JACC: HEART FAILURE
VOL. 4, NO. 7, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.02.018

EDITORIAL COMMENT

# Brain Natriuretic Peptide Treatment and Heart Failure Prevention

## Reliving the Mistakes of the Past or Charting a New Course for the Future?*

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*"What's past is prologue"*
—William Shakespeare,
The Tempest (1)

Because of the global burden of heart failure, there is substantial interest in the concept of heart failure prevention, specifically of therapies that prevent the progression from asymptomatic at-risk patients (stage A) or asymptomatic patients with structural heart disease (stage B) to symptomatic heart failure (stages C and D). The progression from hypertension (the most common risk factor) to symptomatic heart failure with preserved ejection fraction (HFpEF) is characterized by progressive changes in left ventricular (LV) relaxation and filling, structural remodeling, altered geometry, and changes in ventricular compliance (2). Asymptomatic abnormalities of diastolic filling or preclinical diastolic dysfunction (PDD) are known precursors of HFpEF and are readily detectable by echocardiography. Natriuretic peptides play a critical role in the maintenance of cardio-renal homeostasis and promote natriuresis, inhibit the renin-angiotensin-aldosterone system (RAAS), and lead to vasodilation through activation of cyclic guanosine monophosphate (cGMP) (3). Because of these effects, therapy with exogenous natriuretic peptides is inherently attractive as a therapeutic approach in heart failure. This leads to the natural hypothesis that augmenting natriuretic peptide signaling in patients with PDD may prevent progression to symptomatic HFpEF.

Extending previous work by the group on the role of subcutaneous brain natriuretic peptide (SQ BNP) therapy in heart failure (4,5), in this issue of *JACC: Heart Failure*, Wan et al. (6) report a proof-of-concept study to determine if previously described acute improvements in diastolic function are maintained with longer term therapy (7). The study recruited 49 asymptomatic patients with echocardiographic evidence of moderate to severe diastolic dysfunction, without clinical evidence of heart failure, and an EF of >50%. Forty-one patients were eventually randomized in a 2:1 manner to receive SQ

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BNP or placebo for 12 weeks. Compared with placebo, in subjects randomized to SQ BNP, there was significant improvement in LV diastolic function indexes and an increased urine flow response to acute volume expansion. There was no evidence of tachyphylaxis, and adverse events such as hypotension were similar in the 2 treatment groups. These data suggest that SQ BNP therapy can augment natriuretic peptide signaling and improve measures of diastolic function in this patient population, and that this augmentation is not diminished by longer term therapy. Because of these study results, does SQ BNP warrant further large-scale trials in patients with preclinical diastolic dysfunction at risk for developing HFpEF?

Several relevant questions arise as we consider this issue. First, despite the inherent attractiveness of treating heart failure with natriuretic peptides, it must be acknowledged that to date this strategy has not been shown to improve clinical outcomes in adequately powered trials. Although nesiritide

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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(recombinant human BNP) was approved for the treatment of acute decompensated heart failure, the subsequent ASCEND-HF (A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure) trial (8) did not identify any clinically important benefits. A smaller trial from the National Heart, Lung, and Blood Institute Heart Failure Network (ROSE [Renal Optimization Strategies Evaluation] trial) (9) did not demonstrate improvements with lower doses of nesiritide in hospitalized patients with acute heart failure who were at risk for diuretic resistance. Long-term therapy with intermittent nesiritide infusion (FUSION-2 [Second Follow-Up Serial Infusions of Nesiritide]) (10) in high-risk patients also did not show benefit. Furthermore, all 3 studies suggested nesiritide treatment was associated with a higher risk of hypotension. Although these results certainly do not preclude the efficacy of BNP therapy as a heart failure therapeutic strategy, they do suggest the need for caution, especially when considering long-term administration. Importantly, there are key differences between these previous studies and the current evaluation of SQ BNP. A low-dose, long-term treatment subcutaneous approach may mitigate the risk of hypotension seen with intravenous therapy, and use in earlier stage patients could be more effective than in patients with advanced symptomatic disease (as in FUSION-2, ASCEND-HF, and ROSE). Whether these potential advantages of SQ BNP as a prevention strategy for earlier stage disease would translate into efficacy in larger studies is unknown.

An additional issue in considering the clinical importance of the current data relates to the mathematics of heart failure prevention as a concept. PDD is present in a large percentage of the adult population (25% to 33%) (11), or >60 million Americans. Although PDD is a clear precursor for HFpEF, the rate of transition from PDD to symptomatic heart failure is relatively low (2% to 3% per year). Thus, even if SQ BNP as studied in the current trial was highly safe and efficacious in preventing the development of heart failure, the prospect of treating millions of asymptomatic persons with twice daily injections to prevent the development of symptomatic heart failure is both logistically and economically daunting.

Assuming that augmenting natriuretic peptide signaling is an effective strategy for HFpEF prevention, might other less direct methods be more practical? The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortalilty and morbidity in Heart Failure) trial demonstrated that dual inhibition of the RAAS and the neprilysin pathways improved outcomes in heart failure with reduced ejection fraction patients (12), and is currently being tested in symptomatic HFpEF in the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) study (NCT01920711). Among many other biologic effects, neprilysin inhibition augments cGMP signaling, presumably by inhibiting the breakdown of BNP (13). Although it is difficult to compare directly, the study by Wan et al. also demonstrated urinary and plasma cGMP augmentation with SQ BNP, which is encouraging because enhancement of the cGMP pathway is a potential target in the treatment of HFpEF (3). Although the logistics of heart failure prevention remain challenging, the success of "biomarker-guided" prevention strategies for heart failure, as demonstrated in the STOP-HF (St Vincent's Screening to Prevent Heart Failure) (14) and PONTIAC (NT-proBNP Selected Prevention of Cardiac Events in a Population of Diabetic Patients Without a History of Cardiac Disease) (15) studies suggest that intervention in at-risk patients is feasible if sufficient risk can be identified, and effective and safe interventions can be deployed.

"What's past is prologue" was used by Antonio in Shakespeare's *The Tempest* to state that the past has set the stage for the future. The ongoing march toward effective prevention strategies for heart failure will hopefully set the stage for reducing the burden of morbidity and mortality for this condition.

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**KEY WORDS** BNP, heart failure with preserved ejection fraction, HFpEF, natriuretic peptide treatment, prevention