Nesiritide in Acute Decompensated Heart Failure: Current Status and Future Perspectives

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Acute decompensated heart failure (ADHF) is a growing public health problem with high mortality and costs. ADHF often, if not usually, occurs in the setting of cardiovascular and noncardiovascular comorbidities as well as advanced age. New insights provide support for the concept of heart failure as a state of deficiency of and/or resistance to endogenous B-type natriuretic peptide. The primary goals of ADHF therapy are to relieve symptoms and optimize volume status with minimal side effects. Few therapies are proven to effectively do so. Nesiritide is a balanced vasodilator with favorable neurohumoral effects and is superior to placebo in providing rapid symptom relief and to nitroglycerin in reducing filling pressures. Recent trials confirm a lack of renal toxicity at recommended doses. An adequately powered multinational mortality trial is underway. Nesiritide represents a proven therapy for normotensive/hypertensive ADHF patients with severe symptoms at rest.

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Key words: Acute decompensated heart failure • Nesiritide • B-type natriuretic peptide • Renal function

Heart failure (HF) is the leading cause of hospitalization in patients older than 65. The incidence of hospitalization for acute decompensated heart failure (ADHF) is similar to that of acute myocardial infarction (AMI), with approximately 1 million hospitalizations per year. In-hospital mortality is similar to that of AMI at 3% to 4%, but 90-day mortality exceeds that of AMI at nearly 10%.[1] The cost of HF in the United States in 2007 was $33.2 billion, and much of this burden was related to the costs of ADHF hospitalizations.[2]

This article will discuss the treatment of ADHF with nesiritide, a balanced vasodilator. It will examine recent data on efficacy and safety, including proarrhythmic risk, mortality, and renal effects.

The Challenge of Acute Decompensated Heart Failure

Only recently have guidelines for the care of patients with ADHF been developed.[3] The treatment goals for ADHF as outlined in the Heart Failure Society of America guidelines are shown in Table 1.[3] The first 3 goals, to reduce symptoms and optimize volume status while minimizing side effects, represent the targets for drug therapy in ADHF.

The current pharmacologic therapy for ADHF is largely empiric and based on diuretics, vasodilators, and, for those with HF and reduced ejection fraction (EF), consideration of positive inotropic agents. To date, studies targeting ADHF are few and have been largely neutral.[1,4] Efforts to develop and test effective therapies are hampered by the diverse nature of ADHF, incomplete understanding of its pathophysiology, and lack of appropriate endpoints for ADHF trials.[1,4] Fully 50% of admissions for ADHF occur in patients with preserved EF, a condition in which the underlying pathophysiology and appropriate therapy remain incompletely defined.[5] Furthermore, ADHF often, if not usually, occurs in the setting of cardiovascular and non-cardiovascular comorbidities as well as advanced age. Indeed, the level of renal dysfunction and worsening renal function during therapy of ADHF, rather than EF or other cardiac parameters, is one of the most potent prognostic factors in patients with ADHF.[6,7]

Table 1
Treatment Goals for ADHF

Improve symptoms (congestion, low output symptoms)
Optimize volume status
Minimize side effects
Identify etiology
Identify precipitating factors
Optimize chronic oral therapy
Identify patients who may benefit from revascularization
Educate patients
Consider chronic disease management program

ADHF, acute decompensated heart failure. Adapted from the *Journal of Cardiac Failure*, Vol 12, Heart Failure Society of America. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline, pages 10-38,[3] Copyright 2006, with permission from the Heart Failure Society of America.

It is with this view of the challenging arena of ADHF that one should consider the evolution of nesiritide (Natrecor®, Scios Inc., Mountain View, CA) as a therapy for ADHF, its current role in therapy of ADHF, and its potential role in the future. Indeed, as recently emphasized, the nesiritide clinical development program was one of the first attempts at evidence-based medicine in ADHF.[4]

Endogenous Natriuretic Peptide System in HF

The natriuretic peptide (NP) family includes the structurally similar but genetically distinct atrial, B-type, and C-type NPs. B-type natriuretic peptide (BNP) is considered the most biologically potent NP, although this distinction has not been exhaustively proven. BNP is, however, the peptide that has been the focus of most diagnostic and therapeutic testing and commercial development.

