



# The Role of Nesiritide in the Management of Acute Decompensated Heart Failure: Review of Mortality Data and Recommendations for Clinical Use

## NEW CONCEPTS AND EMERGING TECHNOLOGIES FOR EMERGENCY PHYSICIANS

J. Douglas Kirk M.D., F.A.C.E.P., Associate Professor of Emergency Medicine, University of California, Davis, School of Medicine; Vice Chair and Director of Clinical Operations: Medical Director, Chest Pain Evaluation Unit  
Department of Emergency Medicine, University of California, Davis, Medical Center

Dear Colleagues,

The treatment of acute decompensated heart failure (ADHF) remains a tremendous challenge for the practicing clinician in the emergency setting. These patients are often quite ill and require decisive clinical intervention. Traditional approaches to this disease process include diuretics, vasodilators, and inotropic agents. Recently, the development of nesiritide or B-type natriuretic peptide (BNP) as a therapeutic regimen has expanded the treatment options for ADHF.

The use of nesiritide for ADHF has recently been scrutinized by a meta-analysis which examines renal insufficiency and mortality for this agent versus the traditional treatments. In this EMCREG-International Newsletter, Dr. Douglas Kirk, Associate Professor of Emergency Medicine at UC Davis in Sacramento, California discusses the current data regarding nesiritide which provides perspective for the practicing emergency physician. We are pleased at EMCREG-International to provide balanced information regarding controversial topics in emergency cardiovascular and neurovascular care which will improve the care of patients.

Sincerely,



*Andra L. Blomkalns*  
Andra L. Blomkalns, MD  
Director of CME,  
EMCREG-International



*W. Brian Gibler*  
W. Brian Gibler, MD  
President,  
EMCREG-International

## Introduction

The diagnosis of heart failure is becoming common with a prevalence of more than five million patients and over five hundred thousand new cases reported per year.<sup>1</sup> A disease primarily of the elderly, its recent increase is likely due to the general aging of the population as well as improved survival of patients after myocardial infarction or other index events that lead to impaired ventricular function. A clinical syndrome not characterized by a single presentation, heart failure is frequently seen in the emergency department (ED) which is the most common portal of entry for hospital admission. Multiple challenges exist in management of acute decompensated heart failure (ADHF), including appropriate recognition and differentiation from other causes of dyspnea as well as choice of therapeutic regimen. The latter has recently become more of an issue as therapeutic decision-making had been somewhat stagnant over the past two decades due to a paucity of new, effective pharmacologic agents available to treat ADHF. This report will focus on three main objectives: 1) Describe the role of nesiritide in the management of ADHF, with particular emphasis on concerns of increased morbidity and mortality recently raised in two meta-analyses;<sup>2,3</sup> 2) Review additional mortality data not reported in the aforementioned papers in an attempt to further elucidate the potential risk of therapy; and 3) Describe recommendations for current "risk appropriate" use of nesiritide in ADHF, as well as future directions for investigation.

## Therapeutic Management of ADHF

Although there are ample data and guidelines from various sources about the management of patients with heart failure, most pertain to chronic management.<sup>4</sup> There is little consensus regarding the pharmacological management of patients with ADHF in the ED. In fact, no acute therapy for ADHF has demonstrated a mortality benefit in a prospective, randomized controlled trial (RCT). Despite their widespread acceptance as standard therapy, surprisingly little clinical outcome data exist for diuretics and the vasodilators nitroglycerin and nitroprusside to support their use in ADHF. Physician familiarity with nitroglycerin use in patients with chest pain makes the combination of nitroglycerin and diuretics frequent first line therapy for ADHF. The predictable effects of these agents on filling pressure and blood pressure have made them attractive choices. Nitroprusside

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can also be particularly useful in patients with acute pulmonary edema associated with hypertensive emergencies. However, there are several limitations to these therapies, including the need for titration, hemodynamic monitoring, and the deleterious effects of neurohormonal activation (Table 1). This has led to the search for better therapeutic agents, ideally ones that improve acute symptoms and hemodynamics as well as decreasing mortality.

