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Recombinant Human Brain Natriuretic Factor (rhBNP) Therapy for the Treatment of Acute Decompensated Heart Failure

By WARREN T. BALL, MD, MSC, and GORDON MOE, MD, FRCPC

Heart failure (HF) is associated with significant morbidity and mortality. Despite advances in the treatment of chronic HF, few, if any, novel therapies have been developed that successfully alleviate symptoms or improve outcomes in patients with acute decompensated HF (ADHF). Renal dysfunction not only affects the efficacy of therapy in patients with HF, it also correlates directly with prognosis. Recombinant human B-type or brain natriuretic peptide (rhBNP) therapy is a novel agent shown to reduce pulmonary capillary wedge pressure (PCWP) and dyspnea in patients with ADHF. As with other agents tested in ADHF, no trials have yet been designed and/or adequately powered to assess its effects on clinical outcomes. Recent selected pooled analyses have raised concerns regarding the increased incidence of renal failure and mortality associated with this therapy. This issue of *Cardiology Rounds* critically reviews the evidence for rhBNP therapy in patients with ADHF, including the literature suggesting a possible worsening of renal function and mortality in patients treated with this novel agent.

Heart failure (HF) is associated with significant morbidity and mortality. In the United States, HF accounted for >999,000 hospital admissions in 2000;[1] up to 20% of these patients were readmitted within 30 days and 50% within 6 months.[2] In Canada, there are >105,000 admissions for HF annually,[3] with a 53% readmission rate at one year.[4] In-hospital mortality from HF is as high as 5%-7%, with a 60-day event rate of >30%. While these numbers are parallel to, or even exceed those for acute coronary syndromes (ACS), clinical trial data and resultant advances in the treatment of ADHF lag far behind that of ACS. New therapies to reduce symptoms and improve outcomes in these patients are, therefore, urgently needed.

Current therapy for ADHF

The goals of therapy for patients with ADHF include improving: symptoms (dyspnea, edema); hemodynamics (increasing cardiac output and reducing PCWP); laboratory parameters (serum creatinine, brain natriuretic peptide); and clinical course (length of stay, hospitalizations and mortality).

Standard treatment for ADHF in Canada currently includes diuretics, afterload reducing agents (nitroglycerin and nitroprusside), renal perfusion support (dopamine), positive inotropic support agents (dopamine, dobutamine, and milrinone), as well as ventilatory support (bilevel positive airway pressure [BIPAP] and continuous positive airway pressure [CPAP]).

Diuretics are the mainstay of treatment for ADHF, with >98.6% of patients receiving them.[5] It has been suggested, however, that they may have deleterious effects through activation of the neurohormonal system, reducing the glomerular filtration rate, and potentially increasing mortality.[6,7] The debate remains about whether diuretic use is simply a marker or a mechanism for adverse outcomes.

The use of positive inotropic agents, (eg, milrinone and dobutamine) has also been associated with increased mortality in patients with ADHF.[8,9] Recently, levosimendan, a calcium sensitizer,

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was reported to have long-term benefits in the management of patients with HF exacerbations[10] and appeared to be superior to dobutamine. Despite these promising results, it should be noted that if dobutamine (the comparator) is harmful to patients with ADHF, then the true benefit of levosimendan remains to be established.

The cardiorenal syndrome

An important aspect of the pathophysiology of HF is the cardiorenal axis. Renal function, as measured by serum creatinine or calculated creatinine clearance, directly affects the kidney's response to diuretics used to treat HF. Therefore, renal function is also a strong prognostic indicator in this patient population.[11,12] Worsening renal function in HF patients during their hospitalization portends a very poor prognosis. Indeed, an increase in serum creatinine of just 0.1 mg/dL is an independent predictor of poor prognosis. Up to 70% of patients admitted with ADHF experience a creatinine increase of >0.1mg/dL, which has been shown to be an independent predictor of poor outcome.[13] Interestingly, worsening renal function during treatment occurs with equal frequency in patients with HF and severe systolic dysfunction and, in those with preserved ejection fractions, it portends a similarly poor prognosis.

