

# Treatment of the Acute Decompensation of Heart Failure: Efficacy and Pharmacoeconomics of Early Initiation of Therapy in the Emergency Department

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*Most patients admitted with acute decompensated heart failure (ADHF) go through the emergency department as their initial point of care. New diagnostic tests hold the promise to improve the clinical accuracy of the emergency physicians' diagnosis. Beyond that there is growing recognition that the treatment provided initially has an important impact on the subsequent inpatient course. Basic care for ADHF has involved oxygen as needed, diuretics, and, occasionally, topical or sublingual nitroglycerin. A substantial proportion of patients are treated with vasoactive agents including inotropes and vasodilators such as nitroglycerin and nesiritide. Unfortunately, inotropes have not been demonstrated to improve the outcome of heart failure and, in fact, may be deleterious. The newer agent, nesiritide, has the advantage of being a balanced vasodilator with favorable effects on diuresis, symptom relief, and neurohormones. Evidence from registries indicates that early initiation of nesiritide compared to delayed initiation leads to improved outcomes with shorter lengths of stay, shorter stays in the intensive care unit, and a lower mortality rate. This article reviews the initial management of ADHF, the role of early initiation of vasodilator therapy, and the pharmacoeconomics of nesiritide treatment.*

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**Key words:** B-type natriuretic peptide • Acute decompensated heart failure • Nesiritide • Pharmacoeconomics • Vasoactive therapy

The treatment of acute decompensated heart failure (ADHF) begins with accurate diagnosis of the problem. Traditionally, this involves clinical judgement combined with ancillary tests, such as the chest radiograph. However, recent evidence suggests that assessment of B-type natriuretic peptide (BNP) levels also improves our ability to make the early diagnosis of heart failure, leading to shortened time to treatment and decreased length

of hospital stay.<sup>1,2</sup> An accurate, rapid diagnosis of ADHF is conducive to achieving rapid initiation of appropriate treatment. Emerging data suggest that the timing of the initiation of therapy can impact clinical outcomes of ADHF. This article focuses on the clinical impact and pharmacoeconomic benefits of early initiation of aggressive therapy.

### **Airway Management**

Typically the management of patients with ADHF revolves around rapid improvement of respiratory and circulatory status. Patients may present along a spectrum of acuity, ranging from sudden significant deterioration to a gradual decompensation over a period of days to weeks. Data from the Acute Decompensated Heart Failure National Registry (ADHERE<sup>TM</sup>) have shown us that a minority of patients present with rapid onset of pulmonary edema; fewer than 5% of patients arrive within 4 hours of the onset of symptoms.

Patients with impending respiratory failure from pulmonary edema with or without cardiogenic shock require rapid initiation of therapy to avoid further deterioration of their clinical status. Some patients may respond to high-flow oxygen therapy, although this requires close monitoring for patients with chronic obstructive pulmonary disease (COPD). In patients with severe COPD, a Venturi mask may be used to avoid the hypercarbia that may occur due to the Haldane effect.

Several means of noninvasive ventilation are available for managing patients with pulmonary edema. The use of noninvasive ventilation has been demonstrated, for a variety of respiratory conditions, to improve pulmonary status, and the judicious selection of patients for noninvasive ventilation may lead to the avoid-

ance of intubation in about 75% of patients.<sup>3</sup> It seems that continuous positive airway pressure (CPAP) may reduce the intubation rate, as well.<sup>4</sup> The use of bilevel positive airway pressure (BiPAP) may require close attention by medical personnel. Generally, placing a patient on BiPAP requires the presence of a nurse, respiratory therapist, or physician during the initial phases of management. Both CPAP and nasal BiPAP can improve oxygenation and reduce ventricular filling in patients with ADHF.<sup>5,6</sup> When successfully used, these techniques can decrease the length of time spent in the intensive care unit (ICU) and avoid the complications of intubation. The use of nasal BiPAP is somewhat more controversial. A few studies have suggested a higher complication rate when BiPAP is used, although this has not been confirmed in other trials.<sup>7,8</sup> There have not, however, been an adequate number of trials directly comparing the efficacy of CPAP to BiPAP to form a firm judgment.

