

BNP Levels Predict Outcome in Pediatric Heart Failure Patients

Post Hoc Analysis of the Pediatric Carvedilol Trial

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Background—The ability of serum B-type natriuretic peptide levels (BNP) to predict outcomes in children with heart failure (HF) has not been well demonstrated. This study was designed to determine whether BNP levels predict outcomes in patients with moderate symptomatic HF.

Methods and Results—We investigated whether enrollment BNP levels for the Pediatric Carvedilol Trial were associated with baseline characteristics. Freedom from a composite end point of HF hospitalization, death, or transplantation at 9 months was compared using a threshold BNP level identified using receiver operating curve analysis. Median BNP level was 110 pg/mL (interquartile range, 22.4 to 342.0 pg/mL) in 138 subjects. Median age was 3.4 years (interquartile range, 1.1 to 11.0 years). Diagnoses were cardiomyopathy (60%) and congenital heart disease (40%); 73% had a systemic left ventricle. BNP levels correlated moderately with left ventricular ejection fraction ($R=0.39$, $P<0.001$) but did not differ by HF class, age, diagnosis, sex, ventricular morphology, or left ventricular end-diastolic dimension Z-score ($R=0.19$). Outcome events included 25 HF hospitalizations, 4 deaths, and 2 transplants. Sensitivity was 71% and specificity 63%, for a BNP cutoff value of 140 pg/mL. BNP ≥ 140 pg/mL (hazard ratio, 3.7; 95% confidence interval, 1.62 to 8.4; $P=0.002$) and age >2 years (hazard ratio, 4.45; 95% confidence interval, 1.68 to 12.04; $P=0.003$) were independently associated with worse outcomes.

Conclusions—In children with moderately symptomatic HF, BNP ≥ 140 pg/mL and age >2 years identified subjects at higher risk for worse outcome. Further validation is needed to determine the BNP levels necessary to stratify risk in other pediatric cohorts. (*Circ Heart Fail.* 2010;3:606-611.)

Key Words: heart failure ■ pediatrics ■ natriuretic peptides ■ cardiomyopathy

Biomarkers are an increasingly important diagnostic tool in the treatment of the adult patient with heart failure (HF). B-type natriuretic peptide (BNP) is one such biomarker and is produced by ventricular myocytes in response to pressure and volume overload and wall tension.^{1,2} BNP is initially part of a 134-amino acid pre-proBNP, which undergoes processing, resulting in the 76-amino acid N-terminal proBNP (NT-proBNP) and the 32-amino acid molecule BNP.³⁻⁵ In adult HF patients, serum BNP levels have been correlated with New York Heart Association (NYHA) class and are used to estimate the severity of disease and predict adverse outcomes.⁶⁻⁸ Recent recommendations for the use of biomarker testing in adults with HF indicate that BNP and NT-pro-BNP levels are useful in the screening and risk stratifi-

cation of selected patients.^{6,9,10} Studies in both children and adults with acquired or congenital heart disease (CHD) have shown elevated serum BNP levels in patients with increased ventricular wall stress and ventricular dysfunction.¹¹⁻¹⁴ Limited data are available on the predictive value of BNP in pediatric patients with ventricular systolic dysfunction.¹⁵

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Price et al¹⁵ demonstrated that BNP levels predicted worse 90-day event-free survival in a population of children with systolic left ventricular (LV) dysfunction, 58% of whom were asymptomatic. No studies have been performed to determine the ability of BNP levels to predict outcomes in children with symptomatic HF and ventricular dysfunction secondary to

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cardiomyopathy or CHD. It is unlikely that data from adults with HF can be routinely applied to children because there may be age-related differences in normative data and in the neurohormonal response to ventricular dysfunction from cardiomyopathy or congenital heart disease.

The purpose of the present study was to determine whether BNP levels in children with symptomatic HF correlate with the severity of HF and whether they can reliably predict adverse outcomes in children with symptomatic HF and ventricular dysfunction.