BNP is produced in cardiomyocytes, where it is derived from the 108 amino acid (aa) precursor proBNP. ProBNP is believed to be cleaved by the endoprotease corin upon secretion, resulting in the formation of the bioactive 32 aa BNP peptide (BNP_{1-32} or as $proBNP_{77-108}$) and the inert 76 aa N-terminal peptide NT-proBNP ($proBNP_{1-76}$) (Figure 1).[8] This simple proBNP processing scheme suggests only 2 circulating proBNP-derived peptides, which commercially available BNP or NT-proBNP assays are assumed to specifically detect.

The effects of BNP are mediated through binding to the guanylyl cyclase receptor A and consequent activation of the second messenger cGMP. Preclinical animal studies demonstrated potent effects of BNP on a variety of physiologic parameters that appeared of potential benefit in acute or chronic HF. BNP is a balanced arterial and venous vasodilator, is diuretic and natriuretic, is lusitropic, anti-fibrotic, and anti-hypertrophic, and inhibits the renin angiotensin aldosterone and the sympathetic nervous systems.[9]

Circulating concentrations of BNP as assessed by various immunobased assays are increased in HF in *loose* proportion to the level of filling pressures. Indeed, elevated levels of BNP or NT-pro-BNP are excellent diagnostic markers of ADHF.[10] The profound vasoconstriction and sodium retention in HF, despite elevated levels of BNP, suggest a resistance to BNP in HF, either at the receptor or post-receptor level, overwhelming the effects of opposing counter-regulatory systems or resistance based on hemodynamic perturbations in HF.

More recently, an alternative mechanism for the resistance to seemingly high levels of endogenous BNP in HF has been raised. A study of advanced HF patients with high BNP levels demonstrated an absence of endogenous circulating BNP_{1-32} when a highly accurate mass spectrometry technique is used. This finding led the authors to speculate that alternate, biologically inactive forms of proBNP-derived products were responsible for

