Usefulness of Brain Natriuretic Peptide Level at Implant in Predicting Mortality in Patients with Advanced But Stable Heart Failure Receiving Cardiac Resynchronization Therapy

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ABSTRACT

Background: Brain natriuretic peptide (BNP) level has emerged as a predictor of death and hospital readmission in patients with heart failure (HF). The value of baseline BNP assessment in advanced HF patients receiving cardiac resynchronization defibrillator therapy (CRT-D) has not been firmly established.

Hypothesis: We hypothesized that a baseline BNP level would predict all cause mortality and HF hospitalization in HF patients receiving cardiac resynchronization therapy.

Methods: A retrospective chart review of all patients having BNP assessment prior to implantation of a CRT-D for standard indications during 2004 and 2005 was conducted at the Veterans Affairs Pittsburgh Healthcare System. The primary endpoint was all-cause mortality and the secondary endpoint was HF-related hospitalization. We used findings from the receiver operating characteristic (ROC) curve to define low (<492 pg/mL) and high (≥492 pg/mL) BNP groups.

Results: Out of 173 CRT-D recipients, 115 patients (mean age 67.0±10.7 years, New York Heart Association [NYHA] class 2.9±0.3, left ventricular ejection fraction [LVEF] 22.5% ±9.6%, QRS 148.3±30.4 ms) had preimplantation BNP measured (mean 559±761 pg/mL and median 315 pg/mL). During a mean follow-up time of 17.5±6.5 mo, 27 deaths (23.5%) and 31 HF hospitalizations (27.0%) were recorded. Compared to those with low BNP (n = 74), those of high BNP (n = 41) were older, had lower LVEF, higher creatinine levels, suffered more deaths, and HF hospitalizations. In multivariate regression models, higher BNP remained a significant predictor of both the primary endpoint (hazard ratio [HR]: 2.89, 95% confidence interval [CI] 1.06–7.88, p = 0.038) and secondary endpoint (HR: 4.23, 95% CI: 1.68–10.60, p = 0.002).

Conclusions: Baseline BNP independently predicted mortality and HF hospitalization in a predominantly older white male population of advanced HF patients receiving CRT-D. Elevated BNP levels may identify a vulnerable HF population with a particularly poor prognosis despite CRT-D.

Key words: Brain natriuretic peptide, cardiac resynchronization therapy, mortality, heart failure

Background

Brain natriuretic peptide (BNP) level has emerged as a promising marker of heart failure (HF) diagnosis, treatment, and prognosis. Many prospective studies and clinical trials have found that higher BNP levels, using different cut point modalities, have a 2.5-fold to 7.2-fold increase of mortality risk in multivariate models relative to those subjects with lower BNP levels.[1] Data on BNP prognostic value on the subset of HF patients receiving cardiac resynchronization therapy (CRT) are limited. Two recent reports have suggested that BNP may be helpful in predicting HF progression in CRT recipients using composite cardiac endpoints.[2,3] Another recent report suggested that pro-BNP may be associated with an increased risk of death or unplanned cardiovascular hospitalization irrespective of CRT.[4] Nevertheless, the value of baseline BNP assessment in predicting mortality or readmission in advanced HF patients receiving CRT remains unclear. The purpose of this study was to evaluate the value of a single preimplantation BNP measurement in predicting all-cause mortality and HF hospitalization in HF patients receiving cardiac resynchronization defibrillator therapy (CRT-D) for standard clinical indications.

Methods

For the purposes of this study we conducted a retrospective chart review of all cardiac CRT-D recipients (January 2004 through December 2005) at the Veterans Affairs (VA)

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Pittsburgh Healthcare System after obtaining Institutional Review Board approval and in compliance with all regulatory requirements. All patients, older than 21 years, meeting standard clinical indications who underwent transvenous pectoral implantation of CRT-D were included in the database (n = 173). As we intended to exclude patients who had a clinical diagnosis of a recent (≤30 d) acute coronary syndrome, acute decompensation of chronic heart failure (CHF), revascularization procedure, or surgery, only patients receiving their implant electively as outpatients were included. BNP level was measured on-site using the Triage B-Type Natriuretic Peptide test (Biosite, San Diego, Calif., USA). Patients who did not have preimplantation BNP levels measured (within 24 h) were not included in the current analysis.