Declining renal function can also be an obstacle to the institution of evidence-based therapies that improve clinical outcomes in HF patients, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, and aldosterone blockers. Withdrawal of these therapies may, therefore, be associated with a poor prognosis.[14]

Physiological effects of BNP

B-type natriuretic peptide (BNP) is a potent vasodilator that promptly and consistently lowers cardiac filling pressures.[15] It has also been demonstrated to exert multiple potentially beneficial actions on the kidney, including inhibition of renin synthesis, vasodilation of afferent arterioles, and vasoconstriction of efferent arterioles in the glomerulus, and decreased sodium reabsorption in the proximal tubule and collecting duct. BNP has also been shown to reduce systemic concentrations of norepinephrine, aldosterone, and endothelin-1.[16] Unfortunately, clinical studies have failed to convincingly demonstrate that exogenous BNP administered as rhBNP improves renal function, facilitates natriuresis, or improves diuresis in the setting of ADHF.[17,18] However, unlike the positive inotropic agents, rhBNP does not appear to increase the risk for arrhythmias.[19]

These properties of BNP make it an attractive potential agent in the treatment of ADHF. Nesiritide is a recombinant formulation of BNP that is identical to the endogenous hormone released from the cardiac ventricle in response to increases in wall stress, hypertrophy, and volume overload. Nesiritide was designed for therapeutic parenteral administration in patients with ADHF.

VMAC efficacy trial

The Vasodilators in the Management of Acute Congestive heart failure (VMAC) Trial was conducted from 1999-2000 and, ultimately, was responsible for the Food and Drug Administration's (FDA) approval of nesiritide to treat patients admitted with ADHF. Following a number of earlier clinical studies, it was the first large multicentre, randomized, double-blind trial in this patient population to evaluate the hemodynamic and clinical effects of nesiritide versus an intravenous vasodilating agent. The trial enrolled 498 patients admitted to hospital with HF and dyspnea at rest. Intravenous nesiritide (n = 204), intravenous nitroglycerin (n = 143), or placebo (n = 142) was added to standard medical therapy for 3 hours, followed by nesiritide (n = 278) or nitroglycerin (n = 216), added to standard therapy for 24 hours. Pulmonary artery catheterization was performed in 246 patients (at the discretion of the treating physician).

Decompensated HF was defined as: acute or chronic HF, gradual worsening of chronic HF, and new-onset HF. To be randomized, patients had to require hospitalization and intravenous therapy, have a PCWP >20 mm Hg, and 2 of the following: jugular venous distention, paroxysmal nocturnal dyspnea or orthopnea, mesenteric congestion, or findings consistent with HF on chest x-ray. The treating physician was permitted to use inotropic support. HF in the setting of active ischemia, cardiac arrhythmia, and renal failure was included. The major exclusion criteria were requirements for endotrachael intubation, systolic blood pressure <90 mm Hg, cardiogenic shock, or other contraindications to receiving placebo therapy for the initial 3 hours of randomization.

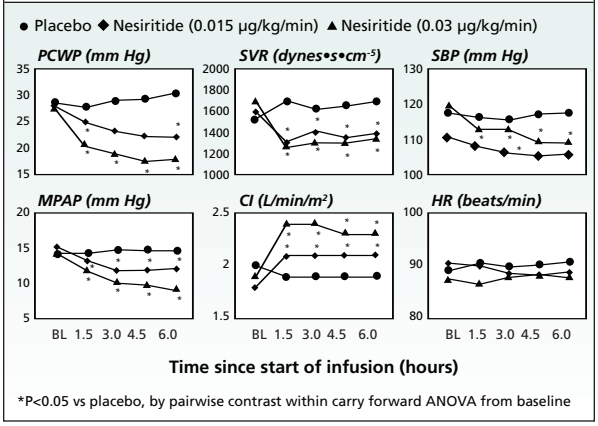
The primary endpoints were the absolute change in PCWP at 3 hours and the patient's subjective evaluation of dyspnea. While all patients had New York Heart Association (NYHA) class IV symptoms at the time of enrollment, 84% of patients had chronic HF classified as NYHA class III or IV prior to decompensation. The majority of patients (85%) had HF with an ejection fraction <40%. At baseline, the nitroglycerin-treated group of patients had fewer patients receiving dopamine or dobutamine. Results are shown in Figure 1.

