Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT II)

A Randomized Controlled Trial of the Effect of Serial B-Type Natriuretic Peptide Testing on Patient Management

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Background—B-type natriuretic peptide is useful to diagnose heart failure. We determined whether the use of serial B-type natriuretic peptide measurements to guide treatment improves the outcome in patients with acute heart failure.

Methods and Results—We conducted a randomized controlled trial of patients with acute heart failure in 10 academic and community emergency departments. The experimental group received serial B-type natriuretic peptide testing (at 3, 6, 9, and 12 hours then daily). The control group received usual care. Our outcomes were hospital length of stay, 30-day readmission rate, and all-cause mortality.

There were 219 controls and 228 experimental patients. Mean age was 64 years, 49% were women, 58% were blacks, and 34% were whites. Groups were similar in baseline characteristics. Comparing the serial testing with the control group, there was no difference in length of stay (6.5 days [95% CI, 5.2 to 7.9] versus 6.5 days [95% CI, 5.6 to 7.3]; difference, 0.1 [95% CI, −1.7 to 1.5]), in-hospital mortality (2.2% [95% CI, 0.9 to 5.0] versus controls, 3.2% [95% CI, 1.6 to 6.5]; difference, 1.0% [95% CI, −2.3 to 4.5]), 30-day mortality (3.7% [95% CI, 1.8 to 7.5] versus 5.5% [95% CI, 3.0 to 9.8]; difference, 1.8% [95% CI, −2.8 to 6.5]), or hospital revisit rate (20.2% [95% CI, 15.0 to 26.6] versus 23.7% [95% CI, 18.0 to 30.6]; difference, 3.5% [95% CI, −5.1 to 12.1]).

Conclusions—In this study of 447 patients hospitalized for suspected heart failure, we were unable to demonstrate a benefit of serial testing with B-type natriuretic peptide in terms of hospital length of stay, mortality, or readmission rate. (Circ Heart Fail. 2009;2:287-293.)

Key Words: acute heart failure ■ B-type natriuretic peptide ■ point-of-care testing ■ mortality

Background and Importance

It is estimated that more than 5 million Americans have heart failure (HF) with ≈550 000 new cases diagnosed each year.1 The total annual cost of treating HF is ≈56 billion dollars, most of which is for hospitalization.2 One third of all acute HF patients are admitted each year, and 80% of those patients presenting to the emergency department (ED) with acute HF are admitted to the hospital each year.3 Despite advances in treatment, patients admitted with acute HF syndromes have significant hospital mortality and early readmission rates.3 Failure to diagnose and treat HF has been shown to increase mortality, delay hospital discharge, and increase treatment costs.4,5

Clinical Perspective on p 293

B-type natriuretic peptide (BNP) is released from the ventricular myocardial cells in response to stretching secondary to pressure or volume overload.6 BNP has both vasodilatory and natriuretic effects that help mitigate the pathophysiological derangement associated with HF. BNP levels can be measured in the serum and have been shown to be helpful in the diagnosis and prognosis of patients with HF.7,8

The Breathing Not Properly study of 1586 patients who presented to EDs with shortness of breath demonstrated that BNP levels alone were more predictive of the presence or absence of HF that any historical, physical, or laboratory...
A BNP cutoff of 100 pg/mL had a sensitivity of 90% and a specificity of 76% for differentiating HF from other causes of dyspnea. The addition of BNP values to history and physical examination reduced the diagnostic indecision rate from 43% to 11%, demonstrating that BNP has significant clinical utility for diagnosis of HF in the ED.

The Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT) raised the issue of whether BNP might perform better than clinical judgment with respect to 90-day prognosis. Eleven percent of admitted patients had BNP levels <200 pg/mL, and these patients had a very low mortality (0% at 30 days and 2% at 90 days), suggesting that they might have actually been safe for discharge. Conversely, 78% of patients discharged from the ED had BNP levels >400 pg/mL, and these patients had 9% mortality by 90 days. There were no deaths in discharged patients with BNP levels <400 pg/mL. The REDHOT study suggests that BNP might be useful to identify low-risk patients that are safe for discharge.

