(%)</td>
<td>94</td>
<td>92</td>
<td>0.21</td>
</tr>
<tr>
<td>Aldosterone antagonists(%)</td>
<td>31</td>
<td>35</td>
<td>0.12</td>
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<tr>
<td>Amiodarone(%)</td>
<td>6</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin(%)</td>
<td>66</td>
<td>60</td>
<td>0.025</td>
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<td>Digitalis(%)</td>
<td>23</td>
<td>34</td>
<td>&lt;0.001</td>
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<tr>
<td>Diuretics(%)</td>
<td>65</td>
<td>75</td>
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<tr>
<td>Statins(%)</td>
<td>68</td>
<td>64</td>
<td>0.10</td>
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Data are presented as percentage or mean ± standard deviation.

*p-value not analyzed since LAVi is a prespecified comparison group.
ACEI = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; BMI = Body mass index; BSA = body surface area; BUN = blood urea nitrogen; CRT-D = cardiac resynchronization therapy-defibrillator; DBP = diastolic blood pressure; LAVi = left atrial volume index; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular endsystolic volume; NYHA = New York Heart Association; RBBB = right bundle branch block; SBP = systolic blood pressure.
Table 2. Multivariable analysis of the effect of baseline LAV on the hazard of heart failure or death and the separate occurrence of all-cause mortality*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Endpoint: Heart Failure or Death</th>
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<th>Endpoint: Death</th>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P Value</td>
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<tr>
<td>Left atrial volume index</td>
<td></td>
<td></td>
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<tr>
<td>Per 1 ml increment</td>
<td>1.03</td>
<td>1.01-1.04</td>
<td>&lt;0.001</td>
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<tr>
<td>Upper quartile vs. quartiles 1 to 3</td>
<td>1.69</td>
<td>1.35-2.11</td>
<td>&lt;0.001</td>
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<tr>
<td>LVESV (per ml increment)</td>
<td>1.00</td>
<td>0.99-1.003</td>
<td>0.4</td>
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Additional covariates

<table>
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<th>Covariate</th>
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<th></th>
<th>Endpoint: Death</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>CRT-D vs. ICD-only</td>
<td>0.64</td>
<td>0.52-0.79</td>
<td>&lt;0.01</td>
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<td>QRS width (per 1ms increment)</td>
<td>0.99</td>
<td>0.98-1.00</td>
<td>&lt;0.01</td>
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<td>NYHA &gt;II 90 days prior to enrollment</td>
<td>1.37</td>
<td>1.02-1.86</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior Revascularization</td>
<td>1.50</td>
<td>1.19-1.89</td>
<td>&lt;0.01</td>
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<tr>
<td>Past atrial arrhythmia</td>
<td>1.53</td>
<td>1.15-2.04</td>
<td>&lt;0.01</td>
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<td>BUN (increment per 1 mg/dl)</td>
<td>1.02</td>
<td>1.01-1.03</td>
<td>&lt;0.01</td>
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<tr>
<td>LVEF (Per 1% increment)</td>
<td>0.96</td>
<td>0.94-0.98</td>
<td>&lt;0.01</td>
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</table>
*The effect of volume changes as continuous and binary measures was assessed in separate models.

Consistent results were obtained after adjustment for baseline medication.

Replacement of baseline left ventricular ejection fraction with baseline left ventricular end-systolic volumes resulted in similar results (see text).

BUN = Blood urea nitrogen  CI = Confidence interval; HR = Hazards ratio; LVEF = Left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association
Table 3. Multivariable analysis: hazard of heart failure or death in patients with CRT-D by the degree of left atrial change at 1-year