## Nesiritide

Approved by the Food and Drug Administration (FDA) in 2001, nesiritide became the first commercially available natriuretic peptide used for the treatment of ADHF. It is structurally identical to human endogenous B-type natriuretic peptide (BNP). Although plasma levels of endogenous BNP are elevated in ADHF, the administration of additional exogenous BNP has beneficial effects. Several mechanisms have been suggested to explain this paradox, including BNP receptor down regulation, increased BNP degradation, and post receptor uncoupling at the tissue level. Probably the most important and significant mechanism is the general counter-balancing of vasoconstrictive neurohormones in patients with poor cardiac output. BNP serves as an antagonist to pathologic neurohormonal activation that occurs during heart failure. This feature is common among heart failure pharmacologic agents with proven mortality benefit such as angiotensin converting enzyme inhibitors and beta-blockers.

Nesiritide produces significant reductions in pulmonary capillary wedge pressure, right atrial pressure, and systemic venous resistance within minutes and produces concomitant increases in stroke volume and cardiac output.<sup>5</sup> In addition, it does not possess many of the untoward properties associated with diuretics, inotropes, or other vasodilators (Table 1). In the PRECEDENT trial, a comparison of nesiritide with dobutamine, the investigators found fewer arrhythmias and no increase in heart rate with nesiritide.<sup>6</sup> Further, readmission rates at three weeks and mortality at six months were higher in the dobutamine arm. As shown in Figure 1, data from the VMAC trial demonstrated nesiritide decreased pulmonary capillary wedge pressure more than either nitroglycerin or placebo at three hours and more than nitroglycerin at twenty-four hours.<sup>7</sup> Dyspnea and global clinical status were improved compared to placebo and were similar to nitroglycerin. In addition, nesiritide's hemodynamic effects were longer lasting, without a need for up-titration. This was frequently necessary in the nitroglycerin group to maintain adequate reduction in wedge pressure.<sup>8</sup>

Nesiritide possesses several characteristics that provide convenience and ease of use: 1) no proarrhythmic effect; 2) no tachyphylaxis; and 3) no need for titration (hence not mandat-



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**Table 1.** Untoward effects of therapeutic agents for ADHF.

Diuretics	Vasodilators	Inotropes
<ul style="list-style-type: none"><li>Decreased renal perfusion</li><li>Volume depletion</li><li>Electrolyte abnormalities (K+, Ca+, Mg+)</li><li>Neurohormonal activation:<ul style="list-style-type: none"><li>↑ renin-angiotensin aldosterone</li><li>↑ sympathetic nervous system</li></ul></li></ul>	<ul style="list-style-type: none"><li>Tachycardia (NTG, NTP)</li><li>Tachyphylaxis (NTG)</li><li>Neurohormonal activation (NTG, NTP)</li><li>Thiocyanate toxicity (NTP)</li><li>Need for titration (NTG, NTP)</li><li>Need for invasive monitoring (NTP, ± NTG)</li></ul>	<ul style="list-style-type: none"><li>Increased mortality</li><li>Proarrhythmic</li><li>Tachycardia</li><li>Neurohormonal activation</li></ul>

DHF = acute decompensated heart failure; NTG = nitroglycerin; NTP = nitroprusside

Adapted with permission from Kirk JD, Diercks DB. Acute Decompensated Heart Failure, in Essentials of Emergency Medicine. Aghababian RV, et al., [editors]. Sudbury, MA: Jones and Bartlett Publishers, Inc., 2006:117-124.

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ing ICU care), making it quite suitable for the ED or observation unit population.<sup>9</sup> In 237 ED observation unit patients randomized to either standard care or at least 12 hours of nesiritide therapy in the PROACTION trial,<sup>10</sup> the investigators report nesiritide use was associated with a 21% decrease in ADHF readmissions and a substantial decrease in the sum length of stay over the ensuing month after the index visit (2.5 vs. 6.5 days,  $p < 0.032$ ). Mortality and complications were uncommon and not statistically different between the two groups.

