Beneficial Effects of Early Initiation of Vasoactive Agents in Patients With Acute Decompensated Heart Failure

Mitchell T. Saltzberg, MD

Midwest Heart Specialists Heart Failure Program, Midwest Heart Foundation Echocardiographic Core Laboratory, Downers Grove, IL

Early diagnosis and treatment of acute decompensated heart failure (ADHF) results in improved clinical outcomes, reduced resource utilization, improved quality of life, and lower treatment costs. Currently, heart failure results in nearly 1 million hospitalizations annually in the United States, and 50% of hospitalized patients are readmitted within 6 months of initial discharge. The costs associated with resource utilization are substantial. Despite the personal and societal burden of this condition, until recently, very little progress had been made in optimizing treatment of ADHF. Nesiritide, a human recombinant B-type natriuretic peptide, is a safe, effective vasodilator that can be easily used early in the emergency department to improve outcomes in ADHF.
[Rev Cardiovasc Med. *2004;5(suppl 4):S17–S27*]

Key words: Heart failure • Nesiritide • Inotropic agents • Treatment algorithm

In the United States, approximately 995,000 hospitalizations for acute decompensated heart failure (ADHF) occur annually, an increase of 164% since 1979.[1,2] The average length of stay (LOS) is 5.4 days, which translates to almost 5.4 million hospital days per year.[2] In addition, 50% of patients who are hospitalized for ADHF are readmitted within 6 months of discharge.[3]

The economic burden of ADHF is substantial. The majority of the costs result from resource utilization associated with hospitalization, with an estimated annual total hospital reimbursement of $13.6 billion.[1] Most patients with ADHF are elderly, and more Medicare dollars are spent on the diagnosis and treatment of heart failure (HF) than on any other diagnosis.[4] The costs of drugs and durables represent only approximately 10% of the total expense for treating this disease. Any measure that optimizes care in the outpatient setting by shortening LOS and decreasing the need for readmission is expected to improve patient quality of life and reduce costs.[5]

Heart failure affects nearly 20% of the population, with a disproportionate portion of the elderly population being affected. HF rarely exists in isolation, and the presence of multiple comorbidities can delay HF recognition. The signs and symptoms of HF are nonspecific, and the primary symptom, dyspnea, is also common in the elderly, the obese, and those with chronic obstructive pulmonary disease or chronic kidney disease.[6–8] In the emergency department (ED), congestive HF has been shown to be misdiagnosed 12% of the time, with overdiagnosis and underdiagnosis occurring with the same approximate frequency.[6,8] Fortunately, the use of endogenous B-type natriuretic peptide (BNP) levels as a marker for HF is a promising approach to achieving a rapid, accurate HF diagnosis and can help to reduce clinical indecision.[6,9]

Management of ADHF

The hemodynamic and clinical profile of the typical ADHF patient is characterized by preserved cardiac output with increased intravascular volume.[10] HF patients in general, and ADHF patients in particular, are characterized by significant neurohormonal changes, with marked upregulation of vasoconstrictors, including norepinephrine, angiotensin II, and endothelin. In addition, levels of aldosterone and arginine vasopressin rise, contributing to salt and free water retention. The insights gained from this neurohormonal understanding of HF form the basis for our efforts to use oral angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and β-blockers to treat HF, and justify further experimental work with other antagonists of the neurohormonal cascade.

Recent studies have raised serious questions about the routine use of inotropic agents in the setting of ADHF.

Triggers of ADHF are varied and include patient noncompliance with treatment and follow-up, arrhythmias, infections, ischemia, comorbidities, and the inevitable progression of the underlying disease.[10] With ADHF, neurohormonal activation is enhanced further, resulting in a vasoconstrictor and vasodilator imbalance that further compromises cardiac output and exacerbates HF symptoms.

Positive inotropic activity usually produces short-term hemodynamic benefits, and inotropic agents have often been used to treat ADHF. However, recent studies have raised serious questions about the routine use of inotropic agents in this setting. Cuffe and colleagues[11] found that, compared with placebo, short-term milrinone therapy for ADHF did not significantly decrease median LOS for cardiovascular diagnoses over a 60-day period after treatment (6 days for milrinone vs 7 days for placebo, $P = .71$) (Table 1). Milrinone and placebo treatments resulted in statistically similar in-hospital mortality (3.8% vs 2.3%, $P = .19$), 60-day mortality (10.3% vs 8.9%, $P = .41$), and composite incidence of death or readmission (35.0% vs 35.3%, $P = .92$). However, significantly more patients who received milrinone experienced sustained hypotension (10.7% vs 3.2%, $P < .001$), and new atrial arrhythmias were more frequent (4.6% vs 1.5%, $P = .004$).[11]