The principal findings of VMAC were:

- Nesiritide had a slightly greater effect on reducing PCWP at 3 hours than nitroglycerin (both agents were better than placebo)
- Nesiritide reduced dyspnea at 3 hours compared to placebo (although it was equivalent to nitroglycerin).

It is possible that the hemodynamic differences between nesiritide and nitroglycerin might have been explained, in part, by the nitroglycerin dose administered

Figure 1: Hemodynamic effects of nesiritide (n=127)[15]



PCWP = pulmonary capillary wedge pressure; HR = heart rate; SVR = systemic vascular resistance; SBP = systolic blood pressure; CI = cardiac index; MPAP = mean pulmonary artery pressure

(42 µg/min). Symptomatic hypotension occurred in 5% of the nitroglycerin group and 4% of the nesiritide group.

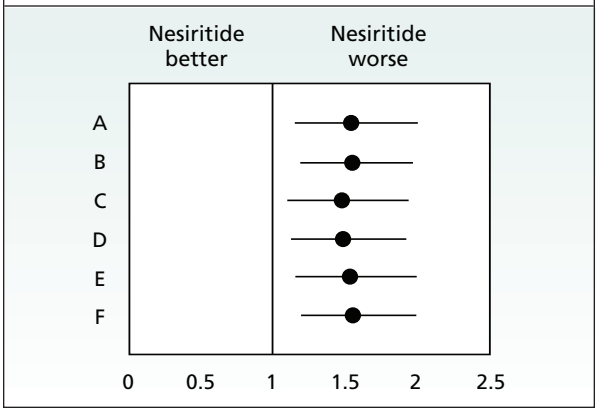
Nesiritide and renal function

Possible concerns have been brought forward regarding worsening renal function among patients taking nesiritide since the 2001 FDA Cardiovascular and Renal Drugs Advisory Committee meeting, at which nesiritide was approved.[20] In the VMAC trial, the incidence of patients with a rise in creatinine >50 mmol/L above baseline at 5 days was 7% in the nitroglycerin group and 8% in the nesiritide group, but this rose to 21% and 28% respectively, by 30 days. Of note, there was no difference in net diuresis between the nesiritide and nitroglycerin groups during the first 24-hours of therapy. In addition, a double-blind, randomized, placebo-controlled crossover study to assess the effect of nesiritide on renal function failed to demonstrate a difference in urine output, renal plasma flow, or glomerular filtration rate.[13]

Sackner-Bernstein and colleagues[21] recently conducted a pooled analysis examining the risk of renal failure in patients treated with nesiritide for ADHF. Trials chosen for analysis included those that met "stringent criteria," ie, randomized, double-blind, parallel-group studies with complete data for the outcome of interest. The data from the 5 clinical trials meeting these criteria were obtained directly from FDA reviews and the sponsor's own briefing documents. A 40% to 50% increased relative risk for a rise in creatinine to >50 mmol/L was observed in patients treated with nesiritide compared to controls; this trend was seen in patients receiving both inotropic and noninotropic (including nitroglycerin) therapy, and at both the approved doses of nesiritide and all other doses studied (Figure 2). In total, creatinine increases of this magnitude were seen in 21% of patients treated with nesiritide and in 15% of control patients. In addition, significantly more patients in the nesiritide-treatment group required a "medical intervention" for worsening renal function as

Figure 2: Relative risk of worsening heart failure with nesiritide, evaluating the effects relative to noninotrope and inotrope-based control therapies.