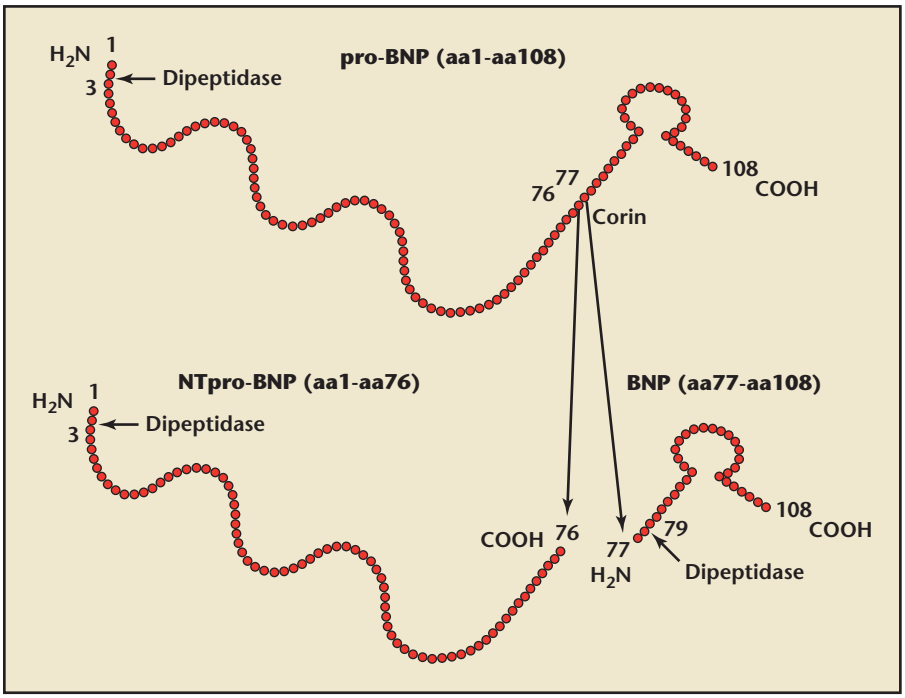

Figure 1. *Processing of ProBNP. ProBNP is cleaved by the endoprotease corin upon secretion resulting in the formation of BNP_{1-32} or as $proBNP_{77-108}$ (biologically active) and $proBNP_{1-76}$ (biologically inactive). Adapted from the* Journal of the American College of Cardiology, *Vol 49, Lam CS, Burnett JC Jr, Costello-Boerrigter L, et al. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population, pages 1193-1202,*[8] *Copyright 2007, with permission from the American College of Cardiology Foundation.*
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the high levels detected by commercial assays.[11] Although this study did not identify what these altered forms might be, others have suggested that intact $proBNP_{1-108}$ may be one such form[12,13] and that commercial BNP and NT-proBNP assays potentially cross-react with $proBNP_{1-108.}$[14] Subsequent studies have supported these findings.[15] Moreover, BNP_{1-32} has been shown to undergo further degradation both in vitro[13] and in vivo,[12] generating a BNP form that lacks the 2 N-terminal aa residues (BNP_{3-32}).[16] This processing may also reduce activity of endogenous or exogenous BNP in HF.[17]

These new insights provide support for the concept of HF as a state of deficiency of and/or resistance to endogenous BNP and, thus, offer additional support for the use of nesiritide or other exogenous natriuretic peptides as therapy for HF.

Evolution of Nesiritide as Therapy for ADHF: Clinical Trials

The first human trial of BNP infusion in congestive heart failure (CHF) was done by Yoshimura and colleagues.[18] A large dose of BNP was used, which resulted in a significant reduction in the pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR), significant increase in stroke volume index, diuresis and natriuresis, and decreased plasma aldosterone levels in mild to moderate CHF patients. Other small-scale human studies reproduced and corroborated the positive hemodynamic effects of (usually) high-dose BNP infusion. However, the effects on blood pressure (BP), as well as the renal effects, were inconsistent, which might be attributed to the differences in the patient population, dose of nesiritide studied, and study design.[19-21]

The Natrecor Study Group investigated longer infusions of nesiritide for 24 hours in patients with ADHF and showed rapid onset and sustained favorable hemodynamic effects of 3 different infused doses.[22] Encouraged by these findings, researchers conducted larger scale human ADHF trials.

A combined efficacy and comparative trial demonstrated significant dose-dependent reduction in the PCWP, right atrial pressure, SVR, and systolic BP, reduced dyspnea and fatigue, and improved global clinical status at 6 hours as compared with placebo. The comparative arm of this study showed sustained improvement in the latter 3 parameters for up to 7 days that was similar to standard intravenous (IV) HF therapy.[23]

The Vasodilation in the Management of Acute CHF (VMAC) study investigated the effect of nesiritide on the PCWP and dyspnea at 3 hours after starting the study drug.[24] The study design included nitroglycerin as a safety comparator, and a secondary analysis compared nesiritide with nitroglycerin, each added to standard therapy. Nesiritide resulted in greater decline in the PCWP at 3 hours compared with placebo and nitroglycerin, and this effect was sustained through the first 24 hours of infusion. Nesiritide resulted in significant improvement in self-reported dyspnea at 3 hours compared with placebo, but not nitroglycerin. At 24 hours, there was no difference in self-reported dyspnea between the 3 groups.[24] The effect of nesiritide on the filling pressure was highlighted by Elkayam and colleagues,[25] who reported more rapid and sustained reduction of the PCWP in the nesiritide group compared with the nitroglycerin group, even when nitroglycerin was aggressively up-titrated.

Based on the effects on filling pressures and symptom relief, nesiritide

was approved by the Food and Drug Administration (FDA) for the treatment of ADHF in 2001. The labeling specified the drug to be "indicated for the IV treatment of patients with ADHF who have dyspnea at rest or with minimal activity."

The Prospective Randomized Outcomes Study of Acutely Decompensated CHF Treated Initially as Outpatients with Nesiritide (PROACTION) trial was a multicenter, randomized, double-blind, placebo-controlled pilot study evaluating the safety and efficacy of nesiritide versus placebo administered in the emergency department or observation unit for ADHF.[26] This trial (237 patients enrolled) failed to demonstrate statistically significant reductions in hospital admissions or length of stay overall, although there was a trend toward fewer HF readmissions. The incidence of hypotension was low and similar between the groups.[26]

Concerns Over Safety

Initial studies of nesiritide provided reassurance that it was devoid of proarrhythmic risk as compared with inotrope-based therapy[27] and, indeed, that it was associated with lower mortality as compared with inotropic therapy.[28] Subsequent data from the Acute Decompensated Heart Failure National Registry (ADHERE) registry have confirmed the safety of nesiritide and nitrates over inotropes.[7]