Although the results of several small studies demonstrated improved outcomes with dobutamine treatment in patients with ADHF, these results have not been supported in large studies, and dobutamine has been associated with an increase in adverse events and death.[12,13] In a study of 255 patients with ADHF, dobutamine treatment significantly increased the number of serious ventricular arrhythmias.[13]

In contrast, patients presenting to the ED with ADHF experienced significant benefits from early intravenous infusion of vasoactive agents.[14–16] Compared with placebo, initiation of intravenous vasoactive therapy with nesiritide in the ED reduced median overall hospital LOS (3.0 days vs 7.0 days) and median LOS in intensive care units (ICUs) and critical care units (CCUs) (2.1 days vs 4.5 days, $P < .001$).[14,15] Furthermore, compared with initiation of nesiritide after hospital admission, initiation of nesiritide in the ED resulted in significantly reduced hospital LOS (4.1 days vs 5.7 days, $P < .0001$).[16]

Endogenous BNP is a counter-regulatory hormone that is produced by the ventricles in response to pressure and volume overload in the setting of acute and chronic HF.[17] Levels of BNP, one of several structurally sim-

Table 1
Outcomes, Adverse Events, and Mortality From Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)

	Placebo (n = 472)	Milrinone (n = 477)	*P*
Primary outcome			
Median days of hospitalization for cardiovascular causes within 60 days of treatment	7	6	.71
Median days of hospitalization from initial treatment to initial discharge	5	5	.99
Death or readmission within 60 days, no. patients/total (%)	164/462 (35.3)	166/474 (35.0)	.92
Adverse event during index hospitalization			
Myocardial infarction	2 (0.4)	7 (1.5)	.18
New atrial fibrillation or flutter	7 (1.5)	16 (4.6)	.004
Ventricular tachycardia or fibrillation*	7 (1.5)	16 (3.4)	.06
Sustained hypotension	15 (3.2)	51 (10.7)	<.001
Death	11 (2.3)	18 (3.8)	.19

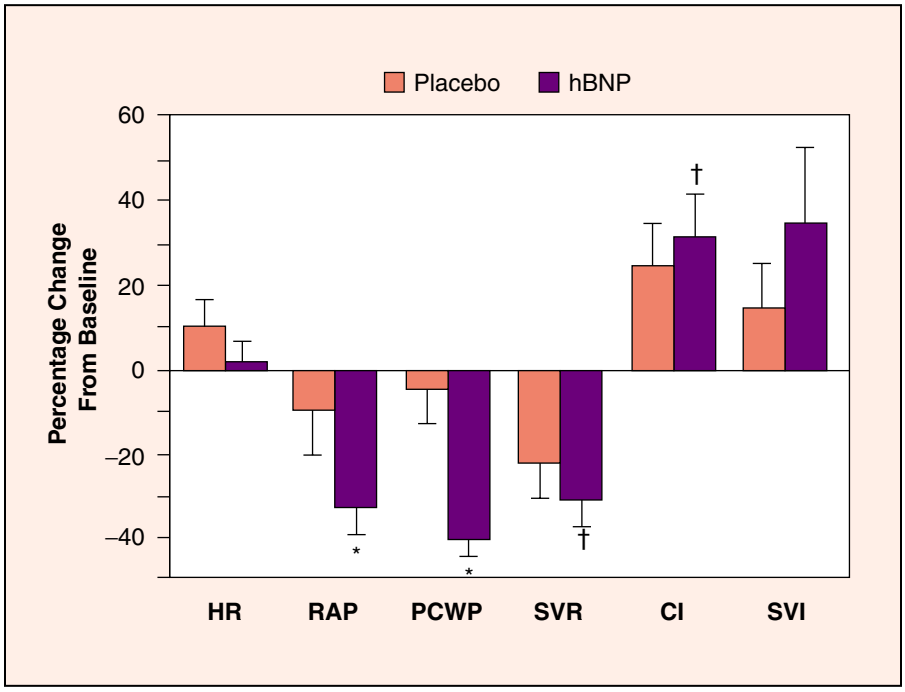
Data are presented as n (%) unless otherwise indicated. Adapted with permission from Cuffe et al.[11]
*Reported by the investigator.

ilar natriuretic peptides, are elevated in HF and are correlated with left ventricular end-diastolic pressure, New York State Heart Association functional class, and prognosis. BNP relaxes smooth muscle cells, decreasing venous return and systemic vascular resistance.[18,19] BNP also has diuretic and natriuretic effects.[20–22] Taken together, the synthesis and release of BNP act to counteract the vasoconstricting and volume-expanding neurohormonal milieu and restore more favorable hemodynamics and resolve symptoms.