There is also evidence that BNP levels correlate with prognosis. Cheng et al found that patients whose BNP levels at the time of discharge were <430 pg/mL had lower rates of readmission. Harrison et al demonstrated that patients with a BNP level <230 pg/mL had excellent outcomes as compared with patients with BNP levels >480 pg/mL in whom half had a cardiac event within 6 months. Betteencourt et al found that failure of BNP levels to decline during hospitalization was a predictor of death and readmissions and that a BNP level of <250 pg/mL was associated with excellent outcomes. The BNP for Acute Shortness of breath Evaluation study suggests that use of BNP levels may also reduce hospitalizations and costs. Patients in whom the BNP was available to the physicians had lower admission rates, less utilization of costly intensive care unit (ICU) beds, and a 26% reduction in total costs. The composite of these data raises the question about whether or not treatment decisions could be based on changes in BNP levels with initial therapy.

The purpose of the current study was to determine whether the use of serial BNP measurements will allow physicians to make more informed treatment and discharge decisions. We hypothesized that the use of serial BNP levels might result in more aggressive treatments that would subsequently result in shorter hospital length of stay (LOS), reduced mortality, and a reduced readmission rate.

**Methods**

**Study Design**

A prospective randomized nonblinded clinical trial to test our hypothesis that use of serial BNP measurements would result in shorter hospital LOS, reduced mortality, and a lower readmission rate over 30 days was performed. The study was approved by the institutional review boards of the participating hospitals. All patients gave written informed consent.

**Setting and Subjects**

The study was conducted in the EDs of 10 academic and community medical centers. Subjects were eligible for enrollment if they were at least 18 years of age and presented to the ED with signs and symptoms of HF that required treatment. Eligible patients had a point-of-care BNP determined and if <100 pg/mL, they were excluded from the study. Also excluded were patients with acute myocardial infarction or acute coronary syndrome with an ST-segment deviation of 1 mm or greater from the baseline, renal failure requiring dialysis, history of hemodialysis within the last month, or patients enrolled in any drug trial. The study subjects represent a convenience sample of patients enrolled when one of the investigators was present.

**Interventions**

After enrollment, patients were randomized to 1 of 2 groups. The assignment of study group was performed at a central site using a computer-generated random numbers table. Group assignments were stratified by study site and contained equal proportions of the 2 study groups. Group allocation was revealed by opening the next of consecutively numbered opaque envelopes that contained the assigned study group. In the serial BNP group, patients had serial BNP testing at baseline and at the following time intervals: 3, 6, 9, and 12 hours after enrollment. If the patient was admitted, additional BNP testing was performed at the time of admission and once daily until hospital discharge. If the patient was discharged to home from the ED, an additional BNP level was obtained at the time of discharge if greater than 2 hours since the last BNP level was determined. Patients were not required to remain in the ED for any additional period of time solely for the purpose of study participation. The results of the serial BNP levels were communicated to one of the patients’ physicians. In the control group, serial point-of-care BNP testing was not performed. Measurement of central laboratory BNP levels was at the discretion of the treating physician. Bedside point-of-care testing was performed by trained research assistants. BNP samples were analyzed using the Triage BNP point of care test (Biosite Inc, San Diego, Calif). The patients and physicians were not masked to treatment assignment. To mirror the real-life clinical scenario, physicians were not given standardized instruction on how to alter therapy based on BNP levels.

**Measures and Outcomes**

Standardized collection of demographic and clinical data was performed by trained research nurses and assistants using special case report forms. Scripted telephone follow-up and medical record review to determine whether the patient was alive or was readmitted for HF or other cardiovascular events were performed at 30 days.

The primary outcome was the hospital LOS. Secondary outcomes were the in-hospital and 30-day mortality and readmission rates for cardiac-related diseases within 30 days. Hospital LOS was measured as the difference between triage time in the ED and discharge time from the ED, the observation unit, or the hospital, depending on the clinical course. Patients who died while in the hospital were excluded from LOS analyses.

**Data Analysis**

Continuous data are presented as means with standard deviations or 95% CIs. Binomial data are presented as the percent frequency of occurrence. Univariate and multivariate analyses were performed to determine the association between predictor variables and outcomes and are reported as unadjusted and adjusted odds ratios with 95% CIs.