A: Nesiritide ≤0.03 µg•kg^{-1}•min^{-1} vs noninotrope-based controls;
B: Nesiritide ≤0.03 µg•kg^{-1}•min^{-1} vs all control therapies, including inotropes;
C: Nesiritide ≤0.015 µg•kg^{-1}•min^{-1} vs noninotrope-based controls;
D: Nesiritide ≤0.015 µg•kg^{-1}•min^{-1} vs all control therapies, including inotropes;
E: Nesiritide ≤0.06 µg•kg^{-1}•min^{-1} vs noninotrope-based controls;
F: Nesiritide ≤0.06 µg•kg^{-1}•min^{-1} vs all control therapies, including inotropes.[21]



compared to the control group (11.1% vs 4.2%). However, there was no difference in the requirement for dialysis (2.5% vs 2.2%), although the number of events was small (14 and 8, respectively).

While provocative, this analysis had a number of limitations, including the use of an arbitrary definition of worsening renal function (albeit the same one utilized by the FDA review panel), the unavailability of primary data, the inability to identify and adjust for baseline differences in treatment groups, and limited information on events or interventions that occurred after the treatment period. Furthermore, 4 of the 5 trials included in the analysis utilized doses higher than the U.S. recommended initiation dose of 2 µg/kg bolus, followed by a 0.01 µg/kg/min continuous intravenous infusion. At FDA recommended doses, the odds ratio (OR) for an increased serum creatinine to >0.5 mg/dL was 1.35.[22]

Increases in creatinine do not necessarily portend a poor prognosis, as experience with ACE inhibitors attests. Furthermore, in this decompensated patient population, multiple other confounders (eg, hypotension and overdiuresis) may be responsible for the increased serum creatinine. Nevertheless, there is no convincing data suggesting that nesiritide improves renal function or increases diuresis in patients with ADHF.

Nesiritide and mortality

None of the existing clinical trials with nesiritide have been powered to definitively assess survival; nevertheless, there have been concerns about increased mortality in patients treated with nesiritide. In the VMAC trial, although not statistically significant, the 30-day mortality

was 8.6% in the nesiritide group and 5.5% in the nitroglycerin group. At 6 months, the mortality rates were 25.1% and 20.8%, respectively.

Conflicting results were reported in the pooled- and meta-analyses on mortality and nesiritide use. A meta-analysis of 6 trials did not demonstrate increased mortality in nesiritide-treated patients relative to controls.[23] Adjusting for the baseline differences in mortality risk predictors essentially eliminated the trend toward increased mortality in the unadjusted analyses. However, a more recent pooled analysis used criteria that were more "stringent" to select trials for inclusion in the analysis. The trials selected were randomized, double-blind studies of single-infusion nesiritide therapy in hospitalized patients, with at least a 30-day follow-up, compared with a control therapy that did not mandate positive inotropic agents.[24] However, only three clinical trials met these criteria. A non-significant trend towards increased 30-day crude mortality with nesiritide was found (relative risk 1.74; p=0.059; Figure 3). Each of the individual studies was not powered to assess mortality and did not collect information regarding the use of additional medications or procedures through the 30-day follow-up period that could have been potential confounders. Nevertheless, this analysis serves as an impetus for larger-scale, adequately powered trials to assess the impact of rhBNP on clinical outcomes in patients with ADHF.

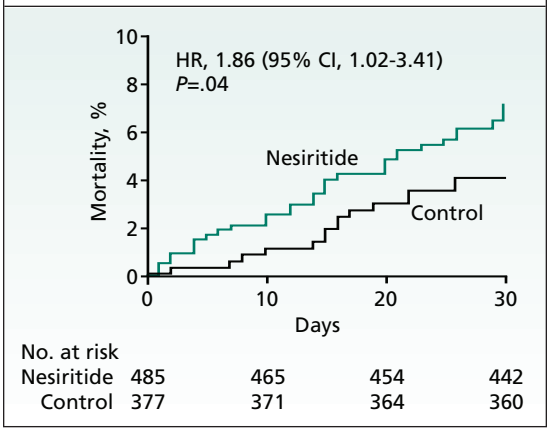
Insights from the ADHERE Registry

Given the significance of HF as a public health problem and the burden of morbidity and mortality associated with this condition, a large national registry was created in the USA to collect data on the clinical characteristics, physician practice and treatment patterns, and outcomes in patients hospitalized with HF. Encompassing 286 hospitals and collecting data since 2001, the Acute Decompensated Heart Failure National Registry (ADHERE) has produced some interesting data. Since FDA approval of nesiritide in 2001, the utilization of this agent in the management of patients treated in hospital for ADHF has increased dramatically. The number of patients treated with nesiritide increased from approximately 7% in 2001 to 19% in 2004. In contrast, the use of nitroglycerin has fallen from 11% to 8% over the same period.