Patients who are not eligible for noninvasive ventilation, including those who are obtunded, uncooperative, or unwilling to undergo a trial of noninvasive ventilation, require early intubation. This may be done either using awake sedation or rapid-sequence intubation. The advantage of rapid-sequence intubation is that it may be associated with fewer side effects.<sup>9</sup> Although various techniques and drugs are available, rapid-sequence intubation generally involves the administration of lidocaine to provide some airway anesthesia, a short-acting barbiturate, and then a paralytic agent.

### **Cardiogenic Shock**

Patients in cardiogenic shock require early, aggressive treatment followed by early consultation with

a cardiologist or intensivist. A trial of fluid administration, with the clinician watching for progressive pulmonary edema, may benefit patients with right ventricular infarction. A variety of inotropic agents are available if the hypotension does not respond to cautious fluid administration. Caution should be used with milrinone administration because it may cause a variable effect on the blood pressure of patients in cardiogenic shock. Milrinone may be useful in patients who have high systemic vascular resistance and in those on chronic  $\beta$ -blocker therapy. Alternatively, dopamine, typically started at 5  $\mu$ g/kg/min, may be titrated using clinical criteria, such as improved hemodynamics to guide therapy. Occasionally, patients benefit from combination therapy with both dobutamine for its inotropic effect and dopamine for its vasopressor effect. Intra-aortic balloon pumps are generally not available in the emergency department, and their use is beyond the scope of this article.

### **Diuretic Treatment**

Most patients presenting to the emergency department with ADHF receive diuretic therapy. The data from ADHERE show that approximately 80% of patients with this diagnosis will receive diuretic therapy in the emergency department. (ADHERE 2003 Q1 National Benchmark Report: [www.adhereregistry.com](http://www.adhereregistry.com)) Of the remaining 20%, approximately one half receive diuretics in the ambulance on the way to the emergency department. The remaining patients presumably do not have the diagnosis of heart failure made in the emergency department, thus are not treated with diuretics.

Furosemide is the agent typically used for the initiation of diuresis.

There has been limited investigation into the appropriate dose therapy for emergency department patients in heart failure. Conventionally, patients receive their total outpatient daily dose as a single intravenous bolus. Patients who have not been treated with diuretics typically receive an initial IV dose of 20 mg to 40 mg. It is important to monitor the patients for a brisk diuresis within the first 30–45 minutes. Patients who are not diuresing within that period of time may require repeated boluses with higher doses. Patients with renal insufficiency, in particular, may require higher doses of diuretics. It has been demonstrated, however, that even a single administration of a diuretic may lead to a subsequent decrease in the glomerular filtration rate, par-

combination of low-dose dopamine and moderate doses of furosemide.<sup>14</sup> A diuretic-based treatment of ADHF can lead to deterioration of renal function as well as activation of the RAAS and sympathetic nervous system.

### Other Agents

Morphine is occasionally used for managing ADHF. It has been shown in patients with chronic heart failure that low doses of oral morphine may improve their sensation of breathlessness.<sup>15</sup> In the acute setting, morphine presumably acts by increasing venous capacitance, although some studies have questioned this.<sup>16</sup> In a study by Timmis et al, patients with heart failure following myocardial infarction showed no improvement in stroke

compared with sublingual nitroglycerin leads to a greater improvement in cardiac index, with more sustained improvement in hemodynamic values.<sup>20</sup> In a study evaluating the addition of sublingual captopril to a regimen of oxygen, nitrates, morphine, and diuretics, patients given sublingual captopril had greater improvement in a respiratory distress score.<sup>21</sup>

Other therapy for patients with ADHF may involve the use of vasoactive agents, either intravenous inotropes or vasodilators. In ADHERE, about one third of patients receive vasoactive agents at some point during their hospitalization for ADHF. Of those patients who receive vasoactive therapy, one half receive inotropic therapy and the others receive vasodilator therapy. The use of inotropic therapy for the management of heart failure, in the absence of evidence of cardiogenic shock, has been shown to be associated with increased complications. Of patients who receive inotropic therapy, only about 20% have these drugs initiated in the emergency department.