To date, nesiritide is the only therapy that has been shown in RCTs of ADHF to provide significant symptomatic and hemodynamic improvement compared to placebo plus standard care.<sup>7</sup> Nesiritide has not been studied in a trial prospectively designed or adequately powered to evaluate its effect on mortality. However, data from the multicenter Acute Decompensated Heart Failure National Registry (ADHERE), suggest that patients treated with an intravenous vasodilator (nesiritide, nitroglycerin or nitroprusside) initiated in the ED versus later in the hospital or not at all had lower mortality (4.3% vs. 10.9%, unadjusted,  $p < 0.0001$ ) and shorter hospital lengths of stay (3 vs. 7 days,  $p < 0.001$ ).<sup>11</sup> These data generate some enthusiasm that early goal directed therapy initiated in the ED for ADHF may be effective and further study is indicated.

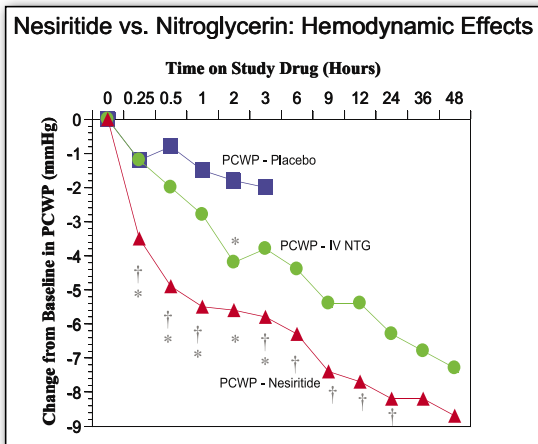
## Mortality risk with nesiritide?

A recent meta-analysis of three trials reported that nesiritide may be associated with an increase in mortality.<sup>3</sup> In this report, the authors conclude that "Compared with non-inotrope based control therapy, nesiritide may be associated with an increased risk of death after treatment for ADHF." These conclusions were drawn from a compilation of data from three prospective, RCTs in which nesiritide was used in ADHF and 30 day follow-up data were available. Inclusion criteria consisted of the following: randomized, double-blind, parallel study group of patients with ADHF; nesiritide administered as a single infusion for at least 6 hours; control therapy that did not mandate use of positive inotropic agent; and reported 30 day mortality. In this review, 485 patients were randomized to nesiritide and 377 to control therapy. There was a statistically insignificant trend of increased 30 day mortality in the nesiritide group 35/485 (7.2%) vs. 15/377 (4.0%) control patients; hazard ratio (HR) 1.80, 95% confidence interval (CI) 0.98-3.31;  $P = 0.057$ . The authors report that their findings were not conclusive, but only hypothesis generating. They recommend



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**Figure 1.** Change in pulmonary capillary wedge pressure (PCWP) from baseline. †Comparison of Nesiritide vs. Nitroglycerin,  $p < 0.05$ ; \*Comparison of Nesiritide vs. placebo,  $p < 0.05$ . Adapted from VMAC Investigators. Intravenous nesiritide versus nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. Reproduced with permission of Peacock W et. al. Management of Acute Decompensated Heart Failure in the Emergency Department. Cong Heart Fail. 2003; 9;5(1),3-18. Copyright 2003 by CHF, Inc.



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that the possibility of an increased risk of death should prompt an adequately powered, RCT comparing nesiritide to "standard" therapy with nitroglycerin and diuretics.