Methods

Study Design

This study is a post hoc analysis of data from the Pediatric Carvedilol Trial. The details of this trial have been described previously.^{16,17} Briefly, the Pediatric Carvedilol Trial was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel design study involving 26 centers that evaluated the effect of carvedilol on clinical HF outcomes in symptomatic pediatric subjects with systolic dysfunction of the systemic ventricle.¹⁶ The overall results of the study failed to demonstrate a treatment benefit of carvedilol on a composite primary end point of HF outcomes including death, transplantation, HF hospitalization, or worsened parental assessment or HF score. Specifically, there was no difference between the placebo and carvedilol treatment groups in the percentage of subjects who improved, worsened, or were unchanged after 8 months. Data from the Pediatric Carvedilol Trial were collected with informed consent, and this post hoc analysis was approved by the Institutional Review Board of Columbia University.

Subject Participation and Outcomes

Subjects included in the original study had the diagnosis of cardiomyopathy or congenital heart disease and systolic ventricular dysfunction. Systolic ventricular dysfunction was defined as an ejection fraction $\leq 40\%$ in subjects with systemic LV dysfunction or qualitative evidence of a dilated ventricle with moderate systemic ventricular systolic dysfunction in patients with a systemic right ventricle or single ventricle physiology. Other inclusion criteria included a Ross or NYHA HF class II to IV, age < 18 years, and a history of a stable outpatient medication regimen for at least 1 month before enrollment. All subjects who had a serum BNP level measured at the time of enrollment were included in the current analysis. Although the primary end point of the Pediatric Carvedilol Trial was assessed 8 months after enrollment, subjects who had not reached the composite end point continued to be followed for 1 more month, making the overall subject follow-up for this secondary analysis 9 months. Subjects actively listed for transplantation at time of entry into the Pediatric Carvedilol Trial or anticipated to undergo heart transplantation or corrective heart surgery during the study follow-up period were excluded.¹⁷ Of the 178 subjects eligible for the Pediatric Carvedilol Trial, 15 were excluded for the following reasons: not stable with medications ($n=7$), good ventricular function ($n=5$), low blood pressure ($n=1$), ventricular arrhythmia ($n=1$), and endocrine exclusion ($n=1$). Study end points included hospitalization for worsening HF, all-cause mortality, or transplantation. The end point of hospitalization for worsening HF was adjudicated blindly by the Pediatric Carvedilol Trial steering committee.

Baseline Assessment

Subject characteristics obtained at enrollment included demographic information, NYHA HF class (generally applied in children ≥ 5 years of age), and Ross HF class (generally applied in children < 5 years of age). Venous samples for BNP level determination were drawn after the patient was in a sitting/supine position in a quiet room for 30 minutes. BNP levels were measured at the Mayo Medical Laboratories using the Beckman Coulter DXI 800 Immunoassay (Beckman Coulter Inc, Fullerton, Calif). This

Table 1. Baseline Subject Characteristics

Characteristics	All Subjects (n=138)	BNP <140 pg/mL (n=74)	BNP ≥ 140 pg/mL (n=64)
Sex, n (%)			
Female	69 (50)	40 (54)	29 (46)
Male	69 (50)	34 (46)	35 (54)
Ethnicity, n (%)			
African American	33 (24)	14 (19)	19 (30)
Asian	3 (2.2)	2 (3)	1 (2)
White	69 (50)	38 (51)	31 (48)
Hispanic	27 (20)	17 (23)	10 (16)
Other	6 (4.3)	3 (4)	3 (5)
Diagnosis, n (%)			
Cardiomyopathy	83 (60)	46 (62)	37 (58)
Congenital heart disease	55 (40)	28 (38)	27 (42)
Ventricular morphology, n (%)			
Systemic non-LV	37 (27)	20 (27)	17 (26)
Systemic LV	101 (73)	54 (73)	47 (73)
Median age, IQR	3.4 (1.1–10.8)	3.1 (0.8–12.9)	3.5 (1.4–10.1)
0 to 2 y, n (%)	55 (40)	32 (43)	23 (36)
2 to 6 y, n (%)	25 (18)	9 (12)	16 (25)
5 to 12 y, n (%)	27 (20)	14 (19)	13 (20)
12–18 y, n (%)	31 (22)	19 (26)	12 (19)
Age > 2 y, n (%)	83 (60)	42 (57)	41 (64)
Ross or NYHA HF class, n (%)			
Class II	100 (72)	55 (74)	45 (70)
Class III-IV	38 (28)	19 (26)	19 (30)
Study arm, n (%)			
Placebo	44 (32)	28 (38)	16 (25)
Low dose	47 (34)	23 (31)	24 (38)
High dose	47 (34)	23 (31)	24 (38)
Mean LVEDd Z-score, \pm SD, n=102	6.6 \pm 3.5	5.5 \pm 2.8	7.8 \pm 3.8*
Mean LVEF, %, \pm SD, n=106	26.5 \pm 7.9	29.4 \pm 7.4	23.2 \pm 7.3*

