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EDITORIAL COMMENT

Subcutaneous B-Type Natriuretic Peptide for Treatment of Heart Failure

A Dying Therapy Reborn?*

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"Yet none of them died, they only changed, were always reborn, continually had a new face: only time stood between one face and another."

—Hermann Hesse (1)

Heart failure (HF) is among the leading causes of death and morbidity worldwide (2). The development of efficacious new therapies (such as angiotensin-converting enzyme inhibitors and beta-blockers) for HF has generally been tied to greater understanding of underlying pathophysiology. Therefore it is not surprising that the essential role played by natriuretic peptides in maintaining cardiac homeostasis has prompted significant enthusiasm for the use of natriuretic peptides as therapeutics in HF.

See page 2305

Within the context of breakthroughs in HF research, the discovery of natriuretic peptides was fairly recent. In 1981, de Bold et al. (3) described an extract from the atria of rats that had a potent diuretic effect. Subsequent research led to the characterization of a family of peptides now known as the natriuretic peptides—atrial natriuretic peptide, B-type natriuretic peptide (BNP), and C-type natriuretic peptide—that counterbalance the neurohormonal activation that is a fundamental aspect of the pathophysiology of HF (4). Of these, BNP plays a particularly central role in the homeostatic response to physiological derangements seen in HF via a rapid release in response to left ventricular (LV) pressure or volume overload. Given the association of elevations in BNP (and the biologically inactive amino-terminal fragment N-terminal proBNP) with hemodynamic perturbations, clinical assessment of these biomarkers has led to significant improvements in diagnosis and risk stratification of HF patients (5). On the basis of the favorable hemodynamic consequences of a functioning natriuretic peptide axis, the natural implication has been that replacement with a biologically active synthetic form would be an effective treatment for HF.

Nesiritide (recombinant human BNP) was approved in 2001 by the Food and Drug Administration for the treatment of acute HF, a decision based on studies showing evidence of favorable hemodynamic and clinical effects (6,7). Initial enthusiasm for this therapy led to its widespread use in the United States, not only for acute HF but also for intermittent outpatient treatment of chronic HF. However, there remained a lack of data showing robust evidence of improvement in clinical outcomes, and ensuing meta-analyses of publically available studies suggested potentially adverse effects of nesiritide on survival and renal function (8,9). As detailed in the following text, the subsequent conduct of the FUSION II (Follow-up Serial Infusions of Nesiritide) and ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) studies failed to show substantial clinical benefits from nesiritide therapy in either chronic or acute HF, findings that led to diminished enthusiasm for the potential of BNP as a therapeutic agent in these disorders.

Amidst the current state of uncertainty about the therapeutic role for BNP in HF, this issue of the *Journal* reports an interesting study by Chen et al. (10) assessing the use of subcutaneous (SC) BNP in ambulatory patients with chronic systolic HF. This was a small proof-of-concept randomized double-blind placebo-controlled study involving 40 patients that compared 8 weeks of twice daily SC BNP with placebo. The outcomes of interest were multimodality imaging and laboratory parameters: changes in LV volume and mass via cardiac magnetic resonance imaging (MRI) (primary outcome), and LV filling pressures measured via Doppler echo as well as measures of neurohumoral activation and renal function (secondary outcomes). They found that SC BNP therapy was associated with significant reductions in cardiac MRI measurements of systolic and diastolic volume index and LV mass index but no improvements in LV ejection fraction. The BNP therapy resulted in echocardiographic evidence of improved LV filling pressures as demonstrated by reductions of the E/e' ratio and left atrial volume index. Significant improvements were noted in the Minnesota Living with Heart Failure score but not in the 6-min walk test. Renal function did not improve, as determined by iothalamate clearance calculated glomerular filtration rate or plasma cystatin C levels. Importantly, considering the small size of this study, 3 patients in the BNP arm (3 of 24) developed clinically significant hypotension and were excluded from the analysis.

Are these findings enough to resuscitate the waning enthusiasm for the use of synthetic BNP in the treatment of

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HF? The results of the current study must be viewed in the context of results from 2 large trials—FUSION II and ASCEND-HF—testing the use of intravenous (IV) BNP in chronic and acute HF, respectively. The FUSION II trial was a randomized, double-blind, placebo-controlled trial of outpatient serial nesiritide infusion in 911 patients with stage C/D chronic HF (11). The drug was administered for 4 to 6 h once or twice weekly for 12 weeks. The investigators found no differences in clinical outcomes between the nesiritide and placebo groups but a greater incidence of hypotension with nesiritide. They concluded that there was "no indication for intermittent outpatient nesiritide infusions in patients with stage C/D HF." The ASCEND-HF trial was the largest clinical trial ever performed in acute HF, randomizing 7,141 patients to either IV nesiritide or placebo for 24 to 168 h (12). The primary results of the ASCEND trial showed no reduction in the clinical endpoint of repeat hospital stay for HF or death from any cause. Once again, there was an excess of hypotension associated with nesiritide use. The ASCEND-HF authors concluded, in terms similar to those used by the FUSION II investigators, "nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure."