As expected with a vasodilator, hypotension was a common side effect with nesiritide. It was dose-dependent, usually mild-to-moderate, usually asymptomatic or mildly symptomatic without reflex tachycardia or increases in epinephrine levels, and usually resolved spontaneously or in response to volume challenge.[23,24,26]

Although preclinical studies suggested that NPs have favorable renal effects in healthy animals or humans and in experimental HF,[9,29] the potential for deterioration in renal function with high doses of nesiritide in human HF was recognized.[9,30] In 2005, a retrospective pooled meta-analysis including 5 different nesiritide trials raised concerns regarding worsening renal function with nesiritide use. This meta-analysis showed significant risk of increased serum creatinine of more than 0.5 mg/dL in the nesiritide group compared with non-inotrope–based therapy as well as inotrope-based control therapy. However, there was no difference in the need for dialysis as compared with the non-nesiritide group.[31] Many of these trials used very high doses of nesiritide (0.03 to 0.06 μg/kg/min, with the clinically recommended dose being 0.01 μg/kg/min), and none of the trials were designed to specifically address the impact of nesiritide on renal function.

A second meta-analysis from the same group raised concerns over trends toward increased 30-day mortality of nesiritide compared with non–inotrope-based therapy. It pooled data from 3 randomized trials in which inotropes were not mandated in the control arm but were allowed in the nesiritide arm. Overall, there were 50 deaths in these 3 trials, with 35 of them in the nesiritide group (7.2%) and 15 in the control group (4%) ($P = .059$).[32] This analysis was subject to several criticisms but engendered further concern over the safety of nesiritide in ADHF.

Addressing Concerns Over Renal Function

In view of the meta-analyses mentioned above, several subsequent studies have specifically looked at the impact of contemporary doses of nesiritide on renal function. In a small but elegant study, Wang and colleagues[33] showed no favorable (or unfavorable) impact of nesiritide at the recommended dose (2 μg/kg IV bolus followed by an infusion of 0.01 μg/kg/min) on renal function in patients who had developed worsening renal function during ADHF therapy. Owan and colleagues[34] showed a slight benefit of standard-dose nesiritide on renal function in ADHF patients randomized to nesiritide plus standard care versus standard care alone.[34] Witteles and coworkers[35] found no impact of nesiritide on renal function in ADHF patients randomized to nesiritide plus standard care versus standard care alone. Two Follow Up Serial Infusions Of Nesiritide (FUSION) trials studied the safety and tolerability of chronic intermittent outpatient nesiritide infusions in advanced chronic decompensated HF.

FUSION I (a pilot study) found no adverse effect of chronic intermittent outpatient nesiritide infusions on renal function, and FUSION II found less worsening of renal function with nesiritide as compared with placebo.[36-38] Neither trial demonstrated a favorable impact on HF events with this strategy. In a retrospective, case-control study of patients with ADHF, Riter and colleagues[39] found a benefit of low-dose nesiritide (≤ 0.005 μg/kg/min, without a bolus dose) on renal function (Figure 2). The Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) trial demonstrated that perioperative nesiritide infusion (0.01 μg/kg/min *without* a loading bolus dose) attenuated renal dysfunction and preserved urine output in patients with left ventricular dysfunction (Stage B or C HF) undergoing coronary artery bypass grafting (Figure 3). Additionally, it showed a shorter hospital stay and lower 180-day mortality.[40] Similarly, Chen and coworkers[41] found beneficial effects of nesiritide (without a bolus) in patients undergoing

