Left atrial volume (LA V) has been shown to be a reliable predictor of cardiovascular outcomes in several conditions, including heart failure (HF), initially by echocardiography and lately by MRI. During ventricular diastole, the left atrium is exposed to pressures of the left ventricle. Thus, LA V often reflects the cumulative effects of filling pressures over time and may, therefore, provide a more sensitive morphophysiological expression of the severity of diastolic dysfunction than the left ventricle.

During the past decade, cardiac resynchronization therapy (CRT) has emerged as an important therapeutic modality for patients with mild to moderate HF. Initially by echocardiography and lately by MRI, CRT has been shown to reduce the risk of HF or death and to improve diastolic function and reverse remodeling effects of the device on the left ventricle.

Methods and Results—The benefit of CRT-D versus defibrillator-only therapy in reducing the risk of HF or death was assessed by LA V (dichotomized at the upper quartile >52 mL/m²) among 1785 patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) study. Landmark analysis was used to evaluate the relationship between LA V response to CRT-D and subsequent clinical outcomes. Multivariable analysis showed that patients with a higher baseline LA V experienced increased hazard for HF or death for all-cause mortality, respectively, independently of baseline left ventricular volume. CRT-D was associated with a significant reduction in LA V compared with defibrillator-only therapy. Landmark analysis showed that after CRT-D implantation each 1% reduction in LA V was independently associated with a corresponding 4% reduction in the hazard of subsequent HF or death. The assessment of LA V change after CRT implantation improved prediction of clinical response to the device compared with assessment of the corresponding changes in left ventricular volume.

Conclusions—LA V is an independent correlate of clinical outcomes in mildly symptomatic HF patients treated with CRT-D. CRT exerts pronounced reverse remodeling effects on the left atrium that independently correlate with improved clinical outcomes after device implantation. Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00180271.
Methods

Study Population

The design and results of the MADIT-CRT study have been reported previously. Briefly, 1820 patients either with ischemic cardiomyopathy and New York Heart Association (NYHA) class I to II, or with nonischemic cardiomyopathy and NYHA class II, QRS duration ≥130 ms, and ejection fraction ≤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, existing indication for CRT, implanted pacemaker, NYHA III or IV functional class during the past 90 days before enrollment, coronary artery bypass graft surgery, percutaneous coronary intervention, or myocardial infarction during the past 90 days before enrollment. In this international multicenter trial, 110 hospital centers from North America and Europe participated, 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 December 22, 2004, through 22 June 2009. After cessation of the study on the recommendation of the safety monitoring board, complete data collection and adjudication of clinical end points were continued through 31 December 2009. The present study includes 1785 patients (98%) who had LAV measurements in accordance with the study protocol.

Echocardiographic Methods

ECGs were obtained according to a study-specific protocol at baseline before device implantation and at 1 year (n=826 in ICD group; n=752 in CRT-D group). Paired ECGs from baseline and at 12 months with the device turned on were available in 1372 patients. Echocardiography investigators and sonographers were qualified to perform echocardiography studies according to the approved echocardiography protocol. Recordings were analyzed offline at the Brigham and Women’s Hospital, Boston, MA, which has been 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 disk method in the apical 4- and 2-chamber views. The coefficients of variation for end-diastolic volume, end-systolic volume, and left ventricular (LV) ejection fraction were 5.2%, 6.2%, and 5.5%, respectively, as reported previously.

Definitions and Outcome Measures

LAV was indexed to body surface area and categorized as high (above or equal to upper quartile LAV index [LAVi]) or low (below upper quartile LAVi). The reverse remodeling effects of CRT-D on left atrium and left ventricle were calculated as the difference between 1-year and baseline LAV and LV end-systolic volume divided by baseline LAV and LV end-systolic volume, respectively (ie, percent change in LAV and LV end-systolic volume).

The primary end points 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. The occurrence of end points was 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 ECG by LA V change at 1 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 χ² 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 CRT-D at 1 year compared with ICD-only patients.

Multivariable analysis for HF or death and all-cause mortality end points was performed 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 end point occurrence subsequent to the 1-year ECG (landmark-type analysis). Covariates 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 with the model in which change in LV end-systolic volume was used to assess which echocardiographic measure of reverse remodeling was associated with improved prediction of clinical response to CRT-D.

All P values were 2-sided, and a P value ≤0.05 was considered significant. Analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

Results

Study patients had a mean LAV value of 94 mL (SD, 22) and a median of 91 mL (interquartile range [IQR], 26). The mean LAVi value (calculated as LAV/BSA) was 47 SD, 29) mL/m² and median was 46 (IQR, 39) mL/m². Thus, the upper quartile used to define patients with enlarged LAV was >52 mL/m². The mean LV end-systolic index value was 88 (SD, 23) mL/m² and median was 84 (IQR, 26) mL/m².