While this analysis is thought provoking, it is important to view the results in the proper context. None of the RCTs included in this analysis were powered to evaluate mortality. There were few deaths in each of these studies, so the CIs around the HR are wide. Each study was designed differently to achieve a specific endpoint and included dissimilar patient populations, control arms, and concomitant medications. Because of the small size and design of the trials included in the review, some potentially important baseline imbalances exist between the nesiritide group and the "control" group. These baseline characteristics are important as several are associated with an increased mortality in ADHF and were not accounted for in this meta-analysis. Deaths in the VMAC<sup>7</sup> trial account for nearly 75% of the 30-day nesiritide deaths cited in the report, and patients randomized to nesiritide were more likely to have a baseline systolic blood pressure <100 mm Hg and a creatinine clearance <60 mL/min. A lesser known fact is that a number of trials have demonstrated that the use of intravenous inotropes in ADHF is associated with increased mortality.<sup>12-14</sup> It is important to note that inotrope use was significantly greater in nesiritide patients compared to controls, 96/478 (20.1%) vs. 44/375 (11.7%),  $p < .001$ . Hence, all of these imbalances could have contributed to an increase in unadjusted mortality.

## Pooled analysis of all RCT data

Rather than speculate about the effect of baseline imbalances, poor study design, omission of important data, and lack of adjustment, further analysis of existing additional data is more worthwhile. In April 2005, additional data was presented to the FDA as part of a revised package insert for nesiritide. Data from all seven trials<sup>5,7,10,15-17</sup> of nesiritide versus standard therapy with at least 30 day reported mortality, including those from the current meta-

analysis,<sup>3</sup> were submitted.<sup>18</sup> A critical review of this pooled data was recently reported by Abraham.<sup>19</sup> The findings from this analysis appear to be different than the previously described meta-analysis of Sackner-Bernstein.<sup>3</sup>

As previously noted, these seven trials are not homogenous with respect to design, clinical endpoints, study population, standardized control therapy, or follow-up. Important trial characteristics are described in **Table 2**. Mortality data at 30 days are presented for all seven trials whereas six month mortality data are only available in four trials. Data from 1717 patients are available, including 1059 who received nesiritide and 658 in the "control" group. There were 84 (5.3%) deaths in the nesiritide group and 28 (4.3%) in the control group at 30 days, a nonsignificant difference,  $p = 0.299$ . Pooled analysis of data reveals a HR (95% CI) of 1.27 (0.81-2.01) for nesiritide relative to control. Because the FUSION<sup>17</sup> trial was essentially an outpatient study of ambulatory patients receiving intermittent infusions of study drug, this study was excluded from the analysis. **Figure 2** describes the 30-day mortality data for the seven individual trials and the two pooled analyses.

For 180-day mortality, pooled data from four of the seven RCTs (involving 1167 patients) were analyzed (**Figure 3**). Overall mortality was 21.7% (154/724) with nesiritide and 21.5% (94/443) with control therapy, HR (95% CI) 1.05 (0.81-1.36),  $p = 0.725$ . As stated previously, results from FUSION were not included in the pooled analysis and data was only available for 16 weeks of follow-up as opposed to six months as in the other trials.<sup>17</sup> However, during this interval there were 13/141 (9.4%) deaths in the nesiritide group vs. 9/69 (13.5%) in the control group, HR (95% CI) 0.68 (0.29-1.60). The Sackner-Bernstein report is a selective analysis of only a portion of existing data.<sup>3</sup> If all available mortality data are taken together, therapy with nesiritide does not appear to significantly increase the risk of mortality. However, these adverse trends warrant further investigation with a well designed RCT.

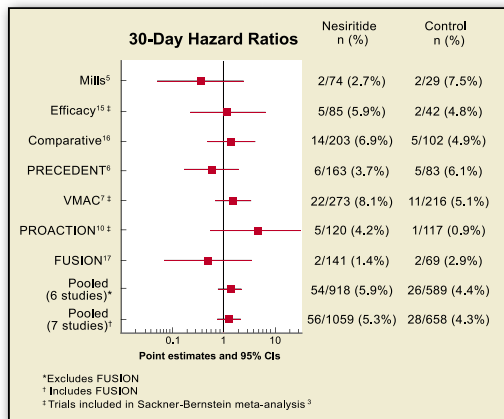


None of the RCTs included in this analysis were powered to evaluate mortality.