The electronic medical record was abstracted and de-identified to create the database. The following baseline patient characteristics were recorded: patient demographics (age, sex, and race), New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), QRS duration (ms), etiology of cardiomyopathy (ischemic versus nonischemic), medical history of hypertension, diabetes, current smoking, chronic obstructive pulmonary disease, atrial fibrillation (AF), serum creatinine level (mg/dl), medication profile including statins, beta-blocker, angiotensin-converting enzyme inhibitor (ACEI), spironolactone, and BNP level (pg/mL).

Clinical endpoints (through November 2006) including death or HF related hospitalizations, as documented in the discharge diagnosis, were recorded. The primary endpoint was all-cause mortality and the secondary endpoint was worsening of HF symptoms that required hospitalization. Mortality events were determined by medical chart review and confirmed using the Social Security Death Index. Patients were censored from any analysis once they reached the primary endpoint. In addition, for the secondary analysis only, patients were censored after their first HF hospitalization.

We determined the BNP cut point using the receiver operating characteristic (ROC) curve. An optimal BNP cut point was chosen to define the low versus high BNP groups. Clinical characteristics of low and high BNP groups were compared using a chi-squared test for categorical variables and a Student *t* test for continuous variables. Follow-up time in months was defined as the time from implant date to the date of an endpoint event, or to the date of last follow-up. Separate survival times were calculated for the primary or secondary endpoints using the Kaplan-Meier method. Endpoint-free survival times were compared between the low versus high BNP groups and the statistical differences were tested using the log-rank test. Separate univariate and multivariate Cox regression models were run to assess the crude and multivariate adjusted predictive effect of high compared to low BNP groups on the primary and secondary endpoints. Age, sex, race, NYHA class, LVEF, QRS duration, type of cardiomyopathy, history of hypertension, diabetes, current smoking, AF and statins use, and creatinine level were adjusted for in multivariate models. All p values were 2-tailed. P values less than 0.05 were considered statistically significant. For all statistical analyses, SPSS software (release 14.0, SPSS Inc., Chicago, Ill., USA.) was used.

Results

A total of 115 outpatients had BNP measured before CRT-D and were included in this analysis. Our population were typically older (67.0±10.7 years) white (91.1%) men (98.3%), who received CRT-D after diagnosis of HF mainly of ischemic origin (75.7%). They had NYHA class of 2.9±0.3, LVEF of 22.5% ±9.6%, QRS of 148.3±30.4 ms. During a mean follow-up time of 17.5±6.5 mo, 27 deaths (23.5%) and 31 HF hospitalization (27.0%) were recorded (Table 1).

Preimplantation mean BNP was 559±761 pg/mL (median 315 pg/mL). ROC curve analysis showed that the areas under the curve were 0.72 and 0.74 for the primary and secondary endpoints respectively and were significantly better than 50% ($p<0.001$ for each). A BNP cut point of 492 was chosen to define the low versus high BNP groups. At that point, the primary endpoint can be detected at a sensitivity of 60% and a specificity of 72% while the secondary endpoint can be detected at a sensitivity of 65% and a specificity of 75% (Figure 1). A total of 74 patients had BNP <492 pg/mL (low BNP group) and 41 patients had BNP ≥492 pg/mL (high BNP group). Compared to those with low BNP, those of high BNP were older (70.4 versus 65.2 years, p = 0.012), had lower LVEF (19.0% versus 24.5%, p = 0.003), and higher creatinine levels (1.38 versus 1.19 mg/dL, p = 0.043). Compared to those with low BNP, those with high BNP suffered more deaths (39.0% versus 14.9%, p = 0.003) and HF hospitalization (48.8% versus 14.9%, p = 0.003; Table 1). Conversely, among those who had HF hospitalization during the first 6 mo after CRT implantation (n = 13), as a measure of nonresponse to CRT, 77% had elevated BNP. The majority of those (7 out of 10) died during the course of the study.

Kaplan-Meier survival analysis showed that those with higher BNP had significantly lower mortality-free survival (mean survival of 21.3 versus 25.8 mo, p = 0.004) and HF hospitalization-free survival (mean survival of 17.2 versus 25.5 mo, $p<0.001$) compared to those with lower BNP (Figure 2).