The baseline clinical and echocardiographic characteristics of study patients, defined by LAVi, are shown in Table 1. The majority of demographic and clinical parameters were similar between the 2 groups, including age, sex, HF cause, NYHA class, diabetes mellitus, hypertension, and previous 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, higher frequency of previous atrial arrhythmias, more prolonged QRS, and higher frequency of left bundle branch block on baseline ECG (Table 1). Baseline echocardiography showed that patients with a higher baseline LAV also had higher baseline LV volumes and lower left and right ventricular function.

Clinical Outcomes by Baseline LAV

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 to Q3 were shown to have a similar cumulative probability of HF or death (in the range of 10% to 14% at 2 years of follow-up; P=0.45 for difference among the 3 groups), whereas patients with upper quartile LAVi showed a pronounced increase in event rate (23% at 2 years of follow-up; P<0.001 for 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) increased hazard of death compared...
Table 1. Baseline Characteristics of the 2 Patient Groups as Defined by LAVi

<table>
<thead>
<tr>
<th></th>
<th>LAVi, Q1–Q3 (n=1339)</th>
<th>LAVi Q4 (n=446)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±11</td>
<td>65±11</td>
<td>0.52</td>
</tr>
<tr>
<td>Age &gt;65 y, %</td>
<td>49</td>
<td>50</td>
<td>0.40</td>
</tr>
<tr>
<td>Cardiac history</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>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>43</td>
<td>44</td>
<td>0.81</td>
</tr>
<tr>
<td>Previous revascularization, %</td>
<td>29</td>
<td>23</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous atrial arrhythmias, %</td>
<td>10</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous ventricular arrhythmias, %</td>
<td>7</td>
<td>9</td>
<td>0.07</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>123±17</td>
<td>120±18</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72±10</td>
<td>70±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>21±9</td>
<td>22±9</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2±0.4</td>
<td>1.2±0.3</td>
<td>0.58</td>
</tr>
<tr>
<td>BNP level, pg/dL</td>
<td>37</td>
<td>30</td>
<td>0.007</td>
</tr>
<tr>
<td>Electrocardiographic findings at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS, ms</td>
<td>157±17</td>
<td>162±22</td>
<td>&lt;0.001</td>
</tr>
<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>
</tr>
<tr>
<td>Echocardiographic findings at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV indexed by BSA</td>
<td>116±21</td>
<td>145±36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESEV 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>
<tr>
<td>Medications at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEIs or ARBs, %</td>
<td>96</td>
<td>96</td>
<td>0.8</td>
</tr>
<tr>
<td>β-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>
</tr>
<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>
</tr>
<tr>
<td>Digitalis, %</td>
<td>23</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>65</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins, %</td>
<td>68</td>
<td>64</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are presented as percentage or mean±SD. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; BUN, blood urea nitrogen; DBP, diastolic blood pressure; LAVi, left atrial volume index; LBBB, left bundle branch block; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESEV, LV end-systolic volume; NYHA, New York Heart Association; and SBP, systolic blood pressure. *P value not analyzed because LAVi is a prespecified comparison group.

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 that were shown to be significantly associated with outcomes included treatment assignment, QRS duration ≥150 ms, NYHA above class II at ≥90 days before randomization, ischemic cause, left bundle branch block, atrial arrhythmias, blood urea nitrogen ≥25 mg/dL, LV end-systolic volume indexed to body surface area at baseline, and LV ejection fraction (Table 2), whereas other factors listed in Table 1 were not included in the final model because of lack of a statistically significant association with study end points.

Notably, the hazard of HF or death associated with LAVi 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 LAVi (hazards ratio, 1.00; 95% confidence interval, 0.99–1.00), suggesting that the left atrium is a more important prognostic correlate compared with the left ventricle in the MADIT-CRT population. The introduction of treatment-by-LAVi interaction terms to the multivariable models for the end points 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 LA Remodeling and Its Relationship to Subsequent Outcomes**

CRT-D was associated with a significant percent reduction in LAVi 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 LAVi change, the cumulative probability of HF or death was inversely correlated with the degree of reverse remodeling effects of CRT-D on LAVi (Figure 4). Notably, the highest rate of clinical events during follow-up was observed among patients in whom CRT-D was associated with lowest reductions in LAVi (Q1, <20%), whereas CRT-D patients with greater reductions in LAVi experienced a significantly lower rate of clinical events during subsequent follow-up (Figure 4).

Consistent with univariable findings, the multivariable analysis, after further adjustment for clinical and echocardiographic covariables (Table 3), showed that among patients treated with CRT each 1% reduction in LAVi 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 LAVi with CRT-D were categorized into approximate quartiles; compared with patients who experienced below first quartile reduction in LAVi at 1 year (<20%) with CRT, those who exhibited greater reverse remodeling effects after device implantation experienced a distinctly (in the range of 50–70%) lower hazard of subsequent HF or death (Table 3).