* $P \leq 0.001$ as compared with BNP < 140 pg/mL.

assay required whole blood to be spun down to remove cells and then isolation of 0.4 to 1 mL of plasma, which was then immediately frozen. Blood samples were rejected if grossly hemolyzed. Echocardiograms were centrally interpreted. Ventricular morphology was defined by the core laboratory as either a systemic LV or a systemic non-LV. All subjects with single ventricle physiology were classified as having a systemic non-LV. In subjects with a LV, ejection fraction and LV end-diastolic dimension (LVEDd) were determined and LVEDd was normalized to body surface area using Z-scores.¹⁸ In subjects with a systemic non-LV, including all subjects with a single ventricle, LVEF and LVEDd were not measured.

Statistical Analysis

BNP levels at enrollment were compared by sex, race, diagnosis, subtype of systemic ventricle, HF class, and age at enrollment. HF class and diagnosis were also compared against these characteristics in order to determine if there were differences between subjects, based on HF class or diagnosis. For comparison, age at enrollment

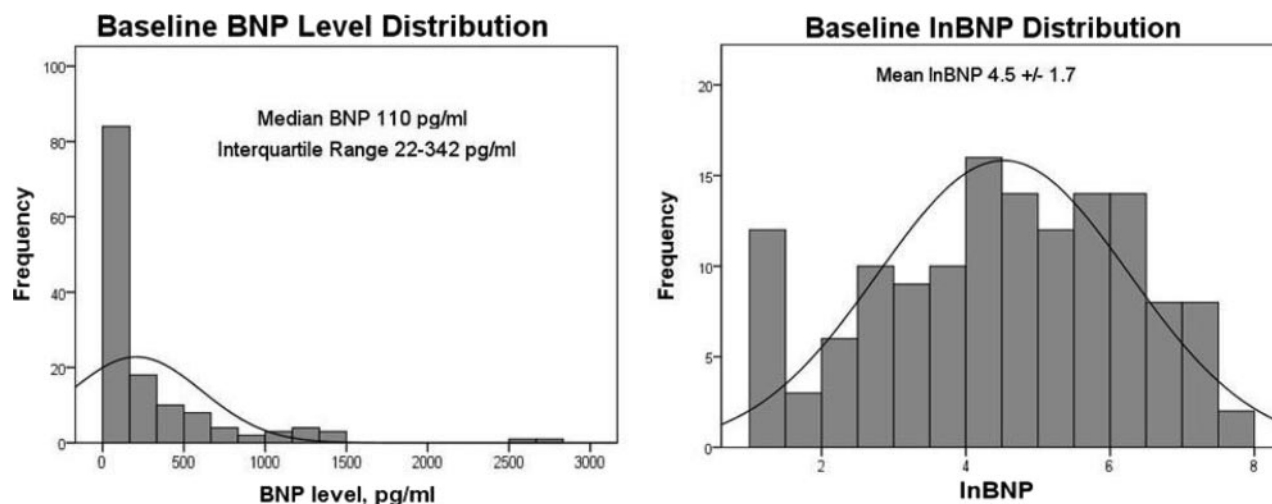


Figure 1. Baseline BNP distribution before (left) and after (right) logarithmic transformation. Baseline BNP levels were significantly skewed rightward, necessitating logarithmic transformation before performing parametric testing. Logarithmic transformation resulted in a normal distribution.

was divided into 4 groups, 0 to 2 years, 2 to 6 years, 6 to 12 years, and 12 to 18 years. Comparisons were also performed between those patients who were younger and older than 2 years. Continuous variables were expressed as mean (\pm SD) or median (interquartile range [IQR]). Skewed data (BNP levels) were transformed logarithmically to produce a normal distribution for appropriate parametric testing. Univariate differences in continuous variables were analyzed with correlation and linear regression as appropriate. Univariate analysis of dichotomous variables was performed with the Pearson χ^2 test and the Mantel-Haenszel common odds ratio estimate. Univariate differences in dichotomous and continuous variables were assessed with the Mann-Whitney *U* test.

