Almost 3 decades ago, we witnessed the discovery of the natriuretic peptides and the role of the heart as an endocrine organ in which peptides of cardiovascular origin emerged as a humoral link between the heart and the kidney in cardiorenal homeostasis. In the United States, one such natriuretic peptide, B-type natriuretic peptide (BNP), was approved by the US Food and Drug Administration in 2001 as a drug (nesiritide) for the treatment of acute decompensated heart failure (ADHF). The rationale for the use of BNP as a cardiovascular therapy was in response to laboratory-based research and a series of clinical trials. What emerged was a theme that BNP was an endogenous ligand for the natriuretic peptide-A receptor that is linked to particulate guanylyl cyclase and the second messenger 3',5'-cyclic guanosine monophosphate (cGMP). After receptor activation, the biological actions of BNP include vasodilatation, diuresis and natriuresis, positive lusitropism, inhibition of the renin-angiotensin-aldosterone system, suppression of the myocardial hypertrophy response to pressure overload, and attenuation of myocardial fibrosis.

Although a hallmark of acute and chronic congestive heart failure (CHF) is an increased plasma level of BNP, there are functional derangements in the BNP/cGMP signaling pathway that provide additional rationale for the exogenous administration of BNP or nesiritide to treat CHF. The 2 most compelling abnormalities include increased production of less biologically active BNP forms and increased renal resistance to BNP in severe experimental CHF.

Since the initial report in 1991 by Yoshimura et al and after several clinical trials over the past decade, the consensus has been that human recombinant BNP (nesiritide) in patients with ADHF improved cardiovascular hemodynamics and/or renal function in association with improved symptoms of HF. Moreover, some investigators reported that nesiritide therapy was safer than the use of positive inotropic drugs in the setting of ADHF. These results increased optimism and expectations that this novel peptide therapeutic strategy was a significant addition to the armamentarium of ADHF therapy. The seminal clinical trial VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) established the superiority of nesiritide over placebo or nitroglycerin in reducing pulmonary capillary wedge pressure and dyspnea in patients with ADHF. Indeed, it was the VMAC trial that eventually resulted in US Food and Drug Administration approval of nesiritide for the treatment of ADHF.

Almost overnight, the enthusiasm for the use of nesiritide as a treatment was dramatically tempered. In 2005, a meta-analysis of 3 clinical trials was published that compared nesiritide with noninotrope control therapy in ADHF and suggested that nesiritide may be associated with increased short-term risk of death. A second meta-analysis conducted by the same group of investigators also advanced the possibility of worsening renal function due to nesiritide administration. The results of these meta-analyses led to a rapid decline in nesiritide use and have impacted the clinical practice of ADHF management.

How do we currently put all of these studies into perspective? First, we are helped by a recent meta-analysis of 7 large, randomized, controlled trials. In addition, there are results obtained from a large, multicenter, retrospective, industry-supported database of inpatient CHF patients (Acutely Decompensated Heart Failure National Registry, or ADHERE, database). Both have failed to find an increase in immediate or delayed death with nesiritide. Moreover, several other studies published since 2005 and new findings from ADHERE have not shown worsening renal function with nesiritide therapy. All published meta-analyses, clinical studies, and observational registries, however, have emphasized a need for large-scale randomized controlled trials with sufficient statistical power to evaluate mortality and morbidity rates with nesiritide. Therefore, the controversy surrounding BNP- or nesiritide-associated mortality and renal dysfunction remains unsolved and underscores the importance of the recently initiated large international, multicenter, placebo-controlled, double-blind ASCEND-HF trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) in 7000 patients with ADHF that was designed to answer safety and efficacy questions.

Beginning in 2004, the proof-of-concept FUSION I trial (Follow-Up Serial Infusions of Nesiritide) investigated nesiritide as a chronic intermittent intravenous outpatient therapy for CHF. What the investigators in the FUSION I trial observed was a neutral effect of nesiritide in patients with chronic CHF, with no difference in rates of adverse events for nesiritide compared with standard care. In a prespecified subgroup analysis of high-risk patients, however, the FUSION I investigators observed a lower rate of all-cause death.

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and hospitalization and more days alive and out of the hospital for patients randomized to nesiritide than for patients treated with standard care. A separate analysis also demonstrated a similar effect in a subgroup of patients with reduced glomerular filtration rate. This pilot study set the stage for the larger FUSION II trial that is reported by Yancy and coworkers\(^24\) in this inaugural issue of Circulation: Heart Failure.