Therefore, a critical question to be addressed with regard to the current study is: are there significant differences between essential elements of the previous large-scale studies and the current study to warrant additional investigation of BNP as a therapy for HF? A comparison of key baseline characteristics, dosing regimens, and side effects between the current study and ASCEND-HF and FUSION II studies is shown in Table 1. Because the ASCEND-HF trial tested short-term infusion of nesiritide in acute HF, extrapolating these findings to ambulatory HF patients is of uncertain validity, given the differences in pathophysiology between these disease states. A comparison with the FUSION II study is more relevant: both included patients with stable chronic HF who were treated with BNP for similar periods of time (12 and 8 weeks, respectively). With regard to patient population, the patients enrolled in the FUSION II study had more severe HF (New York Heart Association [NYHA] functional class III to IV with recent HF hospital stay, vs. NYHA functional class II to III), although there was some degree of overlap, with almost one-half of the patients in the current study (18 of 40) classified as having NYHA functional class III symptoms. Perhaps most importantly, in the FUSION II trial BNP was administered intravenously once or twice weekly rather than subcutaneously twice daily. The pharmacokinetic and clinical ramifications of daily SC versus intermittent IV therapy are unclear. Certainly, for treatment of a chronic condition such as HF, daily dosing would seem to be the most rational approach if feasible; it seems unlikely that other proven HF therapies such as angiotensin-converting enzyme inhibitors or beta-blockers would be effective if given as a large dose 1 to 2 times/week rather than on a daily basis. The concept of SC dosing of BNP thus opens the door to daily use in ambulatory patients, which potentially could allow for lower doses and lessen vasoactive side effects such as hypotension. Prior data from the same investigative group have suggested that low doses of BNP given by IV infusion (approximately 25% to 50% of total daily dose used in current study) might lead to favorable neurohormonal and anti-

Table 1 Select Baseline Characteristics, Rates of Hypotension, and Nesiritide Regimen According to Key Previous Trials and Current Study

	ASCEND-HF	FUSION II	Chronic SC BNP
Trial dates	2007–2010	2004–2006	2003–2008
Number of patients	7,141	911	40
Key inclusion criteria	Diagnosis of ADHF along with clinical and objective measured of HF	≥2 recent HF hospital stays, LVEF <40%, and NYHA III–IV, Cr clearance <60 ml/min	LVEF <35% for at least 2 yrs and NYHA II–III
Male	66*	71	70
Age	67	65	66
NYHA functional class II	N/A	None	55
NYHA functional class III	N/A	47	45
NYHA functional class IV	N/A	53	None
Beta-blocker	58	65	100
ACE inhibitor or ARB	61	59	95
Aldosterone blocker	28	37	20
Loop diuretic	95	75	73
BNP regimen	2-μg/kg bolus followed by 0.01 μg/kg/min	2-μg/kg bolus followed by 0.01 μg/kg/min	10 μg/kg
Route of administration	IV	IV	SC
Duration	24 h–7 days	1–2/week for 12 weeks	2/day for 8 weeks
Incidence of clinically significant hypotension	7	11.7	12.5
Clinicaltrials.gov identifier	NCT00475852	NCT00091520	NCT00252187

Values are absolute values, percentages and means, unless otherwise stated. Values have been rounded to the closest integer. *Median age.

ACE = angiotensin-converting enzyme; ADHF = acute decompensated heart failure; ARB = angiotensin receptor blocker; ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial; BNP = B-type natriuretic peptide; Cr = creatinine; FUSION II = Follow-up Serial Infusions of Nesiritide trial; IV = intravenous; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; SC = subcutaneous.

remodeling effects without causing hypotension in the setting of acute myocardial infarction (13). Whether such a low dose regimen given subcutaneously would have biologic effects and avoid the hypotension seen in the current study is uncertain.

An additional critical question relates to the conundrum of drug development in HF generally: how reliable are surrogate variables in early phase studies for predicting clinical efficacy in larger trials? The authors present compelling data in support of favorable LV remodeling with SC BNP therapy as measured by cardiac MRI. Ventricular remodeling has been shown to be central in the progression of chronic HF, and noninvasive techniques to measure this process have demonstrated strong correlations with subsequent clinical outcomes (14). These findings add credibility to the notion that SC BNP therapy might have beneficial cardiovascular effects in chronic HF that deserve further exploration. As always, the history of drug development in HF must sound a cautionary note, with multiple examples of apparently promising approaches that did not pan out in larger trials (including the initial development of nesiritide itself) (15).

Where do we go from here? As the authors recognize, the ongoing development of the concept of SC BNP for ambulatory HF must grapple with the issue of hypotension, and ideally a dose or regimen could be identified that would maintain the anti-fibrotic and remodeling effects without causing hypotension. Future trials will be needed to refine dosing and patient selection as well as to provide more definitive evidence for clinical efficacy. In the novel by Herman Hesse, Siddhartha experiences various events along his journey toward enlightenment, reinventing himself in the process. Whether BNP therapy can be successfully reincarnated as an "enlightened" therapy for HF therapy remains to be seen, and further investigation will determine whether SC administration of BNP might represent the "middle way" to successful HF therapy.

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