### Inotropic Treatment

Dopamine has some properties that are theoretically beneficial in the heart failure setting, including dilation of the renal vessels. However, the use of dopamine can be complicated by marked vasoconstriction, increased myocardial oxygen demand, and ventricular arrhythmias. Dobutamine is more commonly employed in patients with ADHF. Dopamine is generally started at low doses, then titrated based on either clinical efficacy or measurement of pulmonary capillary wedge pressure (PCWP). Dobutamine has been compared with nesiritide in a prospective trial evaluating these drugs for arrhythmogenic effect. In a study by

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*Even a single administration of a diuretic may lead to a subsequent decrease in the glomerular filtration rate, particularly in patients with renal insufficiency.*

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ticularly in patients with renal insufficiency.<sup>10</sup> Patients who are not responding to furosemide may benefit from the addition of bumetanide. Patients may also benefit from the addition of a nonthiazide diuretic, such as metolazone. Combination treatment with hydrochlorothiazide has also been shown to enhance diuresis in refractory heart failure.<sup>11</sup> On the other hand, the administration of captopril has been shown to decrease the response to loop diuretics in patients with chronic heart failure.<sup>12</sup> Similarly, prior studies have failed to show an enhancement of diuresis by dopamine in ADHF.<sup>13</sup> High-dose furosemide, however, has been associated with reduced creatinine clearance and an increased risk of hypokalemia compared with the

index or left ventricular filling pressure after the administration of morphine. A retrospective study, however, has shown that the use of morphine is associated with an increased intubation rate and increased use of the ICU.<sup>17</sup> In another study, the use of morphine either alone or in combination with nitroglycerin was associated with a higher mortality rate than the use of nitroglycerin alone.<sup>18</sup>

Sublingual captopril has been evaluated in a few studies for the management of patients with acute pulmonary edema. In stable patients, sublingual administration of captopril decreases the time to onset of hemodynamic effect by 50% compared with oral administration of captopril.<sup>19</sup> In patients with severe heart failure, sublingual captopril

Silver and colleagues, patients were randomized to receive dobutamine for at least 24 hours and up to 7 days, or nesiritide at one of two doses, each higher than the current recommended starting dose.<sup>22</sup> The use of dobutamine was associated with an increase in ventricular ectopy, including frequency of premature ventricular complexes, and the occurrence of ventricular tachycardia. Patients receiving nesiritide required a shorter duration of vasoactive therapy. There was a trend toward fewer readmissions for nesiritide compared with dobutamine, with a lower 6-month mortality rate in the nesiritide group.

Milrinone is a phosphodiesterase inhibitor with properties similar to aminophylline. Because it does not act on 1c  $\beta$ -receptors, it may be a useful inotropic therapy for patients who are using 1c  $\beta$ -blockers on an outpatient basis. Compared with nitroglycerin, milrinone has been shown to be more effective in rapidly improving hemodynamics and global clinical status.<sup>23</sup> However, a large study—the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)—failed to show a beneficial effect for milrinone.<sup>24</sup> In that study, patients received milrinone in addition to standard therapy. There was a higher adverse event rate for patients receiving milrinone, without any concomitant decrease in length of stay. There was a trend toward an increased mortality rate in patients receiving milrinone. The adverse effects appear to be related to the etiology of heart failure, with ischemic patients having a worse outcome.<sup>25</sup> Caution should be used when administering milrinone to patients with decreased creatinine clearance, in which case lower doses should be used. Because milrinone

has vasodilator properties, it can lead to hypotension, particularly in the setting of cardiogenic shock.

### Nitroglycerin

Although it has been used for many years, and is often the vasodilator employed in the ED, there is relatively little data to guide the use of nitroglycerin in ADHF. Patients with advanced heart failure may have a greater decrease in systemic vascular resistance, increase in stroke volume, and improved global clinical status when given milrinone rather than intravenous nitroglycerin.<sup>23</sup> Data

of dyspnea, and global well-being.<sup>26</sup> The more rapid clinical improvement may reduce the need for mechanical ventilation in some patients and necessity for an ICU admission.