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**Figure 2.** Mortality hazard ratios, 95% confidence intervals (CI), and percent mortality (Kaplan-Meier estimate) for randomized and treated patients with nesiritide relative to control through day 30 for each of 7 individual trials, pooled analysis of the 6 single-infusion hospital-based trials, and pooled analysis of all 7 trials. Adapted with permission from Abraham WT. Nesiritide and Mortality Risk: Individual and Pooled Analyses of Randomized Controlled Clinical Trials. *Rev Cardiovasc Med.* Spring 2005;6(2).



## Mortality data from ADHERE

Recent data from ADHERE provides further insight on this issue.<sup>14</sup> Data from more than 65,000 patients who were admitted for management of ADHF were examined. Risk factor and propensity score-adjusted odds ratio (OR) for in-hospital mortality were calculated for a cohort of 15,230 patients who received nitroglycerin, nesiritide, milrinone, or dobutamine. The risk factor and propensity score adjusted ORs for nitroglycerin were 0.69 (95% CI 0.53 to 0.89, p<0.005) and 0.46 (95% CI 0.37 to 0.57, p< 0.005) compared with milrinone and dobutamine, respectively. Corresponding ORs for nesiritide were 0.59 (95% CI 0.48 to 0.73, p< 0.005) and 0.47 (95% CI 0.39 to 0.56, p<0.005), respectively. The adjusted OR of nesiritide compared to nitroglycerin was 0.94 (95% CI 0.77 to 1.16, p<0.58). In this report, the risk of in-hospital mortality was similar for nesiritide and nitroglycerin and both were associated with significantly lower in-hospital mortality than positive inotropic therapy in patients hospitalized with ADHF (Figure 4). Although these results are not from a RCT but rather a retrospective review of registry data, the conclusions are still important. The findings

**Table 2.** Randomized controlled nesiritide trials with mortality data.

Study	Median (IQR) Duration of Infusion (hours)	Nesiritide Dose*	Control	Patients		Mortality Assessed (days)
				Nesiritide	Control	
Mills <sup>5</sup>	24.0 (24.0-24.1)	0.015, 0.03, or 0.06	Placebo	74	29	30
Efficacy <sup>15</sup>	24.2 (7.8-47.7)	0.015 or 0.03	Placebo	85	42	30, 180
Comparative <sup>16</sup>	30.4 (23.0-65.1)	0.015 or 0.03	Standard care	203	102	30, 180
PRECEDENT <sup>6</sup>	24.1 (24.0-46.5)	0.015 or 0.03	Dobutamine	163	83	30, 180
VMAC <sup>7</sup>	24.3 (24.0-44.2)	0.01	Nitroglycerin/Standard care	273	216	30, 180
PROACTION <sup>10</sup>	16.9 (12.2-21.9)	0.01	Standard care	120	117	30
FUSION <sup>17</sup>	Not Applicable	0.005 or 0.01	Standard care	141	69	30, 112

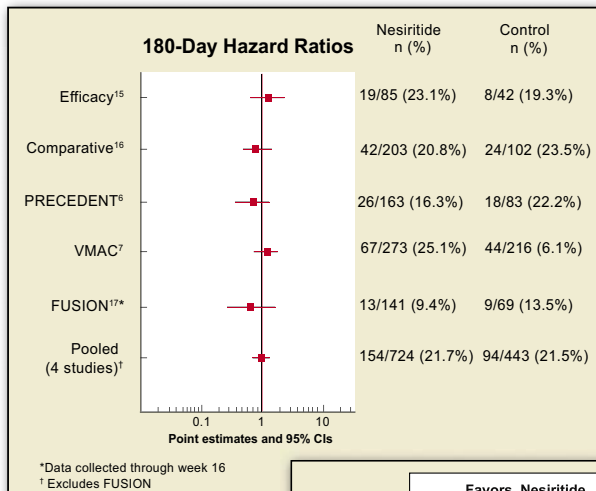
IQR = interquartile range; \*mcg/kg/min  
 Adapted from Abraham WT. Nesiritide and Mortality Risk: Individual and Pooled Analyses of Randomized Controlled Clinical Trials. *Rev Cardiovasc Med.* Spring 2005;6(2).



