Brain Natriuretic Peptide and Cardiac Resynchronization Therapy in Patients with Mildly Symptomatic Heart Failure

Brenyo et al: CRT and Brain Natriuretic Peptide

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Subject Codes: Congestive Heart Failure; Remodeling; Pacemaker; Other diagnostic testing
Abstract

**Background**—There are limited data regarding the prognostic implications of brain natriuretic peptide (BNP) assessment in mildly symptomatic heart failure (HF) patients who receive cardiac resynchronization therapy with a defibrillator (CRT-D).

**Methods and Results**—The effect of elevated baseline and 1-year BNP levels (dichotomized at the upper tertile BNP of 120 pg/ml) on the risk of HF or death was assessed among the cohort of 1197 patients with baseline BNP data enrolled in MADIT-CRT. Elevated baseline BNP was associated with a significant 68% (p = 0.007) and 58% (p = 0.02) increase in the risk of HF or death among MADIT-CRT patients allocated to CRT-D and ICD-only therapy, respectively. At one year of follow up, patients allocated to CRT-D displayed significantly greater reductions in BNP (26% reduction) levels compared with ICD-only patients (8% increase; p = 0.005). CRT-D patients in whom one-year BNP levels were reduced or remained low experienced a significantly lower risk of subsequent HF or death as compared with patients in whom BNP levels were high a one-year. Similarly, the echocardiographic response to CRT-D was highest among those who maintained low BNP levels or in whom BNP at one-year was reduced.

**Conclusions**—Our findings suggest that assessment of baseline and follow-up BNP provides important prognostic implications in mildly symptomatic HF patients who receive cardiac resynchronization therapy.

**Clinical Trial Registration**—URL: [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov). Unique identifier: NCT00180271.

**Key Words:** cardiac resynchronization therapy, brain natriuretic peptide, heart failure
Cardiac resynchronization therapy (CRT-D) has been shown in a number of large randomized controlled trials of appropriately selected patients with variable heart failure (HF) severity to be effective at reducing morbidity and, in some cases, mortality. Despite its success in large studies, a lack of response to CRT-D has been reported in up to one third of device recipients, resulting in a desire to further risk stratify patients prior to CRT-D implant and to detect favorable clinical response following device implantation in an objective reproducible fashion.

Brain natriuretic peptide (BNP) has been suggested to be a useful tool in both pre-CRT-D implant risk stratification and in monitoring for CRT-D response post-implant, primarily in patients with advanced (NYHA class III or IV) HF symptoms. BNP is produced and secreted by the ventricular cardiac myocyte in response to myocardial stretch and elevated ventricular filling pressures. Resulting plasma BNP concentrations are higher in patients with more severe symptoms or worse LV function and are a powerful predictor of mortality and subsequent HF. Currently, however, data regarding the prognostic utility of BNP assessment in patients with mild HF symptoms who are treated with cardiac resynchronization therapy are lacking.

Accordingly, the present study was carried out in a population of mildly symptomatic HF patients with left ventricular dysfunction enrolled in MADIT-CRT, and was designed to determine: 1) the association between baseline BNP and the risk for the development HF or death following device implantation; 2) the relation between baseline BNP and the clinical response to CRT-D; 3) the effect of CRT-D vs. ICD-only therapy on BNP levels during follow-up; and 4) the prognostic implications of BNP assessment following CRT-D implantation.
Methods

Study Population

The design and results of MADIT-CRT have been reported previously. Briefly, 1820 patients enrolled at 110 centers in the United States, Canada, and Europe who had ischemic or non-ischemic cardiomyopathy, an ejection fraction of \( \leq 0.30 \), and abnormal intraventricular conduction with QRS \( \geq 130 \) msec were randomized to receive CRT-D or ICD therapy in a 3:2 ratio. All patients gave informed consent and the study was approved by an institutional review committee. Exclusion criteria included an existing indication for CRT, NYHA class III/IV in the past 90 days before enrollment, pacemaker in situ, and CABG or percutaneous coronary intervention or myocardial infarction within 90 days before enrollment.