A composite end point that included hospitalization for worsening HF, all-cause mortality, and cardiac transplantation was used to assess the predictive value of the baseline BNP level. Before performing survival analysis, a receiver operating characteristic curve was created to determine the BNP level that provided the best combination of sensitivity and specificity for predicting the composite end point. Survival analysis was performed with Kaplan-Meier and Cox proportional hazards modeling. The log-rank test was used to determine statistical significance between Kaplan-Meier survival curves. BNP level, age, diagnosis, HF class, sex, and type of systemic ventricle were all included in the hazard model. Analyses were performed in all subjects, regardless of treatment arm (placebo or carvedilol) because outcomes were previously shown to be no different among treatment groups. All statistical tests were 2-sided, and significance was declared by an α value <0.05 . All statistical analyses were performed with SPSS software versions 15 and 16 (SPSS Inc, Chicago, Ill).

Results

Baseline Assessment

Of the initial 161 subjects randomly assigned, baseline serum BNP levels were available in 138. The most common reasons for a missing baseline BNP level were inability to draw blood or inadequate blood sample. Baseline characteristics for study subjects are shown in Table 1. In the 55 subjects with CHD, 36 (65%) had a systemic non-LV and 19 (35%) had a systemic LV. The majority of subjects were in HF class II at enrollment, and only 2 subjects were HF class IV. Cardiac medications at the time of enrollment included angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (98%), digoxin (88%), loop diuretics (79%), aldosterone antagonists (33%), and antiar-

rhythmics (11%). There was no difference in the proportion of patients in HF class II versus III/IV, based on age group ($P=0.31$), sex ($P=0.25$), race ($P=0.15$), or diagnosis ($P=0.47$). Subjects with a systemic LV were less likely to be in HF class III-IV (odds ratio [OR], 0.43; 95% confidence interval [CI], 0.19 to 0.97). Subjects older than 2 years were less likely to have a systemic LV (OR, 0.32; 95% CI, 0.13 to 0.76) and less likely to have a diagnosis of cardiomyopathy (OR, 0.26; 95% CI, 0.12 to 0.56).

The distributions of baseline BNP levels, before and after logarithmic transformation, are shown in Figure 1, along with baseline median BNP and mean lnBNP levels, respectively. Median BNP levels did not differ by HF class ($P=0.96$), age group ($P=0.21$), diagnosis ($P=0.53$), sex ($P=0.18$), or ventricular morphology ($P=0.95$). In the 101 patients who had a systemic LV, lnBNP correlated moderately with LVEF ($r=0.39$; $P<0.001$) but not with LVEDd Z-score ($r=0.19$, $P=0.054$).

BNP and Outcomes

Outcome events occurred in 31 subjects and included 25 HF hospitalizations, 4 deaths, and 2 transplants. Of the 25 subjects meeting the end point of hospitalization for worsening HF, 7 eventually died. Twelve other subjects meeting the end point of hospitalization eventually underwent transplantation during the study period, with a median time to transplantation of 3 months (IQR, 1.3 to 6.8) after enrollment. The median length of follow-up per subject was 7.7 months (IQR, 7.2 to 8.2). The median time to composite outcome was 2.6 months (IQR, 1.6 to 5.0). Median BNP was higher in subjects who reached the composite end point than for those who did not (308 pg/mL [IQR, 122 to 672] versus 76 pg/mL [IQR, 20 to 267], respectively, $P=0.001$). Analysis using a receiver operating characteristic curve showed that a BNP cutoff value of 140 pg/mL offered the best combination of sensitivity and specificity for the composite end point (Figure 2). Comparison of baseline characteristics between the subjects with BNP <140 pg/mL and those with BNP ≥ 140 pg/mL showed significant differences only in LVEDd Z-score and LVEF in the 101 patients with a systemic LV (Table 1). Kaplan-Meier survival analysis demonstrated