Group comparisons of binary outcomes (ICU admission, in-hospital and 30-day mortality, and unplanned revisits) were compared using the entire sample. Multivariate models of outcomes (LOS, in-hospital mortality, ICU admission, 30-day mortality, and unplanned visit within 30 days) were constructed using age, gender, blood urea nitrogen (BUN), serum creatinine (SC), systolic blood pressure (SBP), heart rate, and group membership (whether serial BNP levels were obtained or not) as predictors. All outcomes were modeled using logistic regression, and the results are shown as odds ratios, except for LOS in which an analysis of covariance model was constructed with the effects shown as the regression coefficients. BUN, SC, and SBP were included as indicator variables (BUN ≥43, SBP <115, and SC ≥2.75) to be comparable with the Acute Decompensated Heart Failure National
Registry study results on mortality. Patients who were lost to follow-up were excluded from the final analysis. The study sample size was designed to be sufficient to detect a 1-day difference in hospital LOS between the 2 study groups at a 2-tailed significance level of $P<0.05$ and a power of 80%.

Results

During the study period (November 2004 to September 2006), we enrolled 480 subjects, 237 in the controls and 243 in the experimental arms (Figure). Twenty-five (13 control, 12 experimental) of these patients were not included because it could not be determined whether they were discharged from the ED or admitted; an additional 8 patients (5 control, 3 experimental) were excluded: 2 left the ED against medical advice, 5 left against medical advice after admission, 1 patient was admitted to an observation unit and then admitted for HF to a hospital at an unknown location. The final sample consisted of 447 patients (219 control, 228 experimental), in whom the mean age was 64 years, 49% were women, 58% were blacks, 34% were whites. Groups were similar in baseline characteristics (Table 1) except blood pressure, which was slightly higher in patients in the serial testing group.

Fifty-four patients (12.1%) were discharged from the ED, and 370 patients (82.8%) were admitted to the hospital from the ED. The remaining 23 patients (5.1%) went to an observation unit from the ED. Of the 377 admits, 14 (3.7%) went to the ICU, 39 (10.3%) went to the intermediate medical care unit, 150 (39.8%) went to telemetry, 163 (43.2%) went to a general unit, and 11 (2.5%) went to another/unknown unit.

None of the patients died before admission. One of the admitted patients had a missing hospital LOS because no date of discharge was recorded. This patient was excluded from LOS analyses but included elsewhere. Follow-up at 30 days was successful for 385 patients (86%). The rate of follow-up success was similar in the 2 groups.

Table 1. Comparison of Baseline Characteristics of the Experimental and Control Groups, All Patients (n=472)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Control (n=232)</th>
<th>Experimental (n=240)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.7 (16.3)</td>
<td>63.2 (15.7)</td>
<td>0.104</td>
</tr>
<tr>
<td>SBP</td>
<td>145 (32)</td>
<td>151 (36)</td>
<td>0.052</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>49.8</td>
<td>51.1</td>
<td>0.779</td>
</tr>
<tr>
<td>Heart rate</td>
<td>88 (22)</td>
<td>88 (22)</td>
<td>0.917</td>
</tr>
<tr>
<td>BUN</td>
<td>27.2 (16.5)</td>
<td>26.4 (18.7)</td>
<td>0.653</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5 (1.1)</td>
<td>1.5 (0.9)</td>
<td>0.559</td>
</tr>
<tr>
<td>BNP levels</td>
<td>1096 (918 to 1274)</td>
<td>1189 (899 to 1389)</td>
<td>0.492</td>
</tr>
<tr>
<td>Admitted, %*</td>
<td>84.9</td>
<td>83.8</td>
<td>0.736</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or value (95% CI).

*Includes those admitted from an observation unit.
Changes in BNP Levels

The percentages of admitted control patients in which central laboratory testing for BNP levels was performed were as follows: day 1, 54.3%; day 2, 7.5%; day 3, 8.1%; and day 4, 9.1%. The percentage of admitted control patients who had central laboratory BNP levels on the day of discharge was 21.0%.