Current recommendations

Given the large number of patients who may potentially benefit from novel therapies in the management of decompensated HF and, conversely, the degree of harm that could be done should a new therapy be associated with adverse outcomes, how are clinicians to view this conflicting evidence?

Figure 3: Kaplan-Meier curves of 30-day mortality associated with control and nesiritide therapies based on NSGET, VMAC, and PROACTION Studies.[24]



HR = hazard ratio

As a result of the controversy surrounding the potential increased risks of renal failure and mortality with nesiritide use, a committee, chaired by Dr. Eugene Braunwald was convened to make recommendations to clinicians regarding the use of nesiritide and to the sponsor regarding the direction of future investigations. It was recommended that:

- The use of nesiritide should be limited to patients with ADHF and dyspnea at rest.
- Physicians should consider the efficacy, possible risk, and availability of alternative HF therapies.
- Nesiritide should not be used in place of diuretics.
- Given limited scientific data, nesiritide should be limited to in-patient use and not be used to improve renal function or enhance diuresis.
- Large, prospective, randomized clinical trials for outcome and safety data should continue.

Summary

ADHF carries significant morbidity and mortality. As a result, novel therapies targeting both symptoms and cardiovascular outcomes are greatly needed. Renal dysfunction not only affects the efficacy of therapy in chronic HF patients, it also directly correlates with prognosis. Nesiritide has been shown to reduce PCWP and dyspnea in patients with ADHF. Although no trials have been powered to adequately assess adverse events, concern has arisen regarding nesiritide-associated renal failure and mortality. As a result, clinicians should carefully consider nesiritide against other existing therapies in the management of ADHF, both in terms of demonstrated efficacy and the potential clinical significance of worsening renal failure and mortality. Ongoing large scale, randomized, double-blind clinical trials, adequately powered for adverse events, will hopefully elucidate the role of rhBNP in patients with ADHF.

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Abstracts of Interest

Standard dose nesiritide does not enhance diuresis nor alter renal function in decompensated heart failure

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Many clinicians believe recombinant brain natriuretic peptide (nesiritide, N) enhances furosemide diuresis and prevents renal dysfunction (RD). A recent meta-analysis of clinical trials using variable N doses suggests that use of N may be associated with an increased incidence of RD.

OBJECTIVE: The objective of this trial was to determine whether recommended dose N enhances diuresis or affects renal function in patients (pts) hospitalized for the treatment of decompensated heart failure (HF).

METHODS: 65 pts with creatinine clearance (CC) between 20 and 60 mL/min were randomized on admission to receive N (2 µg/kg bolus and 0.01 µg/kg/min infusion for 48 hrs) or standard therapy (SRx). Only stable pts not felt to need intravenous vasodilators for rapid symptom relief were enrolled. Randomization was stratified by RD (mild RD = CC 40-60 mL/min; moderate RD = CC 20-39 mL/min). All pts received intravenous furosemide with dose standardized by RD (mild RD = 40 mg bid; moderate RD = 80 mg bid). Humoral function was assessed at randomization and at 48 hrs (before stopping N).

RESULTS: Table (mean ± SD) shows baseline parameters and changes over the first 48 hrs. There was no significant difference in baseline plasma renin activity, angiotensin II, endothelin or aldosterone and no difference in the change in these hormones over 48 hrs in the two groups. Systolic BP was lower in the N group at 24 hrs but not 48 hrs.

