Background—There are limited data on the prognostic implications of brain natriuretic peptide (BNP) assessment in patients with mildly symptomatic heart failure (HF) 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 (Multicenter Automated Defibrillator Implantation Trial)-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 implantable cardioverter defibrillator-only therapy, respectively. At 1 year of follow-up, patients allocated to CRT-D displayed significantly greater reductions in BNP (26% reduction) levels compared with implantable cardioverter defibrillator-only patients (8% increase; P=0.005). Patients with CRT-D in whom 1-year BNP levels were reduced or remained low experienced a significantly lower risk of subsequent HF or death as compared with patients in whom 1-year BNP levels were high. Similarly, the echocardiographic response to CRT-D was highest among those who maintained low BNP levels or in whom BNP level at 1-year was reduced.

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

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

(Circ Heart Fail. 2013;6:998-1004.)

Key Words: cardiac resynchronization therapy • heart failure • natriuretic peptide, brain

Cardiac resynchronization therapy with a defibrillator (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.1-7 Despite its success in large studies, a lack of response to CRT-D has been reported in up to one third of device recipients,7-10 resulting in a desire to further risk stratify patients before CRT-D implant and to detect favorable clinical response after device implantation in an objective reproducible fashion.

Clinical Perspective on p 1004

Brain natriuretic peptide (BNP) has been suggested to be a useful tool in both pre–CRT-D implant risk stratification and in monitoring for post–CRT-D implant response, primarily in patients with advanced (New York Heart Association class III or IV) HF symptoms.11-21 BNP is produced and secreted by the ventricular cardiac myocyte in response to myocardial stretch and elevated ventricular filling pressures.22 Resulting plasma BNP concentrations are higher in patients with more severe symptoms or worse left ventricular (LV) function and are a powerful predictor of mortality and subsequent HF.23-27 Currently, however, data on the prognostic use of BNP assessment in patients with mild HF symptoms who are treated with CRT are lacking.

Accordingly, the present study was performed in a population of patients with mildly symptomatic HF with LV dysfunction enrolled in MADIT (Multicenter Automated Defibrillator Implantation Trial)-CRT, and was designed to determine as follows: (1) the association between baseline BNP and the risk for the development HF or death after device implantation; (2) the relation between baseline BNP and the clinical response to CRT-D; (3) the effect of CRT-D versus implantable cardioverter defibrillator (ICD)-only therapy on BNP levels during follow-up; and (4) the prognostic implications of BNP assessment after CRT-D implantation.

Methods

Study Population
The design and results of MADIT-CRT have been reported previously.3 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 ≤0.30, and abnormal intraventricular conduction with QRS≥130 ms 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, New York Heart Association class III/IV in the past 90 days before enrollment, pacemaker in situ, and coronary artery bypass and grafting 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 1-year follow-up BNP values available in 957 patients. Of the 240 patients who did not have 1-year follow-up BNP data, 30 patients died before 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 end point analyses are displayed in Figure 1.

Echocardiographic Methods
Echocardiograms were obtained according to a study-specific protocol at baseline, which was before device implantation (ICD n=470; CRT-D n=722), and at 1 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. LV volumes were measured by Simpson method of discs in the apical 4- and 2-chamber views and averaged with LV ejection fractions calculated from the resulting values. Left atrial volumes were measured using Simpson 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 1-year BNP >120 pg/mL. Changes in BNP values from baseline to 1 year of follow-up were categorized as high (baseline/1 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, 1-way ANOVA test, or χ2 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 and 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 end point or were unbalanced among the 2 groups (high versus low BNP), including ischemic pathogenesis of LV dysfunction, diabetes mellitus, age at enrollment, sex, New York Heart Association class, blood urea nitrogen, serum creatinine, left bundle-branch block, indexed LV end systolic volume (LVESV), and left atrial volume. Patients missing values for covariates in the multivariate Cox models were excluded as no data imputations methods were used. The CRT-D versus 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 1 year after CRT-D implantation on subsequent outcome was assessed by evaluating response as a categorical variable dependent on the 120 pg/mL cutoff (ie, low baseline and low 1 year, high baseline/high 1 year, low baseline/high 1 year, and high baseline/low 1 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 2-sided, and a P<0.05 was considered significant. Analyses were conducted with SAS software (version 9.2; SAS Institute, Cary, NC).