There was no significant difference in initial mean BNP levels between the control group (1178 pg/mL) and the serial BNP group (1118 pg/mL; difference, 1.0%; 95% CI, 2.8 to 6.5); revisit rate (difference, 2.8% versus 1.3%); and 30-day mortality (difference, 1.7%; 95% CI, -2.0 to 5.4). The use of medications both during hospitalization and at discharge was similar between the 2 study groups (Table 3). For each diuretic administered, the following were compared between groups: the mean dose of all doses given in the ED; the mean dose of all doses given during admission; and the mean dose of all doses given in the ED and during admission combined. Also compared were the total number of doses given in the ED; total number of doses given during admission; and total number of doses given in the ED and during admission combined. None of the comparisons showed a significant difference between groups.

Use of mechanical ventilation was also similar among the control and experimental patients. BNP levels were compared in the control and experimental patients (bias level positive airway pressure, 5.3% versus 4.6%; P=0.73; continuous positive airway pressure, 3.5% versus 3.7%; P=0.94; and endotracheal intubation 3.9% versus 3.2%; P=0.67).

Hospital LOS

Univariate, LOS was not correlated with age, SBP, diastolic blood pressure, BUN, SC, gender, or use of serial BNP. The multivariate model that included all of the predictors showed that admitted patients with reduced SBP (P=0.003) and heart rates (P=0.04) had higher LOS.

ICU Admission

Only an elevated BUN was associated with ICU admission (P=0.035). Age, heart rate, gender, SBP, SC, and serial BNP

Table 2. Comparison of Outcomes in the Serial Testing and Control Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n=232)</th>
<th>Experimental (n=240)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted, %*</td>
<td>84.9 (79.6 to 89.1)</td>
<td>83.8 (78.4 to 88.0)</td>
<td>0.736</td>
</tr>
<tr>
<td>ICU, %</td>
<td>4.3 (2.2 to 8.3)</td>
<td>3.2 (1.5 to 6.8)</td>
<td>0.565</td>
</tr>
<tr>
<td>In-hospital Mortality, %</td>
<td>3.2 (1.6 to 6.5)</td>
<td>2.2 (0.9 to 5.0)</td>
<td>0.512</td>
</tr>
<tr>
<td>30-day Mortality, %†</td>
<td>5.5 (3.0 to 9.8)</td>
<td>3.7 (1.8 to 7.5)</td>
<td>0.423</td>
</tr>
<tr>
<td>Unplanned revisit, %‡</td>
<td>23.7 (18.0 to 30.6)</td>
<td>20.2 (15.0 to 26.6)</td>
<td>0.427</td>
</tr>
<tr>
<td>Mean (SD) length of stay§</td>
<td>6.5 (5.6 to 7.3)</td>
<td>6.5 (5.2 to 7.9)</td>
<td>0.937</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CIs.
*Includes those admitted from an observation unit.
†Includes in-hospital mortality.
‡Denominator excludes patients who died during their index admission (includes all postadmission).
§For admitted patients only.

Multivariate Models of Outcomes

The outcomes for the full sample are presented in Table 2. The control group and serial testing groups were not different with respect to any of the outcomes: In-hospital mortality (difference, 1.0%; 95% CI, -2.3 to 4.5); 30-day mortality (difference, 1.7%; 95% CI, -2.8 to 6.5); revisit rate (difference, 3.5%; 95% CI, -5.1 to 12.1); and LOS (difference, 0.1 day; 95% CI, -1.7 to 1.5). The use of medications both during hospitalization and at discharge was similar between the 2 study groups (Table 3). For each diuretic administered, the following were compared between groups: the mean dose of all doses given in the ED; the mean dose of all doses given during admission; and the mean dose of all doses given in the ED and during admission combined. Also compared were the total number of doses given in the ED; total number of doses given during admission; and total number of doses given in the ED and during admission combined. None of the comparisons showed a significant difference between groups.

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Hospital LOS

Univariate, LOS was not correlated with age, SBP, diastolic blood pressure, BUN, SC, gender, or use of serial BNP. The multivariate model that included all of the predictors showed that admitted patients with reduced SBP (P=0.003) and heart rates (P=0.04) had higher LOS.