This study included all patients with available baseline BNP data enrolled in MADIT-CRT. Enrollment BNP assessment was obtained in 1197 patients with one-year follow up BNP values available in 957 patients. Of the 240 patients who did not have one-year follow-up BNP data, 30 patients died prior to 12 months. All BNP data were derived from patients enrolled in the 85 US centers participating in MADIT-CRT. Numbers of patients available for various endpoint analyses are displayed in Figure 1.

Echocardiographic Methods

Echocardiograms were obtained according to a study-specific protocol at baseline, which was prior to device implantation (ICD \( n = 470 \); CRT-D \( n = 722 \)), and at one year with paired echocardiograms available for 889 patients (ICD \( n = 406 \), CRT-D \( n = 483 \)). Echocardiographic parameters were measured in a core laboratory according to established American Society of Echocardiography protocols. Left ventricular volumes were measured by Simpson’s method of discs in the apical 4-chamber and 2-chamber views and averaged with left ventricular ejection fraction.
fractions calculated from the resulting values. Left atrial volumes were measured using Simpson’s method of discs in the apical 4-chamber view.

**Definitions and Outcome Measures**

High baseline BNP was defined as an enrollment BNP above the study population upper tertile of 120 pg/ml. High follow-up BNP was similarly defined as a one year BNP > 120 pg/ml. Changes in BNP values from baseline to one year of follow-up were categorized as high / high (baseline/one year), high / low, low / high, and low / low.

The primary end point of the present study was the first occurrence of HF or death from enrollment and subsequent to the 1-year follow-up BNP assessment.

**Statistical Analysis**

Enrollment characteristics among patients with high (> 120 pg/ml) and low (≤ 120 pg/ml) baseline BNP were compared with t-test, one way ANOVA test, or Chi square tests as appropriate. Multivariate Cox proportional hazards regression modeling was used to assess the effect of baseline and follow-up (landmark analysis) BNP on the risk for the development of subsequent HF or death. The assumption of proportional hazards was checked graphically using standard log minus log survival density function plots as well as testing the interaction of covariates with follow-up time in the multivariate model. Covariates included in the model were identified using a best subset procedure among variables that were predictive of the endpoint or were unbalanced among the 2 groups (high vs. low BNP) including ischemic etiology of LV dysfunction, diabetes, age at enrollment, gender, New York Heart Association (NYHA) class, blood urea nitrogen (BUN), serum creatinine (Cr), left bundle branch block (LBBB), indexed left ventricular end systolic volume (LVESV) and left atrial volume (LAV). Patients missing values for covariates in the multivariate Cox models were excluded as no data imputations methods
were used. The CRT-D vs. ICD-only risk of HF or death among patients with baseline low or high BNP was assessed by including a treatment-by-BNP interaction-term in the multivariate models.

The effect of BNP change at one year following CRT-D implantation on subsequent outcome was assessed by evaluating response as a categorical variable dependent on the 120 pg/ml cutoff (i.e. low baseline and low one year, high baseline / high one year, low baseline / high one year, high baseline / low one year) in the multivariate models. The cumulative probabilities of HF or death by baseline and follow-up were graphically displayed according to the method of Kaplan and Meier, with comparison of cumulative events by the log-rank test. The test of proportionality for the BNP change groups in the multivariate model did not approach statistical significance with an overall p-value of 0.23). 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, North Carolina).

Results

Patient Characteristics

The present study population comprises 1197 patients with baseline BNP data. Numbers of subjects available for various endpoint analyses are displayed in Figure 1. Median follow up time was 2.9 years (mean of 2.9 years). Patients were dichotomized into low (≤ 120 pg/ml) and high (> 120 pg/ml) baseline BNP (upper tertile cutoff), as detailed above, with 806 patients in the low (mean ± SD: 46 ± 33 pg/ml; median, interquartile range [IQR]: 39, 18 - 71) and 389 patients in the high (mean ± SD: 265 ± 169 pg/ml; median, IQR: 206, 157 - 295) BNP groups, respectively. The clinical characteristics of these two patient groups are presented in Table 1. Patients with an
elevated BNP at baseline were older with a greater proportion of ischemic cardiomyopathy, elevated serum creatinine and BUN and were less likely to have LBBB. Medication use was similar with the notable exception of a lower frequency of aldosterone antagonists usage and increased usage of diuretics in the BNP > 120 group. Echocardiographic parameters differed significantly between the two groups, with larger indexed baseline ventricular and atrial volumes and a lower LVEF seen in the elevated BNP group.