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Endpoint of Heart Failure or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percent change in left atrial volume assessed as a continuous measure †</strong></td>
<td></td>
</tr>
<tr>
<td>Per 1% reduction in left atrial volume</td>
<td>HR 0.96 95% CI 0.94-0.98  P value 0.96</td>
</tr>
<tr>
<td><strong>Percent change in left atrial volume categorized into quartiles †</strong></td>
<td></td>
</tr>
<tr>
<td>% change in left atrial volume: Q₂ vs. Q₁</td>
<td>HR 0.52 95% CI 0.28-0.97  P value 0.047</td>
</tr>
<tr>
<td>% change in left atrial volume: Q₃ vs. Q₁</td>
<td>HR 0.34 95% CI 0.16-0.72  P value 0.005</td>
</tr>
<tr>
<td>% change in left atrial volume: Q₄ vs. Q₁</td>
<td>HR 0.40 95% CI 0.17-0.92  P value 0.03</td>
</tr>
<tr>
<td><strong>Additional covariates</strong></td>
<td></td>
</tr>
<tr>
<td>Prior atrial arrhythmia</td>
<td>HR 1.36 95% CI 0.69-2.7  P value 0.04</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>HR 1.39 95% CI 0.83-2.3  P value 0.2</td>
</tr>
<tr>
<td>QRS (per 1ms increment)</td>
<td>HR 0.97 95% CI 0.97-0.99  P value 0.02</td>
</tr>
<tr>
<td>BUN (per 1mg/dl increment)</td>
<td>HR 1.02 95% CI 0.98-1.05  P value 0.08</td>
</tr>
<tr>
<td>LVEF (per 1% increment)</td>
<td>HR 0.95 95% CI 0.91-1.0  P value 0.048</td>
</tr>
</tbody>
</table>

† Results obtained from separate regression models using the same additional covariates; results shown for additional covaraites are from the
multivariable model that assessed change in LAV as a continuous measure.

BUN = Blood urea nitrogen CI = Confidence interval; CRT-D = cardiac resynchronization therapy-defibrillator; HR = Hazards ratio; LVEF = Left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association
**Figure Legends**

**Figure 1.** Cumulative probability of death (Figure 1A) and the combine probability of heart failure or death (Figure 1B) by indexed LAV quartile. Analysis performed for all the study participants. The upper LAV quartile (Q4) was defined as LAVi > 52 ml/m². LAV = left atrial volume

**Figure 2.** Cumulative probability of heart failure or death at the 12-month echocardiography in the CRT-D group, stratified by indexed LAV quartiles. Q1 was defined as LAVi < 40 ml/m², Q2 as 40 to 45 ml/m², Q3 as >45 to 52 ml/m² and Q4 as LAVi > 52 ml/m². LAV = left atrial volume; LAVi = Left atrial volume indexed to BSA

**Figure 3.** Changes in echocardiographic parameters at the 12-month follow-up by baseline LAV. Numbers are median percent change median with (IQR) between baseline chamber volumes and the 12-month follow-up echocardiography by the baseline LAVI quartile. LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume

**Figure 4.** Cumulative probability of heart failure or death following the 12-month echocardiography in the CRT-D group, stratified by the LAV response to CRT grouped into quartiles. "Landmark" analysis performed for all patients who had a full baseline and 12-month echocardiographic result in the CRT-D group. CRT-D = cardiac resynchronization therapy-defibrillator; LAV = left atrial volume
Figure 1A

Unadjusted P<0.001

Probability of Death

Patients at Risk

Years

LAV_Q1-Q3 1339 1286 (0.02) 826 (0.04) 354 (0.07)
LAV_Q4 446 419 (0.03) 371 (0.07) 206 (0.12)
Figure 1B
Figure 4

Unadjusted P = 0.004

Patients at Risk
LAV %chg Q1 187
LAV %chg Q2 187
LAV %chg Q3 187
LAV %chg Q4 187

Years after 12 month Echo
136 (0.12)
128 (0.06)
121 (0.05)
74 (0.03)
103 (0.18)
76 (0.09)
69 (0.08)
28 (0.05)
67 (0.20)
28 (0.13)
27 (0.08)
6 (0.05)

Probability of HF or Death
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Rafael Kuperstein, Ilan Goldenberg, Arthur J. Moss, Scott Solomon, Mikhail Bourgoun, Amil Shah, Scott McNitt, Wojciech Zareba and Robert Klempfner

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