Nesiritide is safe when administered to patients with ADHF.<sup>29</sup> The incidence of symptomatic hypotension is approximately 4%, similar to that observed with intravenous nitroglycerin. Patients who develop hypotension are generally managed by stopping the drug infusion and, if necessary, administering small fluid boluses. One advantage to administering nesiritide instead of nitroglyc-

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from the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial show that nitroglycerin is associated with a slower onset of effect compared with nesiritide.<sup>26</sup> Additionally, nitroglycerin is associated with the rapid onset of tolerance, occurring within 2 hours of administration.<sup>27</sup> An interesting prehospital trial found that repeated small boluses of nitroglycerin were safer than BiPAP for the management of severe pulmonary edema.<sup>28</sup>

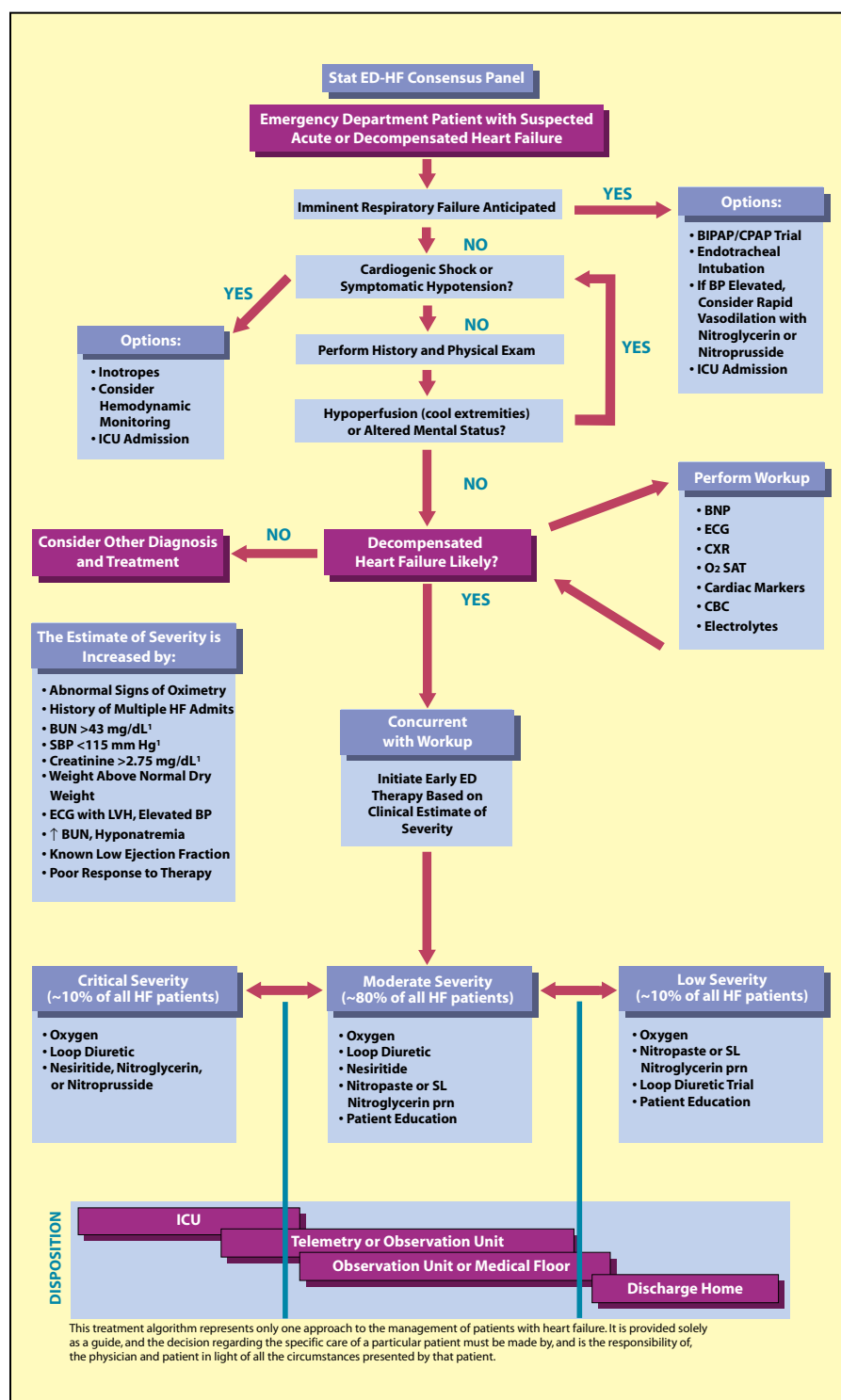
### Nesiritide

Nesiritide belongs to the natriuretic peptide class of drugs. Studies have demonstrated that nesiritide has beneficial properties for patients with heart failure, including vasodilation, diuresis, improvement in PCWP, and reduction in angiotensin and norepinephrine levels. Compared with nitroglycerin, nesiritide has a more rapid onset of effect, with greater improvements in PCWP, and earlier improvement in patient's symptoms

erin is that nesiritide does not lead to reflex tachycardia. A small proportion of patients (<1%) will develop bradycardia, with a few of these patients requiring intervention. The use of nesiritide has been shown to be safe in patients with renal insufficiency, as it has particular renal protective properties. Compared with nitroglycerin, in the setting of renal insufficiency, nesiritide leads to a faster and greater decrease in pulmonary capillary wedge pressure, with a similar safety profile.<sup>30</sup>