In a univariate Cox regression analysis, older age (hazard ratio [HR]: 1.59, 95% confidence interval [CI]: 1.10–2.31, p = 0.014), history of AF (HR: 2.85, 95% CI: 1.28–6.37, p = 0.010), high creatinine level (HR: 1.15, 95% CI: 1.07–1.24, $p<0.001$), and higher BNP level (HR: 2.97, 95% CI: 1.37–6.42, p = 0.006) were significant predictors of all-cause mortality

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Table 1. Baseline clinical characteristics of the study population

Characteristic	Low BNP (<492 pg/mL) n = 74	High BNP (≥492 pg/mL) n = 41	Total (5–4,970 pg/mL) n = 115	p value
Age	65.2±9.7	70.4±11.6	67.0±10.7	0.012
Male	74 (100.0%)	39 (95.1%)	113 (98.3%)	0.055
White	69 (95.8%)	33 (82.5%)	102 (91.1%)	0.018
NYHA	2.9±0.4	2.9±0.3	2.9±0.3	0.768
LVEF	24.5±10.1	19.0±7.4	22.5±9.6	0.003
QRS Duration (ms)	148.6±27.1	147.9±35.9	148.3±30.4	0.912
Ischemic CM	53 (71.6%)	34 (82.9%)	87 (75.7%)	0.176
Hypertension	57 (77.0%)	31 (75.6%)	88 (76.5%)	0.864
Diabetes	33 (44.6%)	21 (51.2%)	54 (47.0%)	0.495
Current smoking	17 (23.0%)	5 (12.2%)	22 (19.1%)	0.159
COPD	27 (36.5%)	18 (43.9%)	45 (39.1%)	0.435
AF History	32 (43.2%)	18 (43.9%)	50 (43.5%)	0.946
Creatinine (mg/dL)	1.19±0.35	1.38±0.52	1.25± 0.43	0.043
Statins	59 (79.7%)	31 (75.6%)	90 (78.3%)	0.608
Beta-blocker	60 (81.1%)	33 (80.5%)	93 (80.9%)	0.938
ACEI	61 (82.4%)	31 (75.6%)	92 (80.0%)	0.381
Spironolactone	16 (21.6%)	7 (17.1%)	23 (20.0%)	0.559
Deaths	11 (14.9%)	16 (39.0%)	27 (23.5%)	0.003
HF Hospitalization	11 (14.9%)	20 (48.8%)	31 (27.0%)	<0.001
Death or HF	20 (27.0%)	27 (65.9%)	47 (40.9%)	<0.001
BNP (pg/mL)†	195 (90–308)	793 (680–1,265)	315 (172–712)	<0.001

*Mean±SD. †Median and inter-quartile range. *Abbreviations*: ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; BNP = brain natriuretic peptide; CM = cardiomyopathy; COPD = chronic obstructive lung disease; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

while history of diabetes was a marginally significant predictor of all-cause mortality (HR: 2.15, 95% CI 0.99–4.64, p = 0.052). However, in a multivariate analysis adjusted for age, sex, race, NYHA class, LVEF, QRS duration, type of cardiomyopathy, history of hypertension, diabetes, current smoking, AF, statins use, and creatinine level, only elevated BNP level remained a significant predictor of all-cause mortality (HR: 2.89, 95% CI: 1.06–7.88, p = 0.038) while history of AF (HR: 2.62, 95% CI: 0.96–7.19, p = 0.061) showed a trend toward being a significant predictor (Table 2). For HF hospitalization, both creatinine level (HR: 1.11, 95% CI: 1.03–1.20, p = 0.006) and BNP level (HR: 4.84, 95% CI: 2.31–10.17, p<0.001) were found to be significant predictors in univariate analysis. On multivariate analysis, only BNP level (HR: 4.23, 95% CI: 1.68–10.60, p = 0.002) remained a significant independent predictor while history of AF showed such a trend (HR: 2.36, 95% CI: 0.98–5.71, p = 0.056; Table 3).