**Baseline BNP, the Risk of Subsequent HF or Death**

From enrollment through three years follow up, patients with elevated baseline BNP had a significantly greater cumulative probability to experience the combined endpoint of HF or death as compared with patients with lower baseline BNP levels. These effects were observed in both the ICD (41 % vs. 22 %, respectively; p < 0.001 [Figure 2A]) and CRT-D (29 % vs. 15 %, respectively; p < 0.001 [Figure 2B]) arms of the trial. Consistent with this finding, after multivariate adjustment (Table 2) patients with elevated baseline BNP were shown to experience a significant increase in the risk of HF or death. Thus, among patients allocated to ICD therapy increased BNP was associated with a significant 58% increase in the risk of HF or death, and among CRT-D patients there was a corresponding 68% risk increase. When assessed as a continuous variable, each ten-fold increase in BNP (1 to 10, 10 to 100, etc.) was associated with a corresponding 2.2 fold increase (p < 0.001) in the risk of HF or death. The clinical benefit of CRT-D vs. ICD-only therapy was maintained among patients with both baseline high BNP (56% reduction in the risk of HF or death) and low BNP (55% risk reduction; p-value for treatment-by-BNP interaction p value = 0.95). In addition, interaction-term analysis did not identify a significant difference in the association between baseline BNP (high and low) and response to CRT between LBBB and non-LBBB patients with an interaction p value of 0.59.
Effect of Cardiac Resynchronization Therapy on BNP Levels at One-Year of Follow-Up

Baseline BNP values were not significantly different between the CRT-D (121 pg/ml) and ICD (106 pg/ml, p = 0.16) groups. At one year follow up, patients allocated to CRT-D therapy had significantly lower BNP levels compared to patients receiving ICD (89 vs. 115 pg/ml, p = 0.003), representing a 26% reduction from baseline values for patients allocated to CRT-D and 8% increase from baseline values for those allocated to ICD (p = 0.005). Both baseline and one year BNP values in the two treatment arm are displayed in Figure 3.

Pattern of BNP Change from Baseline to One-Year and Subsequent Clinical Risk

The cumulative risk of HF or death for each of the baseline to one-year BNP change groups among patients treated with CRT is shown in Figure 4. Patients with low one year BNP values displayed the lowest rate of HF or death at 3-years of follow-up (8% event rate among those with low baseline BNP, and 14% event rate among those with high baseline BNP), whereas patients with high BNP values at one-year displayed experienced a significantly higher rate of HF or death at 3-years (30% event rate among those with high baseline BNP, and 41% event rate among those with low baseline BNP; p<0.001 for the overall difference during follow-up).

After multivariate adjustment, a similar pattern was observed (Table 3). Thus, compared with CRT-D patients in whom BNP levels remained low at 1-year, those in whom BNP increased from low to high experienced the highest risk of HF or death (HR 4.7; p = 0.001); those in whom BNP levels remained high at 1-year experienced intermediate risk (HR 2.1; p = 0.06); and those in whom BNP decreased from high to low experienced a similar risk (HR 0.90; p = 0.88). When assessed as a continuous variable, each ten-fold increase in one year BNP (1 to 10, 10 to 100, etc.) was associated with a corresponding 3.0 fold increase (p < 0.001) in the risk of subsequent HF or death.
Pattern of BNP Change from Baseline to One-Year and Left Ventricular Remodeling

The relationship between the pattern of BNP change and left ventricular remodeling at one year among the 483 CRT-D patients with paired echocardiograms is shown in Figure 5. Baseline LVESV was lowest amongst the low baseline BNP groups and significantly higher for the high baseline BNP groups. Similar to the clinical association with BNP change, patients with low one-year BNP values displayed the largest concurrent mean reductions in LVESV (36% reduction among those with low baseline BNP and 33% among those with high baseline BNP). In contrast patients with high one-year BNP values displayed significantly lower reductions in LVESV (27% reduction among those with low baseline BNP and 23% among those with high baseline BNP; p<0.001 for the overall difference). No significant differences in LVESV reduction was noted between the two groups with low (low / low, high / low) and high (low / high, high / high) follow up BNP values with the overall trend driving statistical significance.