### Benefits of Early Initiation of Therapy

As noted above, emergency physicians have a variety of treatment options in managing patients with ADHF. There have been few randomized clinical trials evaluating the various combinations of treatment options in this setting. The advantage of the ADHERE registry is that it allows an analysis of the various means of treating heart failure, with a comparison to the outcome



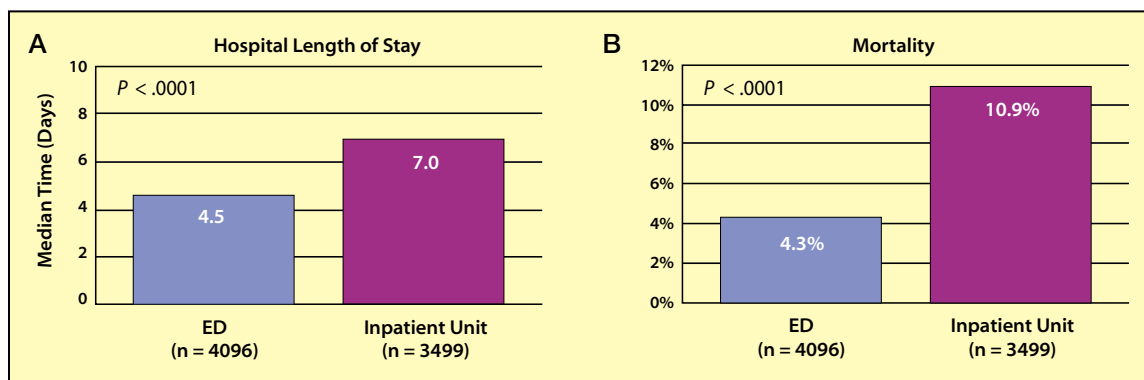
**Figure 1.** Guidelines for the early stabilization and disposition of acute decompensated heart failure (HF) in the emergency department (ED). BiPAP, bilevel positive airway pressure; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood cell count; CPAP, continuous positive airway pressure; CXR, chest radiography; ECG, echocardiography; ICU, intensive care unit; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; SL, sublingual. Adapted by The ADHERE Registry Scientific Advisory Committee and based on Stat ED-HF Consensus Panel.

in those patients hospitalized for this condition (Figure 1). Moreover, the registry is based on a large national sample of ADHF patients. As of April 2003, data from 46,599 patient hospitalizations from over 260 participating hospitals were in the registry. ADHERE enrollment is expected to exceed 100,000 by the fall of 2003, providing tremendous opportunities to learn about and effect changes in the management of ADHF.