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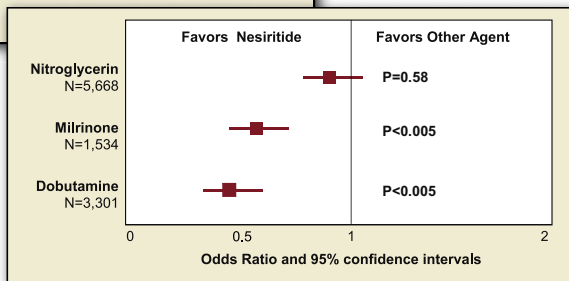
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**Figure 3.** Mortality hazard ratios, 95% confidence intervals (CI), and percent mortality (Kaplan-Meier estimate) for randomized and treated patients with nesiritide relative to control through 180 days for each of the 4 trials in which these data were collected and for a pooled analysis of these 4 trials as well as through week 16 for the FUSION trial. Adapted with permission from Abraham WT. Nesiritide and Mortality Risk: Individual and Pooled Analyses of Randomized Controlled Clinical Trials. *Rev Cardiovasc Med.* 2005;6(2).

**Figure 4.** Results of comparative mortality analysis of nesiritide treatment vs. nitroglycerin, milrinone or dobutamine, adjusted for covariates and propensity score. Adapted with permission from Abraham WT, Adams KF, Fonorow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the ADHERE registry. *J Am Coll Cardiol.* 2005; 46:57–64.



are from “real world” patients and the numbers are quite large. The ORs are not only statistically significant, but also clinically relevant. The findings are similar to the pooled analysis<sup>19</sup> and support the contention that there is no significant risk of increased mortality associated with nesiritide therapy. It should be noted, however, that results and conclusions from pooled analyses are not the same as those obtained from an adequately powered and properly designed RCT.

### Braunwald Panel Report

An expert panel of cardiology and heart failure clinicians chaired by Eugene Braunwald, MD met in June 2005 to review and assess data associated with the use of nesiritide after questions about safety were raised. Scios Incorporated provided additional data from all available trials, including data submitted to the FDA for the original (August 2001) and the cur-

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rent (April 2005) package inserts. The panel convened with the following objectives: 1) review and discuss nesiritide efficacy and safety data; 2) provide guidance on proposed clinical development strategies for nesiritide; and 3) review the current package insert and provide recommendations on the use of nesiritide. After an in-depth discussion of substantial additional analyses of existing data, the panel provided the following conclusions and recommendations:<sup>20</sup>

- 1. Renal function.** Nesiritide was associated with a dose-dependent increase in serum creatinine, even with the dose recommended for initiation of treatment (0.01 µg/kg/min). The mechanism of these creatinine changes, their duration, implications for survival, longer term renal function and other clinical consequences are not clear. Studies to clarify these issues, including the relationship of renal dysfunction and clinical outcomes, should be conducted.
- 2. Mortality.** The panel noted that existing data suggest nesiritide was associated with a trend toward increased mortality at 30 days, with a HR of approximately 1.3. However, the 95% CIs are wide and the total number of deaths in all six of the RCTs (84) was insufficient to accurately determine an excess mortality risk. No increased hazard was identified at 180 days. They also recognized potentially important imbalances in baseline patient characteristics, concomitant treatments, and differences in control groups that may have affected outcomes. Because of the inconclusive nature of these findings, the panel recommended additional studies be conducted to assess the effect of nesiritide on survival.
- 3. Clinical trials.** The panel strongly recommended continued enrollment in ongoing and planned trials that are soon to commence. The panel endorsed the manufacturer's plan to conduct an RCT of several thousand patients to assess further the benefits and risks of nesiritide compared to

standard therapy. The panel reiterated that this trial should include patients with ADHF and should be adequately powered to detect clinically important endpoints (mortality and cardio-renal morbidity) at 30-90 days and mortality at 180 days. Study design should incorporate appropriate risk stratification and subgroup analysis to further elucidate relationships between treatment groups and important clinical outcomes.