Discussion

The present study has several important implications regarding the prognostic value of BNP for patients receiving device therapy with mildly symptomatic HF due to left ventricular dysfunction. We have shown that: 1) elevated BNP at the time of device implant is prognostic of subsequent HF or death independent of the type of device received; 2) CRT-D is associated with significant reductions in BNP levels during follow-up, whereas a similar pattern is not observed among patients who are not treated with the device; and 3) the pattern of BNP change and the absolute BNP value at 1-year following CRT-D implantation are related to the echocardiographic response to the device and the risk of subsequent HF or death. These findings provide further
support for baseline and follow-up BNP assessment in mildly symptomatic HF patients treated with cardiac resynchronization therapy.

With regard to baseline BNP and post CRT outcome, prior studies in the moderate to severely symptomatic HF population have yielded inconsistent results. In an analysis of a 713 patient subgroup of CARE-HF, Berger et al \(^\text{13}\) identified NT-proBNP as predictive of all-cause mortality and pump failure irrespective of treatment arm (medical therapy vs. CRT). This finding is congruent with our data in its support of the use of BNP for the identification of patients pre-CRT-D implant at elevated risk of subsequent adverse events. It appears that this predictive value is related in part to BNP acting as a marker of more advanced HF, larger left ventricular volumes and concurrent co-morbid illness as displayed by the BNP dependent baseline characteristics of this study. However, in the present study adjustment for these important baseline covariates did not alter the predictive value of BNP assessment prior to device implantation, indicating its value as an independent predictor.

Berger et al \(^\text{13}\) have also shown that the benefit of CRT therapy is consistent regardless of baseline NT-proBNP values in patients with advanced HF. Our study extends this finding to patients with mild HF symptoms. Thus, we have similarly shown that CRT-D therapy is associated with a pronounced and significant reduction in the risk of HF or death regardless of baseline BNP values.

In contrast to the present findings, Lellouche et al \(^\text{15}\) in a small retrospective study of 164 moderate to severe HF patients found higher pre-implant BNP to be the only independent predictor of favorable CRT-D response. This discordance may possibly be due to the relatively small sample size and the retrospective design of the study by Lellouche et al \(^\text{15}\).
Several prior studies have examined the association between changes in BNP levels following CRT-D implantation and the subsequent echocardiographic and clinical response to the device. These studies, conducted in patients with advanced HF symptoms, have consistently shown that CRT-D-induced left ventricular remodeling is associated with corresponding reductions in both short- and long-term BNP levels. In addition it supports BNP change as indicative of clinical outcome. Specifically, prior data suggest that an increase in BNP following CRT-D implantation is prognostic of poor outcomes, whereas reductions in BNP are associated with a favorable outcome. In the present study we have further categorized BNP change following CRT-D implantation into 4 groups and have shown that the pattern of BNP change from baseline to one-year is an independent predictor of subsequent clinical response to the device beyond additional clinical or electrocardiographic factors. Thus, we have shown that the risk of HF of death among CRT-D patients is lowest among those in whom BNP levels remained low or were reduced from high to low and highest among patients in whom BNP levels were increased or remained high. However, even patients with elevated follow up BNP displayed significant left ventricular remodeling and a reduction in HF or death associated with CRT although not as profound as patients with low follow up BNP values. These findings suggest that monitoring BNP levels following CRT implantation in mildly symptomatic HF patients can be used for improved risk assessment in this population.

**Study Limitations**

This study is a non-randomized retrospective analysis utilizing no apriori criteria for the definition of elevated vs. low BNP with significant differences in the baseline clinical characteristics of the resulting groups. However, the results were consistent after adjusting for differences in baseline clinical characteristics. As BNP data was only collected in American
centers and therefore is lacking for a significant portion of the MADIT-CRT cohort this may influence our findings and potentially limit the scope of our conclusions. In addition, follow up BNP and echocardiographic data were not available for the entire patient cohort potentially biasing the effect of CRT-D on BNP and the relationship between BNP change and clinical or echocardiographic outcome.