Results
Patient Characteristics
The present study population comprises 1197 patients with baseline BNP data. Numbers of subjects available for various end point 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 (median±SD, 46±33 pg/mL; median and interquartile range, 39 and 18–71) and 389 patients in the high (median±SD, 265±169 pg/mL; median and interquartile range, 206 and 157–295) BNP groups, respectively. The clinical characteristics of these 2 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 blood urea nitrogen and were less likely to have left bundle-branch block. Medication use was similar with the notable exception of a lower frequency of

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Figure 1. Flow chart displaying patient flow and numbers of subjects available for various end point analyses. BNP indicates brain natriuretic peptide; CRT, cardiac resynchronization therapy; and LV, left ventricle.
aldoosterone antagonists usage and increased usage of diuretics in the BNP >120 group. Echocardiographic parameters differed significantly between the 2 groups with larger indexed baseline ventricular and atrial volumes and a lower LV ejection fraction seen in the elevated BNP group.

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

From enrollment through 3-year follow-up, patients with elevated baseline BNP had a significantly greater cumulative probability to experience the combined end point of HF or death as compared with patients with lower baseline BNP levels. These effects were observed in both the ICD (41% versus 22%, respectively; \(P<0.001\); Figure 2A) and CRT-D (29% versus 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 patients with CRT-D there was a corresponding 68% risk increase. When assessed as a continuous variable, each 10-fold increase in BNP (1–10, 10–100, etc.) was associated with a corresponding 2.2-fold increase (\(P<0.001\)). The clinical benefit of CRT-D versus 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 \(P=0.95\)). 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 left bundle-branch block and non–left bundle-branch block patients with an interaction \(P\) value of 0.59.

**Effect of CRT on BNP Levels at 1 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 1-year follow-up, patients allocated to CRT-D therapy had significantly lower BNP levels compared with patients receiving ICD (89 versus 115 pg/mL; \(P=0.003\)), representing a 26% reduction from baseline values for patients allocated to CRT-D and a 8% increase from baseline values for those allocated to ICD (\(P=0.005\)). Both baseline and 1-year BNP values in the 2 treatment arm are displayed in Figure 3.

**Pattern of BNP Change From Baseline to 1-Year and Subsequent Clinical Risk**

The cumulative risk of HF or death for each of the baseline to 1-year BNP change groups among patients treated with CRT...
is shown in Figure 4. Patients with low 1-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 1 year displayed 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 patients with CRT-D in whom BNP levels remained low at 1 year, those in whom BNP increased from low to high experienced the highest rate of HF or death (hazard ratio, 4.7; \( P = 0.001 \)); those in whom BNP levels remained high at 1 year experienced an intermediate risk (hazard ratio, 2.1; \( P = 0.06 \)); and those in whom BNP decreased from high to low experienced a similar risk (hazard ratio, 0.90; \( P = 0.88 \)). When assessed as a continuous variable, each 10-fold increase in 1-year BNP (1–10, 10–100, etc) was associated with a corresponding 3-fold increase (\( P < 0.001 \)) in the risk of subsequent HF or death.

### Pattern of BNP Change From Baseline to 1 Year and LV Remodeling

The relationship between the pattern of BNP change and LV remodeling at 1 year among the 483 patients with CRT-D with paired echocardiograms is shown in Figure 5. Baseline LVESV was lowest among 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 1-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 1-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 were noted between the 2 groups with low (low/low and high/low) and high (low/high and high/high) follow-up BNP values with the overall trend driving statistical significance.

### Discussion

The present study has several important implications on the prognostic value of BNP for patients receiving device therapy with mildly symptomatic HF because of LV 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

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**Table 2. Multivariate Analysis**

<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><strong>High vs low BNP</strong></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>
<tr>
<td><strong>CRT-D vs ICD</strong></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>

Risk of HF or death by treatment arm and baseline BNP group. Findings adjusted for age, LBBB, ischemic CM, diabetes mellitus, BUN, creatinine, LVEF, LVESV, indexed LAV, sex, NYHA class, and baseline use of \( \beta \) blockers, ACE/ARB, and aldosterone antagonists. ACE indicates angiotensin-converting-enzyme; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CI, confidence interval; CM, cardiomyopathy; CRT-D, cardiac resynchronization therapy with a defibrillator; HF, heart failure; ICD, implantable cardioverter defibrillator; LAV, left atrial volume; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; and NYHA, New York Heart Association Class.
Percent reductions in left ventricular end systolic volume by brain natriuretic peptide (BNP) change group.