CONCLUSION: While effective for acute reduction in filling pressures and symptom relief, a broader role for N to facilitate diuresis or protect renal function in stable hospitalized HF pts is not supported by these data. Concomitant diuretic use may attentuate favorable humoral effects of N.

	N (n=34)	SRx (n=31)	p value
Age (yrs)	758	7211	0.29
Baseline Creatinine (mg/dL)	1.80.7	1.70.4	0.35
Baseline CC (mL/min/1.73m2)	4214	4513	0.47
Baseline BNP (pg/mL)	640473	538494	0.19
Baseline Systolic BP (mm Hg)	12927	12925	0.99
weight 48 hr (Kg)	-2.22.4	-3.32.6	0.07
Fluid balance 48 hr (L)	-2.72.2	-3.82.5	0.05
Creatinine 48 hr (mg/dL)	0.120.35	0.07.27	0.59
Blood Urea Nitrogen 48 hr (mg/dL)	2.710.4	1.05.7	0.49
% with Creatinine>0.3 mg/dL	17%	21%	0.71
BNP 48 hrs (pg/mL)	4741662	-59243	0.002
NT-proBNP	-19393450	-17904333	0.44
cGMP 48 hrs (pm/mL)	2.97.9	-0.64.8	0.002
Furosemide 48 hr total (mg)	272121	25594	0.52

J Card Fail 2005;11:S149

Nesiritide does not increase 30-day or 6-month mortality risk

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INTRODUCTION: There is an increased awareness of the importance of mortality risk factors in patients with acute decompensated heart failure (ADHF). Several such factors, including baseline renal function, baseline systolic blood pressure (SBP), the use of inotropic agents, and comorbidities have been recently identified. Meaningful baseline differences in these risk factors may exist in clinical trials not powered to assess mortality and these differences could significantly influence the observed mortality results.

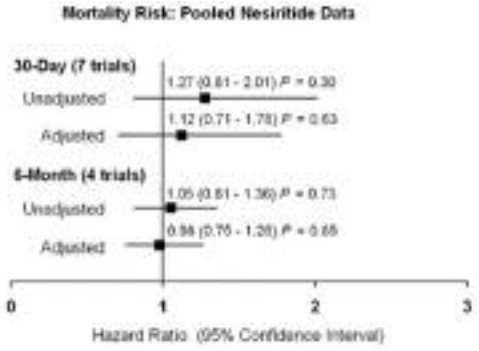
OBJECTIVE: To determine 30-day and 6-month mortality risks for nesiritide (NES) vs control (CON) after adjusting for baseline differences in risk factors.

METHODS: Pooled data from all NES trials with 30-day (7 trials pooled) and 6-month (4 trials pooled) mortality results were analyzed. The mortality effects of all variables with notable (3% absolute) baseline differences between the NES and CON groups were assessed using univariate Cox regression models. Significant univariate mortality risk predictors were then evaluated using multivariate Cox regression models with a stepwise criterion of P <0.05 for entry and P <0.10 for retention in the model. Separate models were developed for 30-day and 6-month mortality risk and these multivariate models were then used to adjust the mortality hazard ratios (HR) and associated 95% confidence intervals (CI) for NES relative to CON.

RESULTS: There were 1717 subjects (NES: N = 1059; CON: N = 658) in the pooled 30-day analysis and 1167 subjects (NES: N = 724; CON = 443) in the pooled 6-month analysis. In both analyses, baseline creatinine clearance 60 mL/min, baseline SBP 100 mmHg, and prior use of dopamine or dobutamine were significant independent multivariate predictors of mortality. A history of ventricular tachycardia and NYHA Class IV were also significant risk predictors in the 6-month analysis. No additional risk predictors were identified in the 30-day analysis. The figure depicts the results of the unadjusted and adjusted mortality risk analyses.

CONCLUSIONS: In a pooled analysis of 7 clinical trials, NES did not significantly increase mortality risk compared to control. A non-significant trend toward increased risk was reduced by adjusting for baseline differences in risk predictors.

J Card Fail 2005;11:S169



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Heart Failure Summit
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