In patients with chronic HF, progressively higher levels of BNP are required to produce the desired compensatory effects.[21] This BNP resistance results from a variety of factors, including receptor interference by angiotensin II. However, a number of studies have demonstrated that further elevating BNP levels with an infusion of exogenous BNP can restore the counter-regulatory effects.[21]

Nesiritide, a recombinant form of BNP, exerts favorable hemodynamic effects in patients with HF (Figure 1).[17,22] Intravenous nesiritide inhibits the renin–angiotensin–aldosterone system, leading to decreased levels of circulating aldosterone, norepinephrine, and endothelin.[20,22–26] Nesiritide treatment also results in improved heart rate variability, which might reflect a de-

Figure 1. *Favorable hemodynamic effects of nesiritide in patients with heart failure. hBNP, human B-type natriuretic peptide; HR, heart rate; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic volume resistance; CI, cardiac index; SVI, stroke volume index. *P < .01; †P < .05. Adapted with permission from Abraham et al.[22]*



crease in sympathetic overactivity.[27] As would be expected, these effects are associated with natriuresis, diuresis, vasodilation, and smooth muscle relaxation.[20,22,25,28,29] Cardiac output is improved, with a notable lack of inotropic, chronotropic, or proarrhythmic effects.[12,13,22,29–31]

A number of studies have demonstrated that further elevating BNP levels with an infusion of exogenous BNP can restore the counter-regulatory effects.

In hospitalized patients, treatment of ADHF with nesiritide reduces resource utilization, improves clinical outcomes, and reduces costs of care. In a randomized open-label evaluation comparing nesiritide to standard care with dobutamine among patients hospitalized for ADHF, those in the nesiritide group required intravenous therapy for a significantly shorter period ($P \leq .012$).[32] There was a trend toward decreased readmissions and lower 6-month mortality with nesiritide treatment. There was no difference in mean LOS between the two groups.[32]

Results from a retrospective, matched case–control study of 216 patients admitted for ADHF also demonstrated significant benefit from nesiritide treatment. Patients who received nesiritide spent significantly less time in the CCU (−22.7 hours, $P < .03$ compared with no nesiritide).[33] The LOS on the general medical ward was not significantly different between the two groups, although there was a trend toward shorter LOS with nesiritide. The net result was a mean savings of $500 per patient for those treated with nesiritide compared with controls.[33]

In-hospital mortality might also be reduced with nesiritide treatment. Multiple regression and propensity analyses of clinical practice data were used to compare outcomes in patients who were treated with nesiritide, nitroglycerin, dobutamine, or milrinone at the discretion of their physician.[34] The odds ratios for mortality in patients treated with nesiritide were 0.83 (95% confidence interval [CI], 0.6–1.1), 0.57 (95% CI, 0.42–0.76), and 0.41 (95% CI, 0.31–0.53) compared with nitroglycerin, milrinone, and dobutamine, respectively.[34]

Another analysis of pooled data comparing nesiritide with dobutamine revealed that the higher cost of nesiritide was offset by the use of fewer resources and a significantly lower readmission rate (4.0% with nesiritide vs 9.4% with dobutamine, $P = .03$).[35] Similar results were found in a retrospective review of consecutive patients treated on a HF service.[36] Nesiritide led to greater reductions in pulmonary capillary wedge pressure at 24 hours (-8.89 ± 1.73 mm Hg with nesiritide vs -3.78 ± 1.56 mm Hg with milrinone, $P = .056$), and these reductions became significantly greater by 48 hours (-10.5 ± 1.69 mm Hg with nesiritide vs -4.0 ± 2.13 mm Hg with milrinone, $P = .026$). Largely owing to a significant decrease in time spent in the ICU (3.9 ± 0.39 hours with nesiritide vs 5.9 ± 0.52 hours with milrinone, $P = .007$), the total treatment costs were lower in the nesiritide group than in the milrinone group.[36]

Nesiritide is generally safe and well tolerated. The most common adverse event associated with nesiritide treatment is dose-dependent hypotension, which is usually asymptomatic or mild. In patients who are symptomatic, hypotension usually responds over a 1- to 2-hour period of observation after discontinuing the infusion and, after restoration of normal blood pressure, reinitiating the infusion at a lower dose.[31] The incidence of hypotension is not significantly greater among nesiritide-treated patients than among patients treated with nitroglycerin or controls (placebo or other comparator).[29,31] Overall, the adverse event profile of nesiritide treatment is superior to that of nitroglycerin when one considers the high rate of headache associated with nitroglycerin use.

Overall, the adverse event profile of nesiritide treatment is superior to that of nitroglycerin.