What does FUSION II tell us? Yancy et al\(^24\) report the safety and efficacy of outpatient treatment with nesiritide in patients with chronic decompensated CHF. The trial was designed as a randomized, double-blind, placebo-controlled trial of outpatient serial nesiritide infusion in patients with American College of Cardiology/American Heart Association stage C/D CHF. A notable design feature of the trial was the dose of nesiritide that was administered, which was a 2 \(\mu g/kg\) bolus with 0.01 \(\mu g/kg\cdot min\) infusion administered for 4 to 6 hours once or twice weekly for 12 weeks. The primary end point was a time to all-cause death or cardiovascular or renal hospitalization at 12 weeks, with 911 subjects randomized in the trial. The investigators reported no differences in the primary end point between the nesiritide and placebo groups. Furthermore, there was no statistically significant difference between groups in any of the secondary end points. Rates of adverse events were similar in both groups, but nesiritide was associated with more hypotension and less predefined worsening renal function. The authors\(^24\) concluded that serial outpatient infusion of nesiritide did not provide a demonstrable clinical benefit or augmented risk over the intensive outpatient management of patients with advanced stage C/D heart failure. An additional observation was an unexpectedly low event rate as compared with results from FUSION I, which led the investigators to conclude that the FUSION II trial was underpowered to evaluate the effect of nesiritide on the primary end point.

What, then, is the take-home message from the FUSION II trial about the ongoing use of nesiritide? The process of integrating what we have learned in the laboratory with the natriuretic peptides and ongoing clinical trials, including FUSION II, raises several questions. These questions relate to both the short- and long-term use of nesiritide in the context of CHF. What are the issues? As discussed below, we believe that they relate to dose, duration of infusion, and frequency of peptide administration if nesiritide is used long-term, which to date has not been demonstrated to be of value. Also, the patient population who would best benefit from therapy remains unclear.

A typical feature of nesiritide administration is a hypotensive response, especially using a bolus of nesiritide followed by an infusion, as was the case in the FUSION II trial. Indeed, the one greater adverse event in FUSION II with nesiritide compared with placebo was more hypotension. Such hypotension could possibly have offset any favorable sympatho-inhibiting actions of nesiritide and reduced renal perfusion pressure, thereby limiting the full favorable actions often reported in animal models and in human subjects without CHF. Indeed, administering doses of nesiritide to humans with CHF that do not induce hypotension uniquely suppresses sympathetic nerve activity.\(^25\) Further, 1 retrospective and 2 prospective clinical trials with low-dose BNP or with BNP without the bolus have demonstrated renoprotection.\(^26–28\) Therefore, no bolus and/or low-dose nesiritide could be advantageous. Interestingly, less predefined worsening of renal function was observed in the FUSION II trial, which may indicate that nesiritide had a renoprotective effect despite induced hypotension, and it is therefore conceivable that had no bolus and/or a lower dose been used, a nesiritide benefit could have been even more obvious.

Where do we go from here? As we learn to better understand the use of endogenous peptides like BNP in cardiorenal therapeutics, we conclude that the clinical development of nesiritide remains incomplete. We therefore propose a series of actions that, in our opinion, are needed. They are as follows; (1) The ASCEND-HF Trial in patients with ADHF, which will address the safety and efficacy of nesiritide, needs to push ahead. (2) Increasing evidence suggests that low-dose nesiritide without the hypotensive effects of nesiritide may have renoprotective and enhancing actions; this should be tested with a randomized clinical trial that uses low-dose nesiritide in patients with ADHF. (3) New studies should be conducted to identify the exact patient population (CHF stage and etiology) who may benefit from nesiritide therapy. This recognizes the importance of individualizing therapy for a disease as complex as ADHF. Investigations should perhaps target hypertensive patients or those with preserved ejection fraction, recognizing the vasodilating and proslitropic properties of nesiritide. (4) Important laboratory-based studies have demonstrated the upregulation of phosphodiesterase V activity in the heart and kidney in CHF, which may limit the favorable actions of the natriuretic peptides. Supporting studies need to be conducted in humans to define the synergy between phosphodiesterase V inhibition and BNP.\(^29,30\)

In summary, the idea that we can take a peptide that is synthesized in the heart and that possesses intrinsic cardioprotective and enhancing actions and transform it into an effective drug for the treatment of CHF is exciting. The FUSION II investigators are to be congratulated for providing us with important new knowledge about nesiritide in a large clinical trial that helps point us in new directions. However, we have not answered all of the important questions in the clinical development of nesiritide, and thus, we cannot realize its potential in the treatment of CHF.

**Sources of Funding**

This work was supported by grants from the Mayo Foundation and the National Heart, Lung, and Blood Institute (PO1 HL76611, RO1 HL36634, and RO1 HL83231).

**Disclosures**

Dr Burnett is Chair of the Scientific Advisory Board of Nile Therapeutics and has received research grant support from Scios and CoGenesys. The Mayo Clinic has licensed designer natriuretic peptides to Nile Therapeutics and Anexon.

**References**


Key Words: Editorials • heart failure • natriuretic peptides