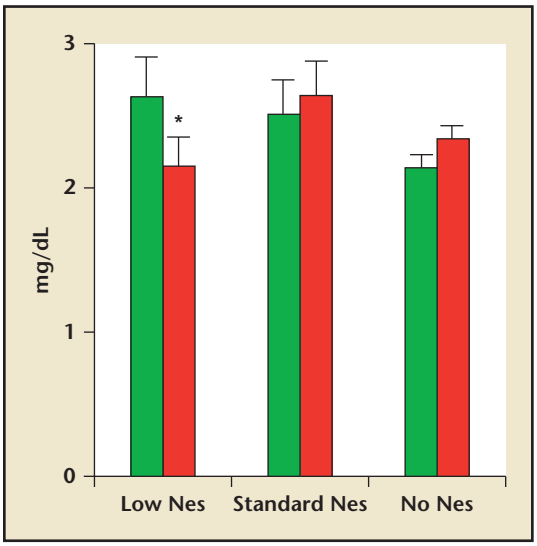

Figure 2. *Effect of low-dose nesiritide (Low Nes), standard-dose nesiritide (Standard Nes), and no nesiritide (No Nes) on plasma creatinine at baseline (green bars) and after intravenous therapy (red bars). *P < .05 versus baseline. Adapted from the* Journal of the American College of Cardiology, *Vol 47, Riter HG, Redfield MM, Burnett JC, Chen HH. Nonhypotensive low-dose nesiritide has differential renal effects compared with standard-dose nesiritide in patients with acute decompensated heart failure and renal dysfunction, pages 2334-2335,[39] Copyright 2006, with permission from the American College of Cardiology Foundation.*
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cardiopulmonary bypass cardiac surgery.[41]

The Riter trial[39] and the perioperative studies on renal preservation[40,41] raise an important issue regarding the dose response of nesiritide and its renal effects. The dose-finding studies for nesiritide were based on hemodynamic and symptom relief endpoints, not renal effects. Nesiritide and other vasodilators have adverse renal effects when the dose is high, and this effect is likely due to precipitous lowering of BP in ADHF.

Addressing Concerns Over Early Mortality

Contrary to the Sackner-Bernstein analysis,[32] a larger meta-analysis by Arora and colleagues[42] of 7 randomized controlled trials (including the 3 trials analyzed before) did not find an increased risk of death with nesiritide use, either at 30 days (7 trials) or 180 days (4 trials). Data from the ADHERE National Registry reported that IV vasodilator therapy with nesiritide or nitroglycerin was associated with similar in-hospital mortality.[7] Furthermore, patients treated with nesiritide or nitroglycerin had significantly shorter stays in the intensive care unit, shorter overall stays in the hospital, and lower in-hospital mortality compared with patients treated with inotropes.[7] Although they are not ADHF trials, the FUSION I and II data suggest safety of nesiritide as outlined above. In these trials, patients with very advanced HF received multiple nesiritide infusions without excess renal dysfunction or mortality, which speaks strongly to the safety of nesiritide. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated HF (ASCEND-HF) is an ongoing multicenter, randomized, double-blind, placebo-controlled international outcome study of 7000 ADHF patients. ASCEND-HF subjects will be randomized to receive, within 48 hours of hospitalization, a standard-care fixed-dose infusion of nesiritide at 0.01 μg/kg/min, preceded by an optional 2 μg/kg IV bolus (which may be withheld if there are concerns regarding the patient's systolic BP), or placebo (www.clinicaltrials.gov). The primary endpoints are rehospitalization due to HF and all-cause mortality from randomization through day 30 and dyspnea symptoms at 6 hours or 24 hours after study drug initiation.

Who Should Receive Nesiritide Now?

Although the aforementioned trials provide reassurance regarding the safety of nesiritide, the controversy

Figure 3. *Changes in serum creatinine with the use of nesiritide over the course of the hospital stay in nesiritide (green line) and placebo (red line) patients. *P < .05 nesiritide versus placebo; †P < .05 change from baseline. Adapted from the* Journal of the American College of Cardiology, *Vol 49, Mentzer RM Jr, Oz MC, Sladen RN, et al. Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery: the NAPA Trial, pages 716-726,[40] Copyright 2007, with permission from the American College of Cardiology Foundation.*
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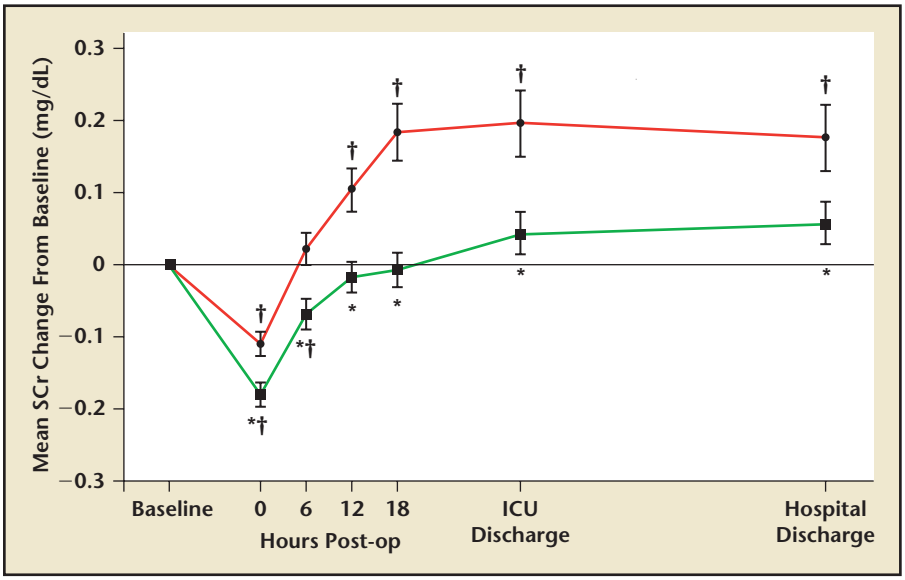