Algorithms for Diagnosis and Treatment of ADHF

At least two similar evidence-based guidelines for the diagnosis and treatment of ADHF have been published recently. A consensus statement was developed that was based on an intensive literature review spanning the years from 1966 to March 2003.[37] The authors recommend that diagnosis be made within 2 hours of patient presentation in the ED (Figure 2).[37]

Intravenous vasoactive therapy should be initiated within 2 hours after diagnosis (≤4 hours after presentation). Assessment of the patient's response to therapy over the ensuing 2 hours should be used to determine the need for further therapy. If these recommendations are followed, the need for inpatient care or transfer to an observation unit can be deter-

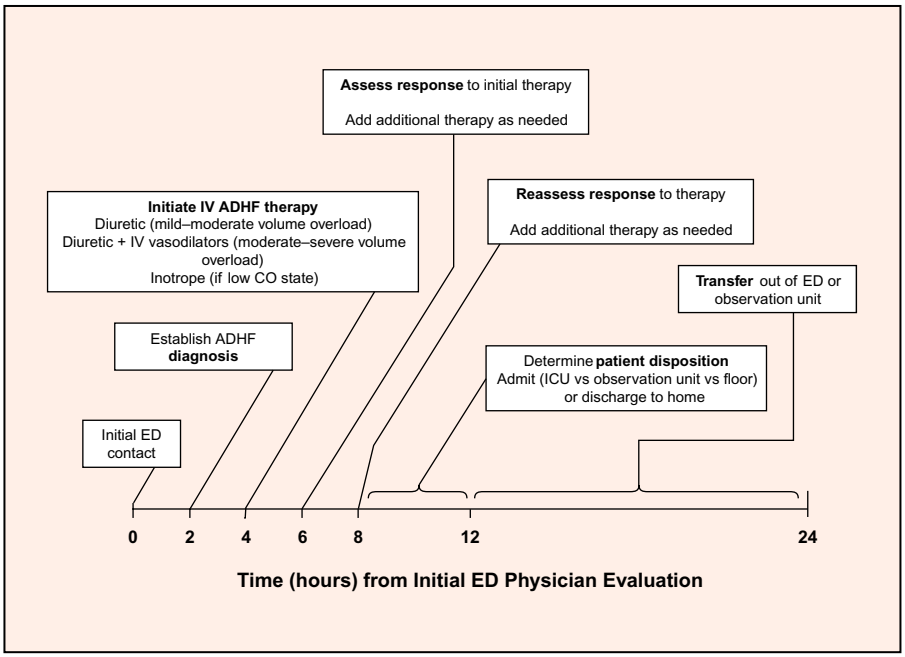
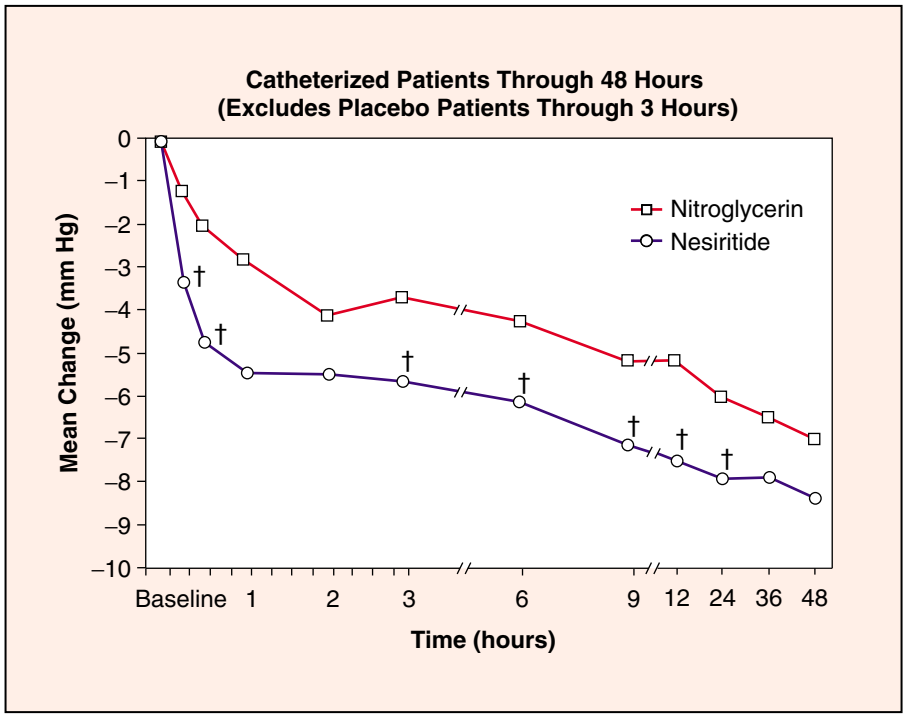


Figure 2. *Timeline for management of acute decompensated heart failure (ADHF) in the emergency department (ED) or observation unit. IV, intravenous; CO, cardiac output; ICU, intensive care unit. Adapted with permission from DiDomenico et al.*[37]