Early studies of the management of heart failure in the emergency department have shown that the patient population mirrors that of the larger group of hospitalized patients. Patients seen in the emergency department for heart failure are older and are a predominately Medicare-covered population. About one half of patients have systolic dysfunction.

Approximately two thirds of patients managed in the emergency department receive diuretic therapy, topical nitroglycerin, or morphine as their sole treatment. About 15% are started on IV vasoactive infusion therapy in the emergency department. This represents about half of the patients who receive vasoactive infusion therapy at some point during hospitalization. For patients who receive vasoactive therapy in the emergency department, the length of stay is about one third shorter than those who do not receive this therapy (Figure 2A).<sup>31</sup> When vasoactive therapy is initiated in the emergency department, the time to administration is about 1 hour, compared with more than 22 hours when this treatment is started on the inpatient units. The early initiation of vasoactive therapy in the emergency department is associated with a lower in-hospital mortality rate, decreased use of invasive procedures, and decreased length of stay in the





**Figure 2. (A)** Effect of ED initiation of vasoactive agents on length of stay. Presented at ACEP Research Forum; Boston, MA, 2003. **(B)** Effect of ED initiation of vasoactive agents on in-hospital mortality rates. Based on ADHERE data, April 2003.

ICU (Figure 2B).<sup>31</sup> These findings are true whether one looks at vasoactive therapy as a whole or only looks at vasodilator therapy with nitroglycerin or nesiritide. Therefore, the early initiation of vasoactive therapy in the appropriate ADHF patient in the ED would seem to be a reasonable goal.

### Pharmacoeconomics of Nesiritide Use

The early use of vasoactive agents, such as nesiritide, is associated with improved outcomes. Compared with the inpatient initiation of vasoactive therapy, the use of this medication in the emergency department is associated with reductions in hospital length of stay, mortality rate, length of stay in the ICU, and use of invasive procedures. When adjusted for other risk factors, including age, systolic dysfunction, and renal insufficiency, patients receiving vasoactive agents in the emergency department are 50% less likely to suffer an adverse outcome compared with those patients who have this therapy initiated on the inpatient units. Although this has not been subjected to a formal economic analysis, it should be clear that a decreased length of stay, decreased time in the ICU, and decreased use of invasive procedures leads to lower overall costs to the patient and to the hospital.

The use of nesiritide versus dobutamine has been tested in the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT)

although the drug cost of nesiritide is higher than that of dobutamine, the savings from the use of nesiritide fully offset the cost of the drug.

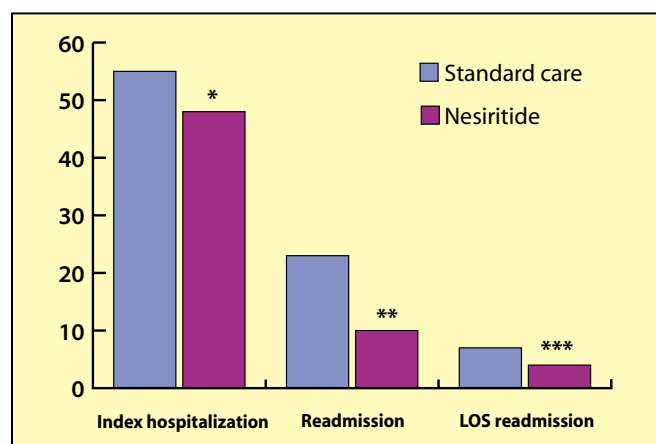
The Prospective Randomized

*The costs associated with the treatment of heart failure, admission, readmission, and length of stay all decreased with the use of nesiritide.*

trial. Dobutamine is associated with substantial proarrhythmic and chronotropic effects in patients with decompensated congestive heart failure, whereas nesiritide actually reduces ventricular ectopy or has a neutral effect.<sup>32</sup> The data from all of the trials comparing nesiritide with dobutamine have been aggregated in an economic model using national hospital cost data.<sup>33</sup> This study shows that