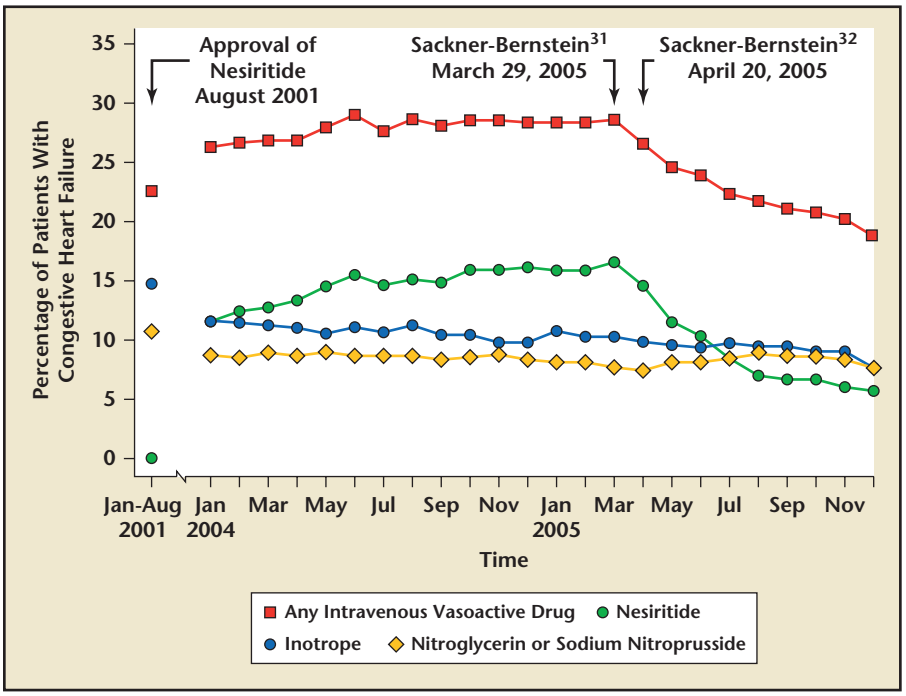

Figure 4. *Trends in the use of intravenous nesiritide and other vasoactive drugs. The use of nesiritide declined following peak use in March 2005, coinciding with the publication dates of the 2 negative meta-analyses. Adapted with permission from Hauptman PJ, Schnitzler MA, Swindle J, Burroughs TE. Use of nesiritide before and after publications suggesting drug-related risks in patients with acute decompensated heart failure.* JAMA. *2006;296:1877-1884.[44] Copyright © American Medical Association. All rights reserved.* www.medreviews.com

resulting from the meta-analyses of pre-approval trial data[31,32,43] has had a dramatic impact on the use of nesiritide[44] (Figure 4).