Figure 3. *Changes from baseline in pulmonary capillary wedge pressure. †$P < .05$ for nesiritide compared with nitroglycerin. Reprinted with permission from Publication Committee for the VMAC Investigators.*[29]



mined within 12 hours of initial contact.[37]

Treatment recommendations are generally based on the patient's fluid volume status and cardiac output. Individuals with mild volume overload (eg, absence of pulmonary congestion) can be treated with intravenous diuretic monotherapy.[37] For patients with more severe volume overload who have adequate blood pressure, a parenteral vasodilator, such as nitroglycerin or nesiritide, can be added to the diuretic therapy.[37] Depending on local hospital policy, patients undergoing nitroglycerin treatment might need admission to an ICU to titrate therapy to high enough doses to produce favorable hemodynamic effects.[37]

Nesiritide treatment has a predictable and sustained effect at the recommended dosage. Dose titration and invasive hemodynamic monitoring are generally not required, so treatment can begin in the ED or the observation unit. In the Vasodilation in the Management of Acute Congestive Heart Failure trial of 489 patients, within 15 minutes, nesiritide treatment resulted in significantly greater reductions in pulmonary capillary wedge pressure than nitroglycerin. This benefit was sustained over 24 hours (Figure 3).[29]

Patients who do not respond to intravenous diuretics, intravenous vasodilators, or both might have low cardiac output. These patients might require additional therapy to achieve symptom relief.[37] Dobutamine is recommended for treatment of patients with low cardiac output and blood pressure of 90 mm Hg or less, provided they are not receiving concomitant β-blocker therapy.[37] For patients with adequate blood pressure who are taking β-blockers, milrinone therapy can be initiated. Patients with adequate blood pressure might benefit from diuretic and vasodilator