Conclusions and Clinical Implications

We have shown that baseline BNP is a powerful predictor of HF events or death among patients with mild HF symptoms who are treated with cardiac resynchronization therapy, and that follow-up BNP can be used to predict current echocardiographic response and future reductions in HF or death. Together these findings indicate that BNP should be monitored in routine fashion both pre and post CRT-D implant. In the setting of elevated baseline or follow up BNP additional device optimization, intensification of medical therapy or referral to an advanced heart failure center should be considered.

Disclosures

The MADIT-CRT was supported by a research grant from Boston Scientific, St. Paul, Minnesota, to the University of Rochester School of Medicine and Dentistry.

References


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Table 1. Baseline clinical characteristics dichotomized by upper tertile enrollment BNP

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>BNP ≤ 120</th>
<th>BNP &gt; 120</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D Enrolled</td>
<td>59.8</td>
<td>62.0</td>
<td>0.47</td>
</tr>
<tr>
<td>Age at enrollment (years)</td>
<td>63.5 ±10.9</td>
<td>67.6 ±10.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>28.7</td>
<td>26.0</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>29.5</td>
<td>34.7</td>
<td>0.075</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63.5</td>
<td>70.1</td>
<td>0.022</td>
</tr>
<tr>
<td>Currently Smoking</td>
<td>11.7</td>
<td>12.5</td>
<td>0.67</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>49.5</td>
<td>62.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NYHA class I</td>
<td>12.9</td>
<td>18.2</td>
<td>0.016</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>36.6</td>
<td>44.0</td>
<td>0.016</td>
</tr>
<tr>
<td>Non ischemic heart disease (NYHA class II)</td>
<td>50.5</td>
<td>37.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.11 ± 0.30</td>
<td>1.24 ± 0.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>20.3 ± 8.4</td>
<td>22.6 ± 9.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QRS (msec)</td>
<td>156.2 ± 18.1</td>
<td>158.2 ± 21.0</td>
<td>0.11</td>
</tr>
<tr>
<td>LBBB</td>
<td>71.5</td>
<td>62.9</td>
<td>0.003</td>
</tr>
<tr>
<td>RBBB</td>
<td>11.9</td>
<td>16.0</td>
<td>0.061</td>
</tr>
<tr>
<td>IVCD</td>
<td>16.6</td>
<td>21.1</td>
<td>0.064</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>BNP ≤ 120</th>
<th>BNP &gt; 120</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>93.8</td>
<td>92.5</td>
<td>0.42</td>
</tr>
<tr>
<td>ACEI</td>
<td>77.2</td>
<td>73.0</td>
<td>0.11</td>
</tr>
<tr>
<td>ARB</td>
<td>20.3</td>
<td>20.1</td>
<td>0.92</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30.0</td>
<td>19.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>58.0</td>
<td>70.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Echocardiography

<table>
<thead>
<tr>
<th>Measure</th>
<th>BNP ≤ 120</th>
<th>BNP &gt; 120</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>29.2 ± 3.4</td>
<td>28.7 ± 3.3</td>
<td>0.027</td>
</tr>
<tr>
<td>LVEDV/BSA (ml)</td>
<td>116.1 ± 24.2</td>
<td>129.3 ± 31.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVESV/BSA (ml)</td>
<td>82.5 ± 19.6</td>
<td>92.7 ± 25.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LAV/BSA (ml)</td>
<td>44.5 ± 9.2</td>
<td>49.0 ± 10.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as percentage or mean ± standard deviation.

IVCD = interventricular conduction delay; LAV = left atrial volume; LBBB = left bundle branch block; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; NYHA = New York Heart Association Class; RBBB = right bundle branch block.
**Table 2.** Multivariate analysis: Risk of HF or death by treatment arm and baseline BNP Group

<table>
<thead>
<tr>
<th>Effect of BNP by treatment arm</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High vs. Low BNP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.62</td>
<td>1.23 - 2.13</td>
<td>0.005</td>
</tr>
<tr>
<td>CRT-D</td>
<td>1.68</td>
<td>1.14 - 2.46</td>
<td>0.007</td>
</tr>
<tr>
<td>ICD</td>
<td>1.58</td>
<td>1.06 - 2.34</td>
<td>0.024</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect of treatment arm by BNP</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D vs. ICD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High baseline BNP</td>
<td>0.44</td>
<td>0.32 - 0.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low baseline BNP</td>
<td>0.45</td>
<td>0.28 - 0.71</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Findings adjusted for age, LBBB, Ischemic CM, Diabetes, BUN, Creatinine, LVEF, LVESV, indexed LAV, Gender, NYHA class, and baseline use of beta blockers, ACE / ARB, and aldosterone antagonists.
Table 3. Risk of HF or death in CRT-D patients by the pattern of BNP change from baseline to one-year