Discussion

In this retrospective cohort study, baseline BNP independently predicted mortality and HF hospitalization in a population with advanced HF receiving CRT-D. Given the short half-life of BNP[5] and its relative variability in HF patients,[6] we deliberately excluded patients with BNP level measured more than 24 h prior to implantation. We also

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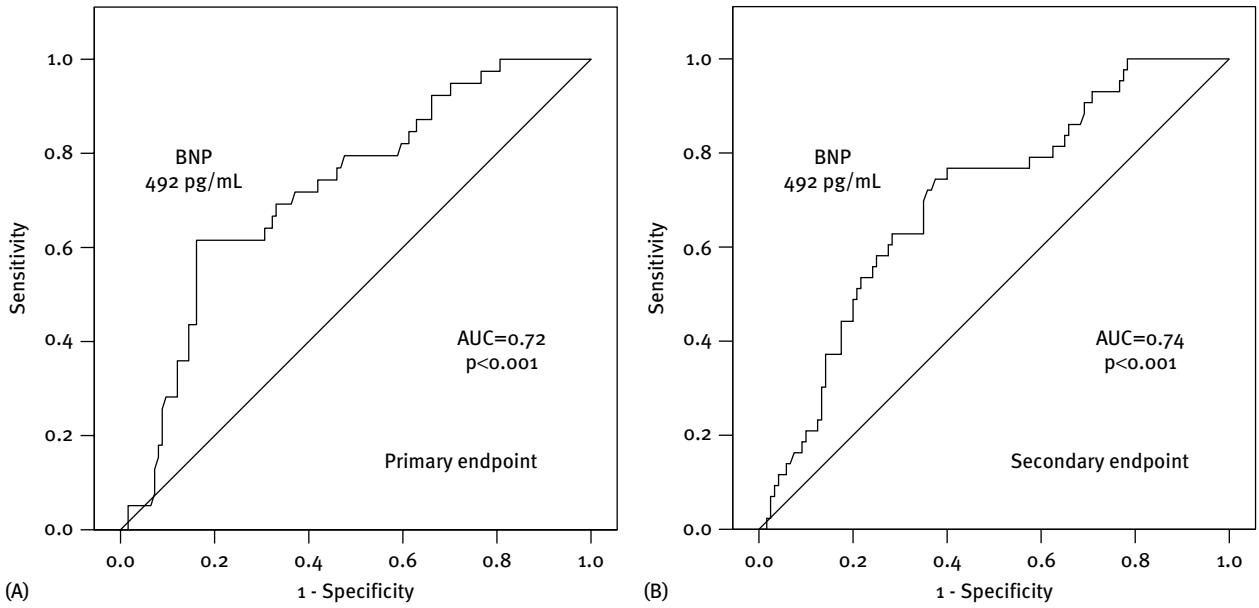

Figure 1. Receiver operating characteristic (ROC) curve to detect the primary (A) and the secondary (B) endpoints using different BNP levels.