Outcomes Study of Acutely Decompensated Congestive Heart Failure Initially Treated in Outpatients with Natrekor (PROACTION) was a study of the addition of nesiritide to otherwise standard care in patients managed in observation and similar units. In the PROACTION trial, patients were initially evaluated in the emergency department and started on therapy with diuretics, oxygen, and, if desired,

**Figure 3. Results from the PROACTION trial.**<sup>34</sup> Data presented as percentage for admission rates and days for length of stay (LOS). \*, not significant; \*\*,  $P = .058$ ; \*\*\*  $P < .032$ .



topical nitroglycerin or morphine. The patients were then randomized to receive either placebo or nesiritide for a minimum of 12–24 hours in the observation unit. Subsequently, patients were either discharged or admitted. Patients who were admitted could be continued on nesiritide at the discretion of the treating physician. This study showed that the use of nesiritide was associated with a trend toward decreased overall admissions, decreased admissions for heart failure, and a reduced readmission rate. The length of stay on readmission was significantly shorter for patients treated with nesiritide when compared with those treated with placebo. The economic aspects of the use of nesiritide were analyzed using national hospital cost data. The costs associated with the treatment of heart failure, admission, readmission, and length of stay all decreased with the use of nesiritide (Figure 3). Again, when aggregating these costs together with the savings associated with the use of nesiritide, the other savings offset the cost of the drug.<sup>34</sup> These findings are similar to those of a retrospective study that found the

addition of nesiritide to baseline therapy was associated with a decreased length of stay.<sup>35</sup> Interestingly, in that study, despite the nesiritide cohort of patients having greater co-morbidities including a lower ejection fraction, higher blood pressure, longer QRS interval, and higher serum creatinine level, superior results were observed in that cohort. Despite increased baseline severity, length of stay was shorter in patients treated with nesiritide. An additional retrospective study has also found that the addition of nesiritide leads to decreased length of stay and reduction in health care resource use, with shorter stays in the ICU and reduced incidence of complications.<sup>36</sup>

### Conclusion

In summary, hospitalization for heart failure is associated with about a 5% in-hospital mortality rate and a 20% readmission rate over 30 days. Many of these patients require prolonged hospitalization and the use of the ICU. Physicians use vasoactive therapy in about one third of patients hospitalized for heart failure. These patients are

characterized by renal insufficiency, elevated systolic blood pressure, anemia, liver failure, pulmonary edema, and depressed systolic function. Identification of these patients early in the course and earlier initiation of aggressive treatment in the emergency department can improve in-hospital mortality rate and reduce the need for invasive procedures, length of ICU stay, and overall length of admission. Nesiritide is a particularly useful agent for ADHF treatment in the emergency department. The savings of early initiation of therapy should outweigh the drug acquisition cost of nesiritide and lead to economic benefits. ■

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### Main Points

- Patients with impending respiratory failure from pulmonary edema with or without cardiogenic shock require rapid initiation of therapy; those in cardiogenic shock require early aggressive treatment followed by early consultation with a cardiologist or intensivist.
- According to the Acute Decompensated Heart Failure National Registry (ADHERE), about 80% of patients with this diagnosis receive a diuretic, typically furosemide, in the emergency department; of the remaining 20%, approximately half receive a diuretic in the ambulance on the way to the emergency department.
- Other agents used in managing acute decompensated heart failure are morphine; captopril; inotropic agents, such as dopamine, dobutamine, and milrinone; nitroglycerin; and nesiritide.
- Studies have demonstrated that nesiritide has beneficial properties for patients with heart failure, including vasodilation, diuresis, improvement in pulmonary capillary wedge pressure, and reduction in angiotensin and norepinephrine levels. Compared with nitroglycerin, nesiritide has a more rapid onset of effect, with greater improvements in pulmonary capillary wedge pressure, early improvement in patients' symptoms of dyspnea, and global sense of well-being.
- The early use of nesiritide is associated with improved outcomes. When nesiritide is initiated in the emergency department rather than in the inpatient unit, it results in a decrease in length of hospital stay, mortality rate, length of ICU stay, invasive procedures, and adverse outcomes. This, in turn, leads to lower overall costs to the patient and the hospital.

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