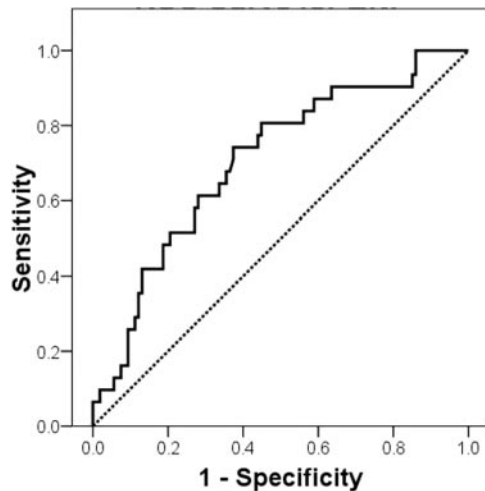


Figure 2. Receiver operating characteristic curve for BNP levels. This receiver operating characteristic curve demonstrates that a BNP level of 140 pg/mL results in a sensitivity of 71% and specificity of 63%, to predict the composite outcome of hospitalization for worsening HF, death, or transplantation. The area under the curve was 0.71 (95% CI, 0.60 to 0.81).

significantly lower event free survival from the composite end point of freedom from HF hospitalization, transplantation, or death for subjects with an enrollment BNP level of ≥ 140 pg/mL (Figure 3). Kaplan–Meier survival analysis was repeated using a more restrictive composite end point of freedom from death or transplantation, which continued to show a statistically significant lower freedom from death or transplantation for subjects with a BNP level of ≥ 140 pg/mL (Figure 4).

After controlling for age, sex, HF class, diagnosis, and ventricular morphology, Cox proportional hazards modeling showed that a BNP level of ≥ 140 pg/mL and an age >2 years each independently increased the likelihood of HF hospitalization, transplantation, or death (hazard ratio [HR], 3.69; 95% CI, 1.61 to 8.44; $P=0.002$; and HR, 4.45; 95% CI, 1.65 to 12.04; $P=0.003$, respectively) (Table 2).

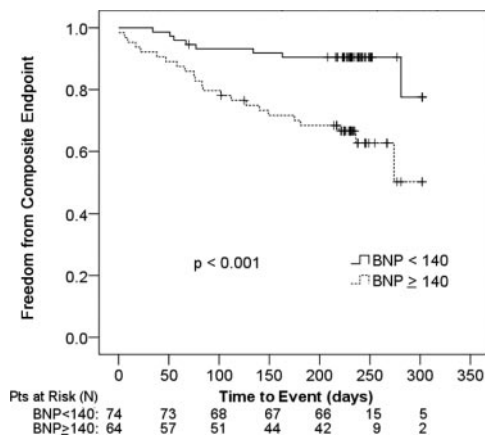


Figure 3. Kaplan–Meier survival curve showing freedom from the composite end point. Survival analysis of time to hospitalization for worsening HF, death, or transplant showed significantly worse event-free survival in subjects with BNP ≥ 140 pg/mL. Event-free survival at 6 and 9 months was 90% and 78%, respectively, for a BNP level <140 pg/mL and 68% and 50%, respectively, for a BNP level of ≥ 140 pg/mL.

