

## **Q: Should target natriuretic peptide levels be used for outpatient management of chronic heart failure?**

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**A:** In the last few years, a number of randomized controlled trials have explored the value of using target levels of natriuretic peptides such as brain-type natriuretic peptide (BNP) and N-terminal BNP in the outpatient management of heart failure. Unfortunately, the results have been inconclusive.

### **■ RATIONALE FOR TARGETING NATRIURETIC PEPTIDE LEVELS**

Heart failure causes devastating morbidity and death, yet its management is guided more often by subjective than by objective data.<sup>1</sup> In other chronic conditions such as hypertension, diabetes mellitus, and hyperlipidemia, numerical targets for blood pressure, hemoglobin A<sub>1c</sub>, and low-density lipoprotein cholesterol levels are used to guide medical therapy, and lower rates of both morbidity and death have resulted.<sup>1</sup> Extensive efforts have been undertaken to use natriuretic peptide levels to similarly guide heart failure therapy and improve outcomes.

### **■ LIMITATIONS TO TARGETING NATRIURETIC PEPTIDES**

The relationship between natriuretic peptide levels and patient symptoms<sup>1</sup> and outcomes<sup>2</sup> is neither predictable nor linear, although the association between these levels and outcomes is stronger at the extremes, ie, at very low and very high levels.

Moreover, baseline levels vary significantly among people and within the same person, affected by factors such as genetic polymorphisms,<sup>3</sup> age, sex,<sup>4</sup> body mass index,<sup>5</sup> and other diseases, such as renal insufficiency.<sup>6</sup>

In addition, natriuretic peptide levels behave differently depending on the type of heart failure, rising much higher in systolic heart failure than in diastolic heart failure.<sup>7</sup>

### **■ ESTABLISHED USES OF MEASURING NATRIURETIC PEPTIDE LEVELS**

Measuring natriuretic peptide levels has proven useful in diagnosing heart failure and in risk stratification of heart failure patients. BNP levels of less than 100 pg/mL practically exclude the diagnosis of heart failure (negative predictive value 89%),<sup>8</sup> as do N-terminal BNP levels less than 300 pg/mL (negative predictive value 99%).<sup>9</sup> Changes from baseline levels during acute hospitalization correlate with heart failure mortality rates, while elevated levels at discharge are associated with a higher risk of heart failure death and of readmission.<sup>10,11</sup>

### **■ NATRIURETIC PEPTIDES TO GUIDE THERAPY**

Of the seven published clinical trials of therapy guided by natriuretic peptide levels, three

**Of the seven clinical trials to date, three were positive, three were negative, and one had mixed results**

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### Three positive trials

**The Christchurch, New Zealand, trial**<sup>12</sup> (with 69 patients) found that there were fewer total cardiovascular events (death, hospital admission, or heart failure decompensation) at 9.5 months in the group randomized to receive treatment guided by the N-terminal BNP concentration than in the control group (19 vs 54,  $P = .02$ ).

**The STARS-BNP trial** (Systolic Heart Failure Treatment Supported by BNP),<sup>13</sup> with 220 patients, showed a significant reduction in the rate of deaths from heart failure and of readmission at 15 months in patients receiving BNP-guided treatment compared with controls (24% vs 52%,  $P < .001$ ).

**The PROTECT trial** (Pro-B Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure Therapy),<sup>14</sup> with 151 patients enrolled, showed a significant reduction in a composite of cardiovascular events (worsening heart failure, hospitalization for heart failure, acute coronary syndromes, ventricular arrhythmias, cerebral ischemia, and cardiovascular death) with N-terminal BNP guidance compared with standard care at a mean of 10 months of follow-up (58 events vs 100 events,  $P = .009$ ). It also showed significant improvements in quality of life, left ventricular ejection fraction, and both left ventricular end-systolic and end-diastolic volume indexes with therapy guided by N-terminal BNP measurement. Moreover, therapy guided by N-terminal BNP was not associated with higher rates of renal dysfunction from more aggressive diuretic use.

### Three negative trials

Conversely, three trials did not find significant reductions in rates of death or hospitalization-free survival between groups:

**The STARBRITE trial** (Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score) (N = 130)<sup>15</sup>

**The BATTLESCARRED trial** (NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) (N = 364)<sup>16</sup>

**The PRIMA trial** (Can Pro-brain-natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?) (N = 345).<sup>17</sup>

### One trial with mixed results

**The TIME-CHF** (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure),<sup>18</sup> the largest of these trials to date (N = 499), did not show a survival benefit, but it did show a lower rate of hospitalization due to heart failure in the group receiving treatment guided by N-terminal BNP levels than in controls. Also, this study found that in the subset of patients younger than 75 years, therapy guided by N-terminal BNP levels reduced the risk of death and hospitalization from heart failure.

### Why the different results in these studies?

Several reasons can be invoked to explain the heterogeneity of results in the studies mentioned above. Most importantly, the small sample sizes in these trials may have prevented differences from reaching statistical significance. Also, the inclusion criteria and methods varied considerably, with different natriuretic peptide targets, doses of medications, and treatment strategies.

### ■ WHAT IS THE CONCLUSION?

Although there are data to suggest that serial natriuretic peptide guidance can reduce the rates of hospitalization and death from heart failure in patients under age 75, there is not enough evidence to recommend routine measurements for the outpatient management of heart failure.

A 2009 focused update to the joint American College of Cardiology and American Heart Association 2005 guidelines<sup>19</sup> concluded that using natriuretic peptide levels to guide heart failure therapy is not well established (class 2b, level of evidence C).

Measurement of natriuretic peptides can be useful in evaluating and risk-stratifying patients presenting in the urgent care setting in whom the clinical diagnosis of heart failure is uncertain. These measurements are to be viewed as part of the total evaluation but are not to be used in isolation to confirm or ex-

Positive results may have been due to better compliance and titration of drugs

clude the presence of heart failure or to monitor the patient for decompensation.

Natriuretic peptide measurement is not a substitute for the information derived from a good history (dyspnea, orthopnea, paroxysmal nocturnal dyspnea) and physical examination (eg, weight, jugular venous distention, crackles, a third heart sound, edema).

The consensus opinion remains that the

favorable outcomes with natriuretic peptide guidance in clinical trials were due to better adherence and continuous up-titration of medications to maximally tolerated target doses of angiotensin-converting enzyme inhibitors and beta-blockers, in addition to closer follow-up of patients in those groups.<sup>20</sup> This can be done without serial natriuretic peptide measurements. ■

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