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

Discussion

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

LAV and Prognosis

Observational studies, including 6657 patients without a baseline history of atrial fibrillation and significant valvular heart disease, have shown that increased LA V is an independent predictor of death, HF, atrial fibrillation, and ischemic stroke. In the echocardiographic studies of HF patients, LA V was shown to independently predict mortality among patients with both ischemic and nonischemic cardiomyopathy. Accordingly, in a recently published report of 483 consecutive patients assessed by cardiovascular MRI, LA V was also shown to be an independent predictor of transplant-free survival and HF outcomes in patients with dilated cardiomyopathy.

Our present findings from the MADIT-CRT study extend these previous findings regarding the prognostic implications on the left atrium in mildly symptomatic HF patients. We have shown that LA V is a strong correlate of mortality and adverse clinical outcomes in this population and that each 1 mL/m² increase in LA Vi 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 LA V 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 LA Vi, suggesting that the left atrium may be a more important prognostic indicator compared with the left ventricle in this population.

CRT-Induced LA Remodeling and Prognosis

Only a few studies have investigated the effects of CRT on LA function and remodeling in patients with advanced HF, focusing mainly on the association with the development of atrial tachyarrhythmia. In a recent analysis of the MADIT-CRT cohort, we have shown that CRT-induced LA remodeling effects are associated with a significant reduction in the risk of development of atrial tachyarrhythmia, including atrial fibrillation or flutter. The results of the present study add to current knowledge by demonstrating the independent prognostic implications of LA V in HF patients who received CRT. Furthermore, we have shown that the LA remodeling effects of the device are also independently associated with a distinctly lower hazard of subsequent HF and mortality in this population.
The possible mechanisms explaining the independent association of CRT-D-induced reverse remodeling effects on the left atrium and subsequent clinical outcomes may relate to the effects of the device on diastolic function. In subjects with congestive HF, increased LA V usually reflects elevated ventricular filling pressures. During ventricular diastole, the left atrium is exposed to the pressures of the left ventricle. With increased stiffness or noncompliance of the left ventricle, LA pressure rises to maintain adequate LV filling, and the increased atrial wall tension leads to chamber dilatation and stretching of the atrial myocardium. Thus, LA V increases with severity of diastolic dysfunction. Deteriorating LV diastolic dysfunction further causes the stretching of myocytes, leading to LV remodeling and intense neurohormonal activity. The structural changes of the left atrium express the chronicity of exposure to abnormal filling pressures 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 associated reverse remodeling of LAV after CRT implantation.

Considering that the MADIT-CRT cohort included patients with less severe symptoms and a lower hemodynamic burden to the left atrium compared with 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 LA 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, because diastolic function assessment by Doppler velocities and time intervals are highly variable and relate to the hemodynamic status of the patient at the time of examination. Conversely, LA V measurements are highly feasible and reliable, often reflecting the cumulative effects of filling pressures over time.23 Because only 2% of patients in the MADIT-CRT study had severe mitral regurgitation at baseline, the effect of LA V on outcome was not adjusted for this factor in the present study. Another potential limitation relates to the effects of LV mass on LA volumes, which was not available in MADIT-CRT. It should be noted that all our analyses in the present study (LAVi assessed as a continuous measure or quartile analysis) were prespecified, whereas the statistical significance of selecting a cut-off after an receiver operating characteristic analysis may be criticized because of 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 left atrium, which may provide improved clinical assessment response to CRT. These findings suggest that baseline and follow-up measures of the left atrium should be routinely used and considered in the assessment of patients who underwent CRT-D implantation.

Disclosures
Drs Moss, Solomon, and Zareba received research support for the conduct of the MADIT-CRT study from Boston Scientific through a grant to the University of Rochester. Dr Goldenberg receives research grant support from Boston Scientific and the Mirowski Foundation. The other authors have no conflicts to report.

References

**CLINICAL PERSPECTIVE**

Left atrial volume (LAV) is a reliable predictor of cardiovascular outcomes in heart failure, because it provides a more sensitive expression of the severity of diastolic dysfunction than the left ventricle. The clinical benefits associated with cardiac resynchronization therapy (CRT) are related to the reverse remodeling effects of the device on the left ventricle and have been associated with reduction in mitral regurgitation severity and improvement in diastolic function. In the present study, we evaluated the association of baseline LAV with the hazard of heart failure (HF) and death, the relationship between LAV and the clinical benefit of CRT, and the association between the reverse remodeling effects of CRT on LAV and subsequent clinical outcomes in mildly symptomatic HF patients. We found that LAV independently correlated with clinical outcomes and that CRT exerts pronounced reverse remodeling effects on the left atrium, which independently correlate with improved clinical outcomes after device implantation. These findings suggest that baseline and follow-up measures of the LAV are useful markers to be considered in the assessment of patients who underwent CRT implantation with a defibrillator.
Left Atrial Volume and the Benefit of Cardiac Resynchronization Therapy in the MADIT-CRT Trial
Rafael Kuperstein, Ilan Goldenberg, Arthur J. Moss, Scott Solomon, Mikhail Bourgoun, Amil Shah, Scott McNitt, Wojciech Zareba and Robert Klempfner

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