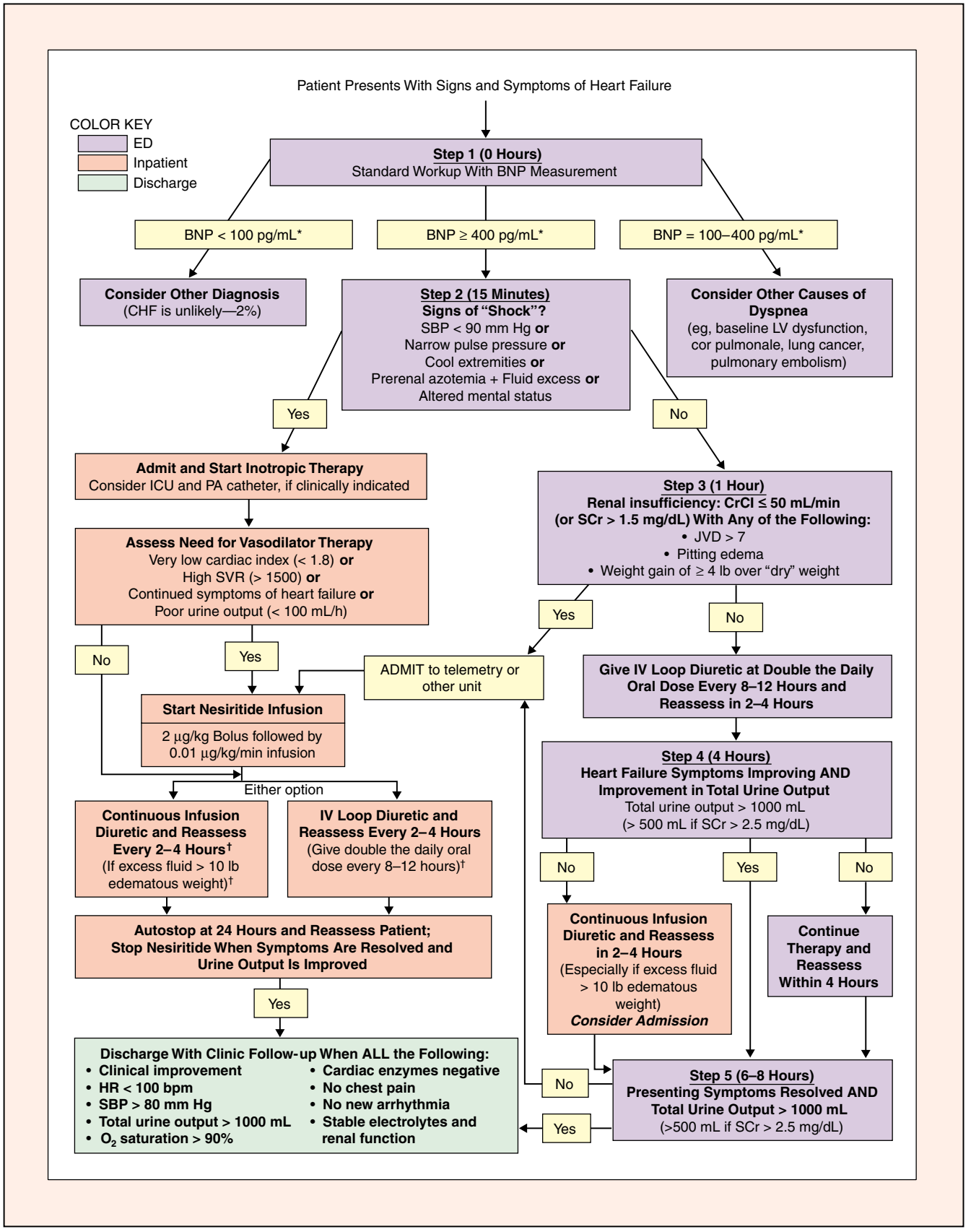

Patient Presents With Signs and Symptoms of Heart Failure
COLOR KEY
ED
Inpatient
Discharge
Step 1 (0 Hours)
Standard Workup With BNP Measurement
BNP < 100 pg/mL*
BNP ≥ 400 pg/mL*
BNP = 100–400 pg/mL*
Consider Other Diagnosis
(CHF is unlikely—2%)
Step 2 (15 Minutes)
Signs of "Shock"?
SBP < 90 mm Hg or
Narrow pulse pressure or
Cool extremities or
Prerenal azotemia + Fluid excess or
Altered mental status
Consider Other Causes of Dyspnea
(eg, baseline LV dysfunction, cor pulmonale, lung cancer, pulmonary embolism)
Yes
No
Admit and Start Inotropic Therapy
Consider ICU and PA catheter, if clinically indicated
Assess Need for Vasodilator Therapy
Very low cardiac index (< 1.8) or
High SVR (> 1500) or
Continued symptoms of heart failure or
Poor urine output (< 100 mL/h)
No
Yes
Start Nesiritide Infusion
2 µg/kg Bolus followed by
0.01 µg/kg/min infusion
Either option
Continuous Infusion Diuretic and Reassess Every 2–4 Hours†
(If excess fluid > 10 lb edematous weight)†
IV Loop Diuretic and Reassess Every 2–4 Hours
(Give double the daily oral dose every 8–12 hours)†
Autostop at 24 Hours and Reassess Patient;
Stop Nesiritide When Symptoms Are Resolved and Urine Output Is Improved
Yes
Discharge With Clinic Follow-up When ALL the Following:
• Clinical improvement
• HR < 100 bpm
• SBP > 80 mm Hg
• Total urine output > 1000 mL
• O2 saturation > 90%
• Cardiac enzymes negative
• No chest pain
• No new arrhythmia
• Stable electrolytes and renal function
Step 3 (1 Hour)
Renal insufficiency: CrCl ≤ 50 mL/min
(or SCr > 1.5 mg/dL) With Any of the Following:
• JVD > 7
• Pitting edema
• Weight gain of ≥ 4 lb over "dry" weight
Yes
No
ADMIT to telemetry or other unit
Give IV Loop Diuretic at Double the Daily Oral Dose Every 8–12 Hours and Reassess in 2–4 Hours
Step 4 (4 Hours)
Heart Failure Symptoms Improving AND
Improvement in Total Urine Output
Total urine output > 1000 mL
(> 500 mL if SCr > 2.5 mg/dL)
No
Yes
No
Continuous Infusion Diuretic and Reassess in 2–4 Hours
(Especially if excess fluid > 10 lb edematous weight)
Consider Admission
Continue Therapy and Reassess Within 4 Hours
No
Yes
Step 5 (6–8 Hours)
Presenting Symptoms Resolved AND
Total Urine Output > 1000 mL
(>500 mL if SCr > 2.5 mg/dL)

Figure 4. *Algorithm for early goal-directed therapy for acute decompensated heart failure. ED, emergency department; BNP, B-type natriuretic peptide; CHF, congestive heart failure; ICU, intensive care unit; PA, pulmonary artery; SVR, systemic vascular; HR, heart rate; SBP, systolic blood pressure; LV, left ventricular; CrCl, creatinine clearance; SCr, serum creatinine; JVD, jugular venous distention. *Clinical decisions should not be based solely on BNP level. BNP levels shown are for the Triage (Biosite) assay. †Consider decreasing dose of diuretic by ≤50% if receiving nesiritide. Adapted with permission from Costanzo et al.[38]*

therapy. Admission to the ICU and aggressive management might be needed for patients with very low cardiac output; a pulmonary artery catheter can be placed to more accurately assess the hemodynamic function of these patients.[37]

The Midwest Heart Specialists Heart Failure Program, in conjunction with Cardinal Health, has produced an algorithm for the early goal-directed therapy (EGDT) of ADHF patients (Figure 4).[38] Several key decision points are emphasized: 1) early and accurate diagnosis of HF with clinical variables and BNP testing; 2) identification of those ADHF patients with shock, followed by prompt admission; 3) treatment of the ADHF patient with renal insufficiency with vasoactive medication and early admission; and 4) frequent re-evaluation of the ED-treated patient to identify early treatment failures, followed by prompt admission and institution of vasoactive therapy in these patients. The algorithm includes the use of plasma BNP levels in conjunction with other clinical information to improve the accuracy of diagnosis.[38] ADHF can be difficult to diagnose, and this test can add significant independent predictive power to other clinical variables, thereby greatly decreasing the time to initiation of treatment.