Nesiritide is an FDA-approved, safe and effective IV vasodilator that produces rapid symptom relief in patients with ADHF and dyspnea (at rest or with minimal activity). It is easy to use, well tolerated, does not require dose up-titration, and is not associated with tolerance. Data from HF registries suggest that 29% to 50% of patients with ADHF have a systolic BP greater than 140 mm Hg and that 30% to 40% have symptoms at rest.[1] Patients with ADHF who have normal or increased BP and symptoms at rest (including orthopnea or paroxysmal nocturnal dyspnea) represent the ideal setting for use of standard-dose nesiritide. These are the patients most in need of rapid symptom relief, and symptom relief is the primary indication for use of nesiritide. The drug can be discontinued once standard therapy has been implemented or augmented, such that discontinuation of the IV therapy is likely to be tolerated without the return of resting symptoms. Unlike nitroglycerin or sodium nitroprusside, nesiritide has favorable neurohumoral effects with suppression of aldosterone and endothelin and is devoid of reflex tachycardia, suggesting suppression of catecholamines.[23,36]

Surprisingly, both registry data[7] and a recent analysis of a large hospitalization database[44] indicate that approximately 18% to 25% of patients with ADHF were treated with an IV vasodilator prior to recent declines in nesiritide use. Although nesiritide use has decreased dramatically since 2005, the use of other IV vasodilators has not increased, suggesting that no attempts at rapid symptom relief are being made in a significant proportion of the ADHF population in whom use of a vasodilator would be appropriate. Although multiple studies demonstrate the adverse effects of inotropes on mortality in ADHF,[7] inotrope use remains stable.

Cost-Effectiveness of Nesiritide

Given the tremendous burden of HF to our health care system, the impact of new therapies on the cost of care should be considered. However, these studies are difficult to perform in the hospital setting, where so many factors influence resource utilization. The appropriate comparator for IV vasodilator therapies is unclear, and the "benefit" of symptom relief (the primary goal of hospitalization for ADHF) is difficult to quantify in a cost-benefit analysis. When vasodilator therapy is compared with inotropic therapy, studies have found mixed results depending on the inotrope used as a comparator and the type of assumptions used in the calculations, with some studies suggesting benefit and others not.[45-47] Data from ASCEND may provide more insight into this important question.

Future of Nesiritide in ADHF: "Renal-Dose" Nesiritide

Although studies with standard-dose nesiritide in ADHF do not indicate a significant favorable (or detrimental) impact of nesiritide on renal function, the findings of the NAPA trial,[40] FUSION II,[37] and studies with low-dose nesiritide in ADHF[39] are intriguing and suggest that there still may be a role for nesiritide to improve or preserve renal function in ADHF or chronic HF. The dose of nesiritide needed to provide rapid reduction in filling pressures and symptom relief may not be the proper dose to preserve renal function. This is not an approved indication for nesiritide

use, thus more studies are needed to explore this possibility.

Future of Nesiritide and Other Natriuretic Peptides in Chronic HF and Hypertension

Acute nesiritide infusion is an effective strategy to provide acute symptom relief in ADHF, and its potential as a chronic therapy in stable HF and systemic hypertension is only beginning to be explored. Novel peptide delivery strategies, including subcutaneous injections of BNP or albumin-BNP conjugates and orally active compounds, are being tested.[48-51]

Conclusion

Nesiritide is an effective and FDA-approved IV vasodilator that provides rapid symptom relief and reduction in filling pressures in ADHF patients with symptoms at rest. A large number of recent studies suggest that recommended-dose nesiritide is devoid of adverse renal effects in ADHF. Although most studies do not support an adverse effect of nesiritide on mortality, an ongoing randomized controlled trial is testing the effect of nesiritide versus standard therapy on 30-day mortality. ■

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Main Points

- The current pharmacologic therapy for acute decompensated heart failure (ADHF) is largely empiric and based on diuretics, vasodilators, and, for those with heart failure (HF) and reduced ejection fraction, consideration of positive inotropic agents.
- New data provide support for the concept of HF as a state of deficiency of and/or resistance to endogenous B-type natriuretic peptide and, thus, offer additional support for the use of nesiritide or other exogenous natriuretic peptides as therapy for HF.
- Initial studies of nesiritide showed it was devoid of proarrhythmic risk as compared with inotrope-based therapy. Nesiritide was also associated with lower mortality as compared with inotropic therapy.
- Nesiritide and other vasodilators have adverse renal effects when the dose is high, and this effect is likely due to precipitous lowering of blood pressure in ADHF.
- Data from the ADHF National Registry reported that intravenous vasodilator therapy with nesiritide or nitroglycerin was associated with similar in-hospital mortality.

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