ICU Admission

Only an elevated BUN was associated with ICU admission (P=0.035). Age, heart rate, gender, SBP, SC, and serial BNP

Table 3. Percent Admitted Patients Receiving Drugs from Specified Drug Classes During Admission and as Take-Home Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Control</th>
<th>Experimental</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>66.3</td>
<td>66.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Diuretics</td>
<td>90.2</td>
<td>93.2</td>
<td>0.30</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>10.3</td>
<td>10.5</td>
<td>0.96</td>
</tr>
<tr>
<td>CA channel blockers</td>
<td>26.1</td>
<td>30.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>73.4</td>
<td>71.2</td>
<td>0.64</td>
</tr>
<tr>
<td>ARBs</td>
<td>6.0</td>
<td>6.8</td>
<td>0.74</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>1.6</td>
<td>5.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Inotropics</td>
<td>1.1</td>
<td>3.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Heparin</td>
<td>69.6</td>
<td>66.0</td>
<td>0.46</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>31.0</td>
<td>33.0</td>
<td>0.68</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>2.2</td>
<td>0.5</td>
<td>0.16</td>
</tr>
</tbody>
</table>

ACE inhibitors indicates angiotensin-converting enzyme inhibitors; CA, calcium; ARB, angiotensin receptor blocker.
measurements were not associated with ICU admission. The full logistic regression showed that none of the factors, after adjustment for the others, was significantly associated with ICU admission (Table 4).

In-Hospital Mortality
Patients who died during admission had higher initial BUN, higher SC, and lower SBP than those who survived. Using logistic regression model, age, SC, and study group were not significantly associated with in-hospital mortality (Table 4). This model showed that SBP <115 mm Hg, elevated heart rate, and male gender were associated with mortality. The results for this model would be expected to be similar to that for 30-day mortality because most deaths were during hospitalization.

30-Day Mortality
Patients who died within 30 days of discharge had higher initial BUN, higher SC, and lower SBP. Study group, age, heart rate, and gender were not associated with 30-day mortality.

Using logistic regression model, gender, age, SC, and study group were not significantly associated with 30-day mortality (Table 4). This model showed that SBP <115 mm Hg and elevated BUN and heart rate were associated with mortality.

Unplanned Revisit Within 30 Days
None of the predictor variables was significantly associated with unplanned revisits. This was true on a single-variable level as well as when adjusted for the other predictors (Table 4).

Discussion
The current study was designed to test the hypothesis that performance of serial point-of-care testing for BNP in patients presenting to the ED with acute HF syndromes would reduce hospital LOS and both in-hospital and 30-day mortality. Although there were positive trends associated with the experimental arm, in this study serial BNPs did not reduce hospital LOS or mortality. Furthermore, ICU admission rates and readmissions for HF over the subsequent 30 days were also not improved by performing serial BNPs in these patients. Thus, unnecessary aggressive treatments may be avoided by not performing serial BNP measurements. We believe that our results, from multiple academic and community hospital settings, are fairly representative of other hospitals throughout the country.

Prior studies have evaluated the impact of BNP-guided versus physician-guided therapy in patients with chronic HF. In a study by Troughton et al,16 69 patients with impaired systolic function (left ventricular ejection fraction <40%) and symptomatic HF (New York Heart Association class II to IV) were randomized to receive treatment guided by either plasma BNP concentration (BNP group) or standard clinical assessment (clinical group). During follow-up (minimum 6 months, median 9.5 months), there were fewer total cardiovascular events (death, hospital admission, or HF decompensation) in the BNP group than in the clinical group (19 versus 54, P=0.02). At 6 months, 27% of patients in the BNP group and 53% in the clinical group had experienced a first cardiovascular event (P=0.034). Changes in left ventricular function, quality of life, renal function, and adverse events were similar in both groups. Murdoch et al,17 in a study of 20 patients with mild-to-moderate congestive HF receiving stable conventional therapy, including an angiotensin-converting enzyme inhibitor, were randomly assigned to titration of angiotensin-converting enzyme inhibitor dosage according to serial measurement of plasma BNP concentration (BNP group) or optimal empirical angiotensin-converting enzyme inhibitor therapy (clinical group) for 8 weeks. Only the BNP-driven approach was associated with significant reductions in plasma BNP concentration throughout the duration of the study and a significantly greater suppression when compared with empirical therapy after 4 weeks (~42.1%, 95% CI, −58.2 to −19.7 versus −12.0%, 95% CI, −31.8 to 13.8; P=0.03). Both treatment strategies were well tolerated and associated with favorable neurohormonal and hemodynamic effects; however, in comparison between groups, mean heart rate fell (P=0.02) and plasma renin activity rose (P=0.03) in the BNP group when compared with the clinical group. In the STARS-BNP Multicenter Study, a total of 220 New York Heart Association functional class II to III patients considered optimally treated with angiotensin-converting enzyme inhibitors, β-blockers, and diuretics by HF specialists were randomized to medical treatment according to either current guidelines (clinical group) or a goal of decreasing BNP plasma levels by >100 pg/mL (BNP group).18 At the end of the first 3 months, all types of drugs were changed more frequently in the BNP group. During follow-up (median 15 months), significantly fewer patients reached the combined end point of HF-related deaths or admissions in the BNP group (24% versus 52%, P<0.001). Inomata et al18a also found that patients with