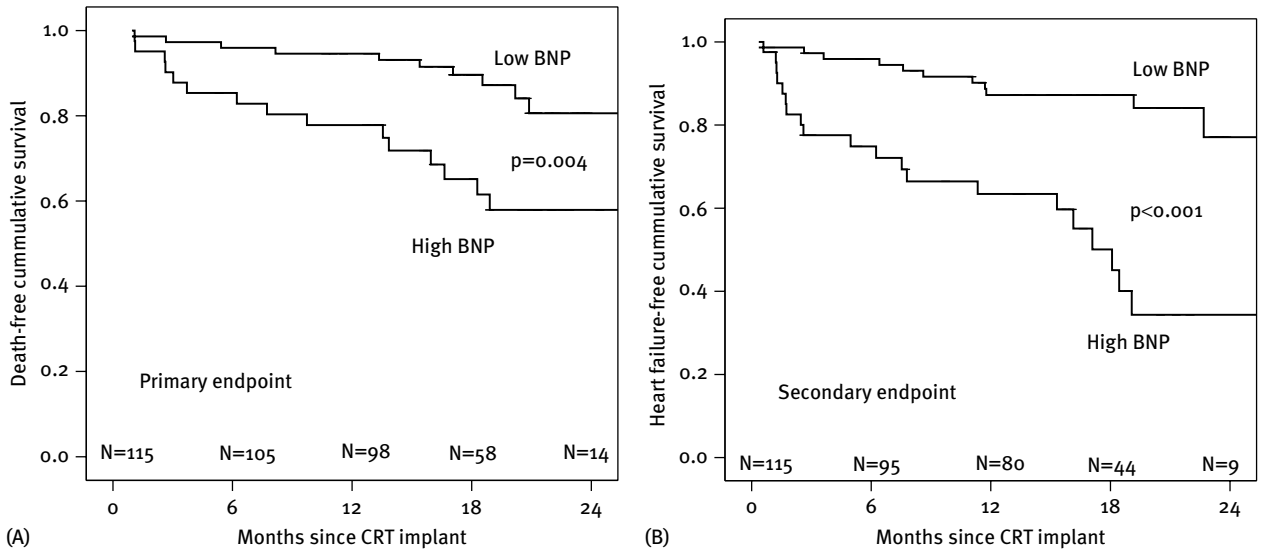

Figure 2. Kaplan-Meier for death-free survival (A) and heart failure hospitalization-free survival (B) by BNP level groups.

excluded patients with acute events that would reflect on the BNP level. Thus, our cohort represents patients with stable advanced HF.

Despite using different BNP cut points as well as different definitions of HF progression, the current results confirm findings from recent studies that have reported on the predictive value of preimplantation BNP or pro-BNP levels in HF patients receiving CRT.[2–4] Lellouche and colleagues[2] reported that the preimplantation BNP value independently predicts CRT response (using a composite variable including death, HF hospitalization, and NYHA functional class). However, the short follow-up time (6 mo) limited their ability to address the predictive effect of BNP on individual components of the composite outcome, particularly mortality. In contrast, we encountered more deaths in our cohort, probably reflecting the older age of our patients and the longer duration of follow-up. Using a small number of patients (n = 50) and a different

Table 2. Cox regression univariate and multivariate predictors of death in all patients (n = 115)

Characteristic	Univariate Analysis Hazard Ratio (95% CI)	Multivariate Analysis Hazard Ratio (95% CI)
Age (per 10 years)	1.59 (1.10–2.31)*	1.42 (0.82–2.45)
Female Sex	2.08 (0.28–15.40)	1.68 (0.15–19.20)
Black Race	1.15 (0.35–3.82)	0.63 (0.13–3.05)
NYHA Class	2.25 (0.56–9.08)	1.73 (0.28–10.57)
LVEF (per 5%)	0.87 (0.69–1.11)	0.88 (0.67–1.17)
QRS Duration (per 10 ms)	1.06 (0.93–1.20)	1.00 (0.87–1.15)
Ischemic CM	1.50 (0.57–3.97)	0.72 (0.19–2.75)
Hypertension	2.87 (0.86–9.58)	2.77 (0.75–10.27)
Diabetes	2.15 (0.99–4.64)	1.51 (0.56–4.09)
Current Smoking	0.74 (0.26–2.16)	2.18 (0.43–11.05)
AF History	2.85 (1.28–6.37)*	2.62 (0.96–7.19)
Statins Use	0.74 (0.32–1.71)	0.68 (0.23–2.02)
Creatinine (per 0.1 mg/dL)	1.15 (1.07–1.24)‡	1.06 (0.97–1.16)
BNP (≥492 pg/mL)	2.97 (1.37–6.42)†	2.89 (1.06–7.88)*

*p<0.05. †p<0.01. ‡p<0.001. *Abbreviations*: AF = atrial fibrillation; BNP = brain natriuretic peptide; CM = cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 3. Cox regression univariate and multivariate predictors of heart failure hospitalization in all patients (n = 115)

Characteristic	Univariate Analysis Hazard Ratio (95% CI)	Multivariate Analysis Hazard Ratio (95% CI)
Age (per 10 years)	1.24 (0.88–1.74)	1.07 (0.69–1.65)
Female Sex	2.21 (0.30–16.27)	2.11 (0.20–22.39)
Black Race	2.40 (0.92–6.27)	2.67 (0.67–10.68)
NYHA Class	1.70 (0.55–5.30)	2.93 (0.64–13.40)
LVEF (per 5%)	0.86 (0.70–1.07)	1.05 (0.82–1.34)
QRS Duration (per 10 ms)	1.01 (0.89–1.14)	0.97 (0.86–1.10)
Ischemic CM	1.80 (0.69–4.70)	1.59 (0.45–5.62)
Hypertension	1.23 (0.53–2.87)	1.28 (0.47–3.47)
Diabetes	1.50 (0.74–3.04)	1.10 (0.44–2.74)
Current Smoking	1.00 (0.41–2.44)	2.55 (0.72–9.04)
AF History	1.79 (0.88–3.63)	2.36 (0.98–5.71)
Statins Use	0.68 (0.31–1.47)	0.98 (0.37–2.61)
Creatinine (per 0.1 mg/dL)	1.11 (1.03–1.20)†	1.06 (0.97–1.15)
BNP (≥492 pg/mL)	4.84 (2.31–10.17)‡	4.23 (1.68–10.60)†