- 4. Mandatory prescribing information.** Nesiritide should be strictly limited to patients presenting to the hospital (ED, observation unit, or inpatient) with ADHF and dyspnea at rest or with minimal activity. Clinicians should consider its efficacy, possible risks, and the availability of alternate therapies. Nesiritide should not be used for intermittent outpatient infusion, scheduled repetitive use to improve renal function, or to replace diuretics.

## Recommendations for Clinical Use of Nesiritide

Appropriate management of ADHF is both challenging and controversial. Adverse trends in short term clinical outcomes from selective reports have caused concerns about the safety of nesiritide. However, the data, when examined in total, fail to firmly establish a deleterious effect. Conclusive evidence identifying suitable patients who clearly benefit from a particular therapy are lacking, as are specific guidelines to drive ED management. It does appear, however, that patient risk stratification<sup>21</sup> and initiation of aggressive treatment in the ED<sup>11</sup> may avoid potentially irreversible myocardial toxicity, especially in those with moderate to severe ADHF. It is for these patients that integrating the use of nesiritide into a management protocol seems most prudent. The algorithm (Figure 5)<sup>22</sup> shown here attempts to provide some guidance for the diagnostic and prognostic evaluation of the suspected ADHF patient, in addition to recommendations for therapeutic strategies and disposition decisions.

While initiating a work-up for suspected ADHF, the algorithm addresses the potentially life threatening complications of respiratory failure or cardiogenic shock. Using typical historical information, physical examination, and diagnostic test features, a clinical profile is defined that identifies patients in whom pulmonary congestion is the central feature of the clinical presentation. A minority of patients will have mild exacerbations of ADHF and the mainstay of therapy for them is intravenous diuretics, particularly if they



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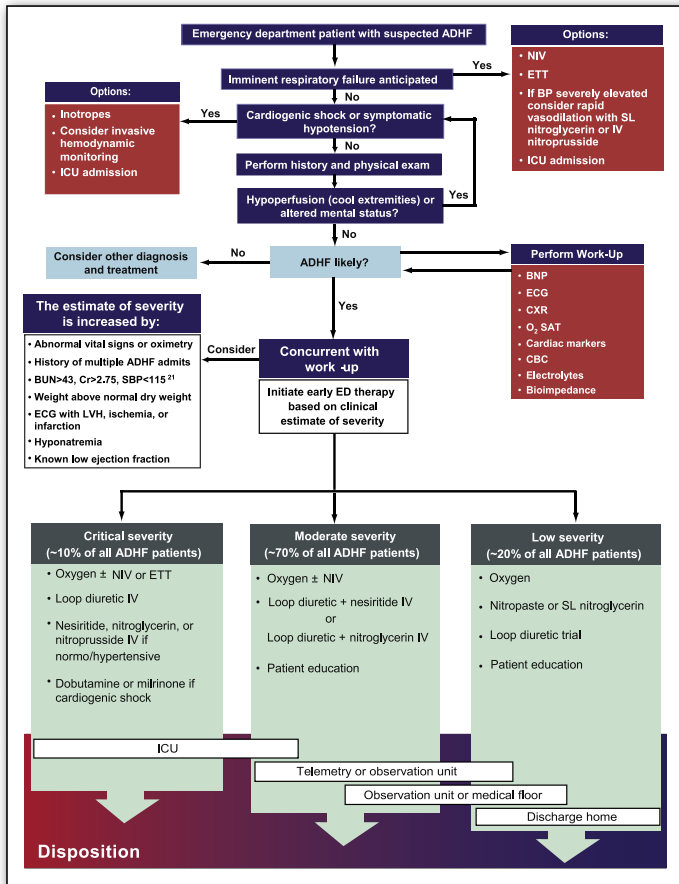
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**Figure 5.** Algorithm for the early stabilization of acute decompensated heart failure in the emergency department. ADHF = acute decompensated heart failure; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine; CXR = chest radiograph; ECG = electrocardiogram; ETT = endotracheal tube; ICU = intensive care unit; LVH = left ventricular hypertrophy; NIV = non-invasive ventilation; O<sub>2</sub>SAT = oxygen saturation; pm = as needed; SBP = systolic blood pressure; SL = sublingual. Reproduced with permission of Peacock W et. al. Management of Acute Decompensated Heart Failure in the Emergency Department. Cong. Heart Fail. 2003; 9;5(1),3-18. Copyright 2003 by CHF, Inc.