Table 4. Adjusted Odds Ratios (95% CI) of Selected Factors on Binary Outcomes (In-Hospital Mortality, 30-Day Mortality, ICU Admission, Unplanned Revisit)

<table>
<thead>
<tr>
<th></th>
<th>In-Hospital Mortality</th>
<th>30-Day Mortality</th>
<th>ICU Admission</th>
<th>Unplanned Revisit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0 (0.96 to 1.04)</td>
<td>1.0 (0.98 to 1.05)</td>
<td>1.0 (0.97 to 1.05)</td>
<td>1.0 (0.97 to 1.01)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>5.5 (1.06 to 28.8)</td>
<td>1.7 (0.6 to 5.0)</td>
<td>0.7 (0.2 to 2.2)</td>
<td>0.8 (0.5 to 1.4)</td>
</tr>
<tr>
<td>BUN &gt;43</td>
<td>5.1 (1.1 to 23.1)</td>
<td>4.6 (1.3 to 16.1)</td>
<td>2.7 (1.6 to 3.7)</td>
<td>2.3 (1.6 to 4.6)</td>
</tr>
<tr>
<td>Creatinine ≥2.74</td>
<td>2.6 (0.5 to 13.1)</td>
<td>2.2 (0.5 to 9.3)</td>
<td>1.9 (0.4 to 8.5)</td>
<td>1.7 (0.6 to 4.6)</td>
</tr>
<tr>
<td>SBP &lt;116</td>
<td>4.6 (1.3 to 16.6)</td>
<td>4.6 (1.5 to 13.9)</td>
<td>1.9 (0.5 to 7.5)</td>
<td>1.7 (0.7 to 7.1)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.03 (1.01 to 1.06)</td>
<td>1.03 (1.01 to 1.06)</td>
<td>1.01 (0.98 to 1.03)</td>
<td>1.0 (0.99 to 1.01)</td>
</tr>
<tr>
<td>Serial BNP testing</td>
<td>0.6 (0.2 to 2.3)</td>
<td>0.6 (0.2 to 1.8)</td>
<td>0.7 (0.2 to 2.1)</td>
<td>0.8 (0.5 to 1.3)</td>
</tr>
</tbody>
</table>
chronic HF randomized to BNP-guided therapy had fewer total cardiovascular events after 2 years. In contrast, Beck-da-Silva et al\textsuperscript{19} concluded that the BNP-guided group was not better than expert clinical assessment for \(\beta\)-blocker titration but may be useful for physicians who do not see patients with HF on a regular basis.