Although shock is present in less than 5% of patients with ADHF, the urgent need for intervention makes assessment for shock a critical step in patient evaluation.[38] Inotropic therapy might be needed in these patients to restore and maintain cardiac output. ADHF patients with signs and symptoms of shock should be admitted to the ICU promptly. Vasodilator therapy (eg, nitroprusside, nitroglycerin, or nesiritide) can on rare occasions be combined with inotropic support in the setting of very low cardiac output (<1.8 L/min/m^2), high systemic vascular resistance (>1500 dyne-sec cm^{-5}), continued symptoms, or poor urine output (<100 mL/h), despite the use of inotropic agents. These patients can be managed with continuous invasive hemodynamic monitoring, and therapy should be tailored individually. Strong consideration should be given to other methods of improving cardiac output in these settings, including placement of an intra-aortic balloon pump or ventricular assist device.

It is important to emphasize that in the presence of ADHF with volume overload, diuretic therapy is usually needed, but dosing must be adequate to achieve the desired response. Diuretics can be administered intravenously at twice the outpatient dose (up to the maximal recommended doses) either by bolus administration or as a continuous infusion to achieve more consistent drug delivery to the loop of Henle.[38]

Assessment of renal function is also essential in making treatment decisions for patients presenting with signs and symptoms of ADHF and is a key element of the EGDT algorithm. Renal insufficiency is associated with increased risk of death, prolonged length of stay, and increased resource utilization.[39–41] Patients with ADHF and renal insufficiency (defined as a creatinine clearance of ≤50 mL/min) should be admitted to the hospital, and treatment with intravenous vasoactive medication can be started. Patients with preserved renal function can be treated in the ED with an intravenous loop diuretic and reassessed after 2 to 4 hours of treatment. In the presence of more than 10 lb of edematous weight and where adequate diuresis in the ED is unlikely, early admission should be considered.[38]

Diuretic resistance is common in patients with HF and is associated with increased mortality. Nitroglycerin, nitroprusside, and loop diuretics might indirectly contribute to stimulation of the neurohormonal factors responsible for the acute decompensation. Therefore, nesiritide therapy should be considered for patients who are not responding to other interventions. Nesiritide suppresses aberrant neurohormonal activation and has been found to increase urine output in the absence of diuretics in animal models.[20] It might relieve diuretic resistance by potentiating the effects of loop diuretics.[30]

It is estimated that approximately 10% of ADHF patients can be easily managed in the ED and discharged directly. The criteria for hospital discharge are shown in Table 2. Patients should not be sent home until they

Table 2
Criteria for Hospital Discharge of Heart Failure Patients

Clinical improvement (symptom resolution)
Heart rate < 100 bpm
Systolic blood pressure > 80 mm Hg
Total urine output > 1000 mL
O_2 saturation > 90%
Normal cardiac enzyme levels
No chest pain
No new arrhythmia
Stable electrolyte levels and renal function

Adapted from Costanzo et al.[38]