Table 3. Risk of HF or Death in Patients With CRT-D by the Pattern of BNP Change From Baseline to 1 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-y 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-y 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-y 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-y BNP (n=344)</td>
<td>1.00</td>
<td>(Reference)</td>
<td></td>
</tr>
</tbody>
</table>

Findings adjusted for age, LBBB, ischemic CM, diabetes mellitus, BUN, creatinine, LVEF, LVESV, indexed LAV, sex, NYHA class, and baseline use of β-blockers, ACE/ARB, and aldosterone antagonists. ACE/ARB, and aldosterone antagonists. ACE indicates angiotensin-converting-enzyme; BL BNP, baseline brain natriuretic peptide; BUN, blood urea nitrogen; CI, confidence interval; CM, cardiomyopathy; CRT-D, cardiac resynchronization therapy with a defibrillator; LAV, left atrial volume; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; and NYHA, New York Heart Association Class.

are not treated with the device; and (3) the pattern of BNP change and the absolute BNP value at 1 year after CRT-D implantation is 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 patients with mildly symptomatic HF treated with CRT.

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 (Cardiac Resynchronization in Heart Failure Study), Berger et al13 identified N-terminal pro-BNP as predictive of all-cause mortality and pump failure irrespective of treatment arm (medical therapy versus 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 seems that this predictive value is related in part to BNP acting as a marker of more advanced HF, larger LV volumes, and concurrent comorbid 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 before device implantation, indicating its value as an independent predictor.

Berger et al13 have also shown that the benefit of CRT therapy is consistent regardless of baseline N-terminal pro-BNP 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 al15 in a small retrospective study of 164 moderate-to-severe patients with HF found higher preimplant BNP to be the only independent predictor of favorable CRT-D response. This discordance may possibly be because of the relatively small sample size and the retrospective design of the study by Lellouche et al.15

Several prior studies have examined the association between changes in BNP levels after CRT-D implantation and the subsequent echocardiographic and clinical response to the device.11,12,16-21 These studies, conducted in patients with advanced HF symptoms, have consistently shown that CRT-n-induced LV 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 after 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 after CRT-D implantation into 4 groups and have shown that the pattern of BNP change from baseline to 1-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 patients with CRT-D 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 LV 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 after CRT implantation in patients with mildly symptomatic HF can be used for improved risk assessment in this population.

Study Limitations

This study is a nonrandomized retrospective analysis using no apriori criteria for the definition of elevated versus 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 were only collected in American centers and, therefore, is lacking for a significant portion of the MADIT-CRT cohort, this may influence our findings.

Figure 5. Baseline and mean reduction in left ventricular end systolic volume by brain natriuretic peptide (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 patients with cardiac resynchronization therapy with a defibrillator (CRT-D) with BNP data and available paired baseline/1-year echocardiograms. BNP trend groups were determined using the 120 pg/mL cutoff at both baseline and 1-year time points. High=BNP >120 pg/mL; low=BNP ≤120 pg/mL; BNP change groups (baseline–1 year): low-low, low-high, high-low, and high-high. LVESV, left ventricular end systolic volume.
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

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 CRT, 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 HF center should be considered.

Sources of Funding

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.

Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

There are limited data on the prognostic implications of brain natriuretic peptide (BNP) assessment in patients with mildly symptomatic heart failure (HF) who receive cardiac resynchronization therapy with a defibrillator (CRT-D). We assessed 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 among the cohort of 1197 patients with baseline BNP data enrolled in MADIT (Multicenter Automated Defibrillator Implantation Trial)-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 implantable cardioverter defibrillator-only therapy, respectively. At 1 year of follow-up, patients allocated to CRT-D displayed significantly greater reductions in BNP (26% reduction) levels compared with implantable cardioverter defibrillator-only patients (8% increase; P=0.005). Patients with CRT-D in whom 1-year BNP levels were reduced or remained low experienced a significantly lower risk of subsequent HF or death as compared with patients in whom 1-year BNP levels were high. Similarly, the echocardiographic response to CRT-D was highest among those who maintained low BNP levels or in whom BNP at 1-year was reduced. Our findings suggest that assessment of baseline and follow-up BNP provides important prognostic implications in patients with mildly symptomatic HF who receive cardiac resynchronization therapy.
Brain Natriuretic Peptide and Cardiac Resynchronization Therapy in Patients With Mildly Symptomatic Heart Failure

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