In a study of serial biomarker measurements in 190 ambulatory patients with chronic HF, Miller et al\textsuperscript{20} found that an elevation of BNP from normal at any time during the study was associated with poor outcome. However, once elevated, further increases or decreases in BNP levels did not change the risk. In contrast, a retrospective study by Valle et al\textsuperscript{21} suggests that the addition of a predischARGE BNP level to a clinical decision rule for discharge in patients admitted for HF may contribute to a reduction in the number of subsequent readmission and overall costs. Most recently, Pfisterer et al compared 18-month outcomes of N-terminal BNP-guided versus symptom-guided HF therapy in 499 patients aged 60 years or older with systolic HF (ejection fraction \(\leq 45\%\)), New York Heart Association class of II or greater, prior hospitalization for HF within 1 year, and N-terminal BNP level of 2 or more times the upper limit of normal. HF therapy guided by N-terminal BNP did not improve overall clinical outcomes or quality of life as compared with symptom-guided treatment.\textsuperscript{22} These results are in agreement with ours and suggest that therapy based on clinical signs and symptoms is as effective as therapy based on serial changes in BNP levels.

The main question raised by this study is why serial BNPs did not significantly improve outcomes in ED patients with acute HF syndromes. There are several possible explanations. It is possible that our study was underpowered to detect small differences in outcomes, especially for mortality. It is also possible that clinicians may have chosen to ignore the results of the point-of-care testing for BNP, relying on other clinical factors to determine treatment and disposition. Also, it is known that changes in BNP levels lag after clinical improvement, which may explain the lack of utility of serial BNP in acute HF. Finally, the results may have been compounded by the fact that some patients were being admitted or kept in the hospital for reasons not related to HF.

Of note, the results of our study confirm those of prior studies that found that renal function (BUN and SC) and hemodynamics (blood pressure and heart rate) are associated with in-hospital and 30-day mortality.\textsuperscript{14,15}

Limitations

Our study has several limitations that merit further discussion. Although no outcomes were statistically better in patients randomized to serial BNP testing, all had a small absolute difference favoring the direction of serial BNP testing. We cannot exclude the possibility that a larger study might have demonstrated some statistical differences. Post hoc power analysis found that 200 subjects per group provide 81\% power to detect a difference of 11\% points between groups assuming that the control group revisit rate was \(\approx 24\%\) and using a 2-tailed test with a significance level of 0.05.

Second, follow-up was limited to 30-day telephone inquiries and chart review. Some studies suggest that follow-up to 6 months may be required to detect differences between the groups. Furthermore, 30-day follow-up was not completed in up to 14\% of study patients from both groups. Third, our study used a convenience sample and is subject to sampling and selection bias. Fourth, few data are available regarding if and how the results of the serial BNP levels were used. Instead, we used the medications prescribed as a surrogate for the clinical decision making. The results of the BNP point-of-care testing were reported to one of the treating physicians on the patient’s medical team. This may have been a resident or an attending physician. This is not dissimilar to the normal scenario in which a team member checks the central laboratory results and then reports them to the rest of the team including the attending physician. Fifth, there was no guidance provided regarding what to do with the BNP levels. For example, there was no goal to lower the levels with treatment. This was by design to reflect the real-life scenario in which physicians may alter their care at their own discretion. Sixth, the physicians in the control group were not restricted from obtaining BNP levels from the central laboratory platform at anytime during patient care. However, only a minority of control patients had multiple BNP measurements during their hospital stay.

In summary, performance of serial BNP point-of-care testing in 447 ED patients admitted for acute HF syndromes did not significantly reduce hospital LOS, in-hospital mortality, ICU admission rates, 30-day mortality, and readmission within 30 days of initial ED visit when compared with a group that had BNP ordered at the discretion of the treating team.

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Disclosures

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Brain natriuretic peptide (BNP) has been shown to be helpful in the diagnosis and prognosis of patients with heart failure. The current multicenter randomized clinical trial was designed to determine whether performing serial bedside point-of-care BNP levels would alter management and improve patient outcomes in patients with acute heart failure compared with standard BNP testing. In this study of 447 patients hospitalized for suspected heart failure, we were unable to demonstrate a benefit of serial BNP testing in terms of hospital length of stay, mortality, or readmission rate. Therefore, we do not recommend routine serial BNP testing in patients with acute heart failure.
Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT II): A Randomized Controlled Trial of the Effect of Serial B-Type Natriuretic Peptide Testing on Patient Management

Adam J. Singer, Robert H. Birkhahn, David Guss, Abhinav Chandra, Chadwick D. Miller, Brian Tiffany, Phillip Levy, Robert Dunne, Aveh Bastani, Henry C. Thode, Jr and Judd E. Hollander

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