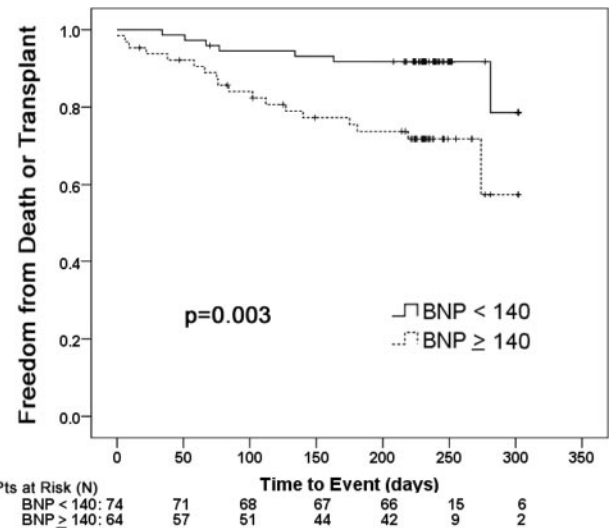


Figure 4. Kaplan–Meier survival curve showing freedom from death or transplantation only. Survival analysis was repeated using a composite end point of time to death or transplantation and showed significantly worse event-free survival in subjects with BNP ≥ 140 pg/mL. Event-free survival at 6 and 9 months was 92% and 78%, respectively, for a BNP level <140 pg/mL and 76% and 57%, respectively, for a BNP level of ≥ 140 pg/mL.

Discussion

This post hoc analysis of data from the Pediatric Carvedilol Trial demonstrates that serum BNP levels in children with moderately symptomatic HF are higher than normal values reported in children. The median BNP in children with HF was 110 pg/mL, compared with 20 to 40 pg/mL reported in normal children.¹⁴ BNP levels did not differ by sex, diagnosis, or subtype of systemic ventricle. There was a moderate correlation between lnBNP level and LVEF but no significant correlation between lnBNP levels and LV dimension. It is interesting, however, that a BNP level of ≥ 140 pg/mL was associated with a higher LVEDd Z-score and lower EF, which is consistent with the data that BNP levels increase with increasing wall stress.^{9,13} This is the first prospective, multicenter study showing BNP to be predictive of clinical outcomes in a cohort of children with symptomatic HF.

BNP levels were not different among HF classes in this study. Previous studies have shown a correlation between higher BNP levels and worsening HF classes and measures of functional status.^{6,13,19} These studies included subjects with HF classes I to IV, whereas in the current study, 72% of the subjects had HF class II and 27% had HF class III or IV, with

Table 2. Multivariate Cox Proportional Hazards Model: BNP and Age Independently Predict Adverse Outcomes

	n = 138, Events = 31 HR (95% CI)	P Value
BNP >140 pg/mL	3.69 (1.61–8.44)	0.002
Age >2 y	4.45 (1.65–12.04)	0.003
Cardiomyopathy	3.02 (0.75–12.12)	0.12
HF class III–IV	1.35 (0.62–2.97)	0.45
Male sex	1.02 (0.49–2.14)	0.95
Systemic LV	0.29 (0.07–1.23)	0.09

only 2 subjects with class IV. This suggests that BNP levels are not sensitive enough to distinguish between HF class II and III in children.

In the present study of children with class II and III HF on a standard oral anticongestive regimen, 22% reached the composite end point of hospitalization for worsening HF, all-cause mortality, or transplantation within 9 months. A BNP level ≥ 140 pg/mL in this cohort was predictive of adverse outcomes. Although these data are consistent with previous studies showing that BNP levels can predict adverse outcomes in both children and adults with HF, further validation is needed to determine the BNP level necessary to stratify risk in other specific and/or broader cohorts.^{15,19} In a cohort of mostly asymptomatic older children, all of whom had a diagnosis of dilated cardiomyopathy with anatomically normal hearts, Price et al¹⁵ reported a positive association of a BNP level of 300 pg/mL with a 90-day composite outcome of HF-related hospitalization, HF-related death, or listing for transplantation. Our study population was very different in that all subjects were symptomatic and 40% of the subjects had a diagnosis of CHD, 27% with a non-LV systemic ventricle. This heterogeneity of ventricular morphology and homogeneity of symptoms may be the reason for the lower sensitivity and specificity for the ability of BNP levels to predict outcomes by receiver operating characteristic curve analysis when compared to a population of children with mostly asymptomatic ventricular dysfunction and anatomically normal hearts.