<table>
<thead>
<tr>
<th>CRT-D BNP Change Group</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BL BNP and High 1 Year BNP (n = 47)</td>
<td>4.7</td>
<td>1.8 – 12.0</td>
<td>0.001</td>
</tr>
<tr>
<td>High BL BNP and High 1 Year BNP (n = 100)</td>
<td>2.1</td>
<td>0.9 – 5.2</td>
<td>0.06</td>
</tr>
<tr>
<td>High BL BNP and Low 1 Year BNP (n = 101)</td>
<td>0.9</td>
<td>0.3 – 2.5</td>
<td>0.88</td>
</tr>
<tr>
<td>Low BL BNP and Low 1 Year BNP (n = 344)</td>
<td>1.00 (Reference)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Findings adjusted for age, LBBB, Ischemic CM, Diabetes, BUN, Creatinine, LVEF, LVESV, indexed LAV, Gender, NYHA class, and baseline use of beta blockers, ACE / ARB, and aldosterone antagonists.
Figure Legends

**Figure 1.** Flow chart displaying patient flow and numbers of subjects available for various endpoint analyses.

**Figure 2.** Kaplan-Meier estimates of the cumulative probability of HF or death in (A) ICD; and (B) CRT-D patients by high (>120 pg/ml) or low (≤120 pg/ml) baseline BNP. CRT-D = cardiac resynchronization therapy-defibrillator; ICD = implantable cardioverter defibrillator.

**Figure 3.** Mean baseline (blue), one year (red) and percent reductions (green) in BNP in ICD and CRT treatment arms. *p = 0.16, †p = 0.003, §p = 0.005.
Percent reductions in BNP were calculated as the difference between 1-year and baseline BNP, divided by baseline BNP, among the 957 patients with available paired baseline and 1-year BNP data.
CRT-D = cardiac resynchronization therapy-defibrillator; ICD = implantable cardioverter defibrillator.

**Figure 4.** Kaplan-Meier estimates of the cumulative probability of HF or death by time-dependent BNP change among CRT-D patients treated with CRT-D, with follow-up time beginning after 1-year echocardiographic and BNP assessment.
High (>120 pg/ml) and low (≤120 pg/ml) BNP at both baseline and one year time points were determined utilizing the same cutoff. For each KM curve the time point is listed first (baseline
[BL] or 12 months [12]) followed by the BNP value relative to the 120 pg/ml cutoff (high = +, low = -).

(-) = low BNP; (+) = high BNP; 12 = one year; BL = baseline; CRT-D = cardiac resynchronization therapy-defibrillator; ICD = implantable cardioverter defibrillator.

**Figure 5.** Baseline and mean reduction in left ventricular end systolic volume by BNP change group.

Percent reductions in left ventricular end systolic volumes were calculated as the difference between 1-year volume and baseline volume, divided by baseline volume, among the 483 CRT-D patients with BNP data and available paired baseline / 1-year echocardiograms. BNP trend groups were determined utilizing the 120 pg/ml cutoff at both baseline and one year time points. CRT-D = cardiac resynchronization therapy-defibrillator; High = BNP > 120 pg/ml; Low = BNP ≤ 120 pg/ml; LVESV = left ventricular end systolic volume; BNP change groups (baseline – one year): low – low, low – high, high – low, and high - high.
Patients Enrolled in MADIT-CRT  
N = 1820

Excluded: Absent Baseline BNP Data  
(Not collected in European Centers)  
N = 623

Patients with Baseline BNP Data  
N = 1197

Patients without One Year BNP Data  
N = 240

Patients with Paired Baseline and One Year BNP Data  
N = 957

Patients with One Year BNP Data and Without Paired Echocardiogram  
N = 68

Patients with One Year BNP Data and Paired Echocardiogram  
N = 889
Brain Natriuretic Peptide and Cardiac Resynchronization Therapy in Patients with Mildly Symptomatic Heart Failure

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