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have been noncompliant with diet or medications. Topical or sublingual nitrates may be warranted if hypertension is present or a history of diastolic dysfunction exists.

The majority of ADHF visits is of moderate severity and is often characterized by significant hypertension. An abrupt increase in blood pressure may precipitate acute pulmonary edema, especially in patients with diastolic dysfunction. This presentation is more related to "vascular failure" rather than "cardiac failure."<sup>23</sup> Accordingly, the clinical target

is blood pressure control with early, aggressive vasodilation, more so than diuresis. This is particularly true when pulmonary congestion is related to fluid maldistribution and not an increase in total fluid volume. Preliminary data suggest these patients should be aggressively treated with intravenous vasodilators early in the ED course<sup>11</sup> and a substantial number may be appropriate for observation unit management.<sup>10</sup> Conventional vasodilators and diuretics are effective in symptomatically improving these patients but are associ-

ated with neurohormonal activation and several limitations to their ED use (Table 1). The use of nesiritide may have a significant role here.

Management of severe ADHF complicated by respiratory embarrassment and/or cardiogenic shock provides the greatest challenge to the emergency physician. These patients frequently require complex combinations of vasoactive medications, typically guided by invasive hemodynamic monitoring and airway support in an intensive care unit. The role and beneficial mortality effects of all therapies, including nesiritide, are less clear in this scenario. Fortunately, this represents a minority of patients presenting to the ED.

## Summary

In summary, the relationship between cardio-renal interactions, neurohormonal adaptation and clinical events should be a major focus of clinical decision making for ADHF and future drug development. The best approach to these patients, including the role of nesiritide and more traditional therapies such as nitroglycerin and diuretics, remains to be determined. Systematic appraisal of all existing data, thoughtful design of prospective clinical investigations, and evidence based, protocol and guideline driven care are ultimately critical to the current successful management of ADHF in the ED.



**Nesiritide should not be used for intermittent outpatient infusion, scheduled repetitive use to improve renal function, or to replace diuretics.**

### Disclosures

In accordance with the ACCME Standards for Commercial Support of CME, the authors have disclosed the following relevant relationships with pharmaceutical or device manufacturers: Dr. Kirk has received honoraria and/or research support, either directly or indirectly, from Scios.

### CME Accreditation

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# The Role of Nesiritide in the Management of Acute Decompensated Heart Failure: Review of Mortality Data and Recommendations for Clinical Use



## CME Post-Test Answer Form and Evaluation Questionnaire

### CME Post Test

After you have read the monograph, carefully record your answers by circling the appropriate letter for each question.

(Please circle answers below)

- In the pooled analysis performed by Sackner-Bernstein, there was a clear and statistically significant increase in mortality in patients treated with nesiritide.**
  - True
  - False
- Nitroglycerin, nitroprusside, and diuretics all cause neurohormonal activation.**
  - True
  - False
- Nesiritide is recommended for use in the outpatient setting.**
  - True
  - False
- Nesiritide causes reduction of pulmonary capillary wedge pressure and systemic vascular resistance.**
  - True
  - False
- Nesiritide use should be restricted to patients presenting to the hospital with ADHF and dyspnea at rest.**
  - True
  - False

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