The threshold level of BNP associated with adverse outcome in the children with HF in this study is lower than what has been previously reported in adults. Healthy children have been shown to have lower baseline BNP levels than healthy adults, but no study has directly compared BNP levels in children and adults with comparable HF symptoms or severity.²⁰ An important difference between the pediatric and adult HF populations is that a significant proportion of children have symptomatic HF caused by failed palliation of CHD. Children with CHD have been found to have lower BNP levels than children with similar ejection fraction, end-diastolic pressures, and functional status with a diagnosis of dilated cardiomyopathy.¹³ In particular, children with single-ventricle physiology who have undergone Fontan palliation have also been noted to have lower than expected BNP levels relative to their ventricular function and functional status, which has been postulated to be secondary to reduced preload and limited preload reserve.^{21–23} Another possible explanation for the lower threshold BNP level in children is that this study had a longer follow-up period after measurement of the baseline BNP level when compared with prior studies. A higher BNP threshold level may be more accurate for predicting short-term outcomes, whereas a lower threshold BNP level may predict adverse outcomes with longer follow-up.^{6,15,19}

Although the purpose of this analysis was to evaluate the ability of BNP levels to predict clinical outcomes, it was also interesting to find that subjects who were >2 years of age were >4 times more likely to meet the composite end point in multivariate analysis. It seems reasonable to speculate that a larger proportion of subjects with CHD with ventricular dysfunction may also contribute to the increased risk of poor outcome in the older subjects. However, the Cox proportional

hazards model controlled for diagnosis and ventricular morphology and still found age to be an independent predictor of outcomes in this cohort. This finding is consistent with a recent study of predictors of clinical outcome in subjects with dilated cardiomyopathy, in which patients ≥ 6 years of age had a higher risk of adverse outcomes.²⁴ The differences in diagnosis and ventricular morphology may explain the lower age cutoff in our study.

Our findings suggest that BNP levels in stable pediatric outpatients with mild-to-moderately symptomatic HF can be used to identify children at risk for hospitalization for worsening HF, death, or transplantation. The major strength of this multicenter study is that it represents the largest cohort of subjects studied to date to determine the ability of BNP levels to predict the risk of adverse events in children with symptomatic HF. The data were obtained prospectively during a randomized placebo controlled trial and the end-points for worsening HF were adjudicated by an end point steering committee. There are, however, several limitations of this study. The heterogeneous subject population may have introduced variability in the values of BNP levels that limited the sensitivity and specificity analysis. The numbers of subjects were insufficient to allow for analyses to determine if the BNP level can predict the composite outcome in subgroups of children with congenital heart disease and different ventricular morphologies and numbers of ventricles. Also, the study did not include determination of NT-proBNP levels, which have also been shown to be predictive of outcome in HF patients.²⁵

In conclusion, our findings suggest that BNP levels of ≥ 140 pg/mL in stable pediatric outpatients with mild-to-moderately symptomatic HF can be used to identify children at risk for hospitalization for worsening HF, death, or transplantation. Further studies are needed to validate the cutoff BNP level of 140 pg/mL in other specific and/or broader cohorts. BNP levels should be included in the risk stratification of children with HF, and higher BNP levels should warrant increased surveillance and management for worsening HF in this population. This knowledge may be used in the future to tailor medical treatment to individual patients and to determine the optimal timing of transplantation. Whether escalating treatment regimens in patients with elevated BNP levels leads to improved outcomes requires further investigation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The goal of this study was to determine the ability of B-type natriuretic peptide (BNP) levels to predict adverse outcomes in euvoletic children on a stable outpatient medication regimen with moderate symptomatic heart failure. We tested the hypothesis that elevated BNP levels can predict heart failure–related events. BNP levels were determined to be a fair test for predicting adverse outcomes. Subjects with a BNP level of ≥ 140 pg/mL were at significantly higher risk of having a heart failure–related event. BNP levels can serve as a marker of compensation in pediatric heart failure, and BNP levels of ≥ 140 pg/mL should alert clinicians that clinical deterioration may occur in the near future. Elevated BNP levels may be particularly helpful when symptoms are difficult to elicit in the history, as is the case with many pediatric heart failure patients. Further study is needed to determine whether and which BNP levels should guide individual decisions when managing a broader population of heart failure patients. Whether goal directed therapy to target specific BNP levels is safe or efficacious requires further investigation.