*p<0.05. †p<0.01. ‡p<0.001. *Abbreviations*: AF = atrial fibrillation; BNP = brain natriuretic peptide; CM = cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

outcome definition (death, urgent heart transplantation or hospitalization due to increased HF, or significant increase of medications needed to control HF symptoms), Pitzalis and colleagues[3] reported a hazard ratio of more than 2 per natural log increase of BNP preimplantation level. However, the authors did not report on preimplantation BNP cut points as the primary study goal was to predict outcome using postimplantation (after 1 mo) BNP levels. Recently, Richardson et al.[4] reported that N-terminal pro-BNP may be associated with an increased risk of death or unplanned cardiovascular hospitalization irrespective of CRT in patients with heart failure and cardiac dyssynchrony.

Widely applicable BNP cut points remain elusive, perhaps reflecting variability in study methods, for example, the rational of the cut point determination, the sample size, and the population's severity of HF. Using ROC findings, we used a BNP cut point of 492 pg/mL to define low versus high preimplantation BNP groups. This was quite higher than the 170 cut point used by Boriani and colleagues,[7] based on a smaller sample size (n = 36), but comparable to the 447 cut point used by Lellouche and colleagues,[2] based on a larger sample size (n = 164).

Indeed, several studies have reported that BNP levels generally decrease after CRT implantation.[7–11] A number of these studies reported that BNP level is reduced after CRT implantation among those who show early significant clinical improvement but increase in those who do not show clinical improvement.[8–10] Despite the small sample size of these studies, different definitions of clinical improvement after CRT implantations, and absence of covariate adjustments, these reports support the use of BNP levels in predicting response to CRT in HF patients.

In a recent review of 38 studies on the prognostic value of BNP in HF patients, Balion et al.[1] reported the baseline BNP level to be an independent predictor of mortality or composite endpoints (typically including death, other cardiac events, readmission, or worsening HF) across various cut points (mainly mean, median, or using cut points based on ROC analysis). The adjusted HR showed a 2.5-fold to 7.2-fold mortality increase and 1.7 to 3.2 composite endpoint increase relative to those subjects with lower levels of BNP.[1] The importance of this study is the finding that BNP as a risk stratifier continues to hold value with the application of CRT.

Preimplantation BNP level may identify advanced HF patients who do not respond or have limited response to

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CRT-D therapy and who are at a greater risk of death. We chose HF hospitalization within the first 6 mo after CRT implementation as a measure of nonresponse to CRT, as a relatively reliable endpoint in a retrospective analysis where repeat echocardiography or physical assessment within prespecified windows were not obtained. We find it interesting that in the current analysis, BNP level outweighed well-known survival predictors in HF patients[12,13] including CRT recipients,[14] (NYHA functional class, renal insufficiency, QRS duration, and AF) suggesting its importance in preimplantation risk stratification and containing increasing health care costs.

Our current study included a relatively large sample size and ample follow-up time allowing for the study of succinct outcome endpoints namely mortality, as well as HF hospitalization. Furthermore, we adjusted the results for a variety of cardiac and medical covariates. We excluded patients with BNP levels obtained more than 24 h prior to implant and those with acute events in the preceding month. We believe such criteria result in a more homogenous sample of advanced but stable HF. We recognize that the sample consisted mostly of older white males reflecting the population served by a VA medical center in our geographic location. Finally, due to the retrospective nature of this analysis and the lack of postmortem device interrogation data, we could not specify arrhythmic versus nonarrhythmic cause of death.

In summary, baseline BNP independently predicts mortality and HF hospitalization in a predominantly older white male population with advanced, but stable HF receiving CRT.

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