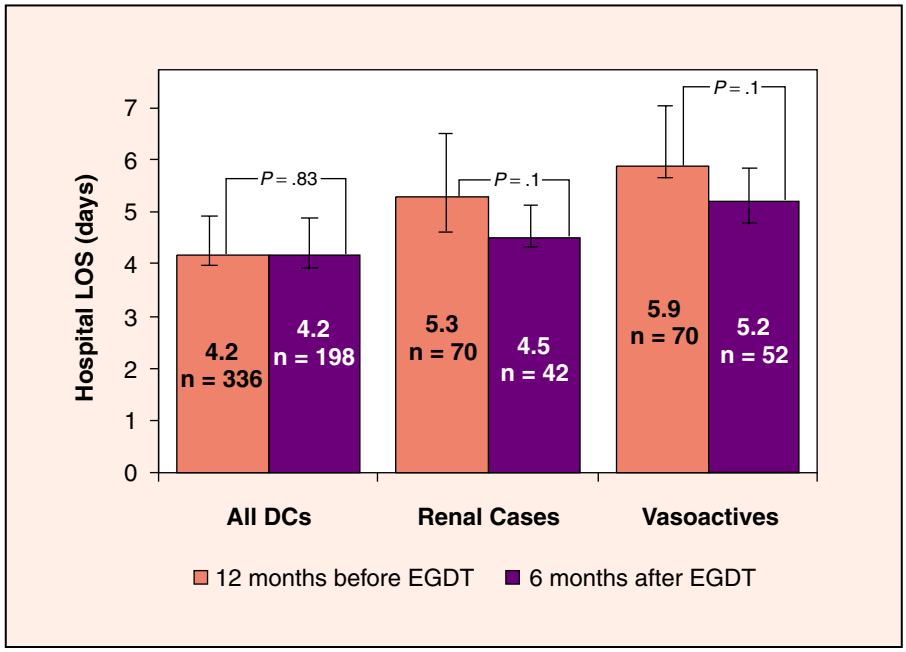


Figure 5. *Hospital length of stay (LOS) for patients with acute decompensated heart failure, for the 12 months before and 6 months after early goal-directed therapy (EGDT) implementation. DC, discharge.*

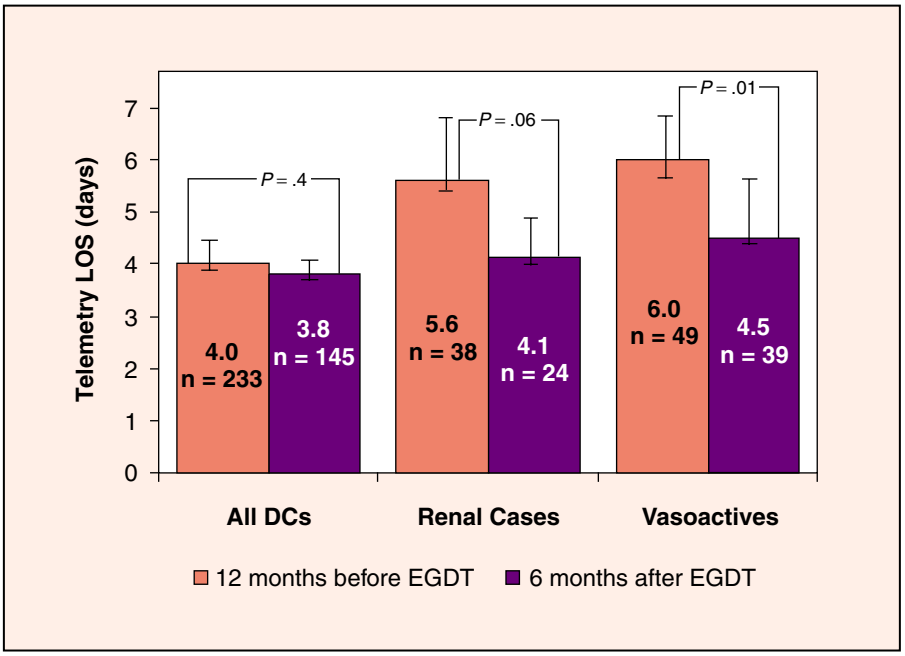
have met all the criteria listed; premature discharge is thought to contribute to an increased risk of early rehospitalization.[38]

The EGDT algorithm has been implemented, and data from the 12 months before and first 6 months after algorithm implementation have now been analyzed and provide insights into the potential impact of such approaches. Hospital and telemetry unit LOS were the two factors most significantly affected among patients with concomitant renal insufficiency and those requiring intravenous vasoactive therapy (Figures 5 and 6). Vasoactive use increased after algorithm utilization (Figure 7) but still was seen in only one third of all hospitalized ADHF patients. Nesiritide use as an overall percentage of vasoactive therapy was approximately 50% in the 12 months before and 6 months after algorithm implementation (Figure 8), and only 15% of all ADHF patients who were admitted had been treated with nesiritide. In patients with renal insufficiency, use of the treatment algorithm resulted in a doubling of nesiritide utilization when compared with similar patients for whom the algorithm was not used. Perhaps most interesting was the observation that despite increased use of vasoactive medication (ie, nesiritide), overall drug costs and costs associated with vasoactive therapy were actually reduced (Figure 9), which suggests that an early goal-directed approach can be instituted in a cost-effective manner while simultaneously improving outcomes.

Early Initiation of Nesiritide

The Acute Decompensated Heart Failure National Registry (ADHERE) was developed as a large, observational, multicenter database of patient profiles, patterns of care, and outcomes for patients hospitalized with ADHF.[42] As of August 2004, more than 140,000 patient episodes have been registered in ADHERE. Participating hospitals are from all regions of the United States and include community, tertiary care, and academic hospitals. The broad range of hospitals participating in ADHERE ensures that data are based on actual clinical practice with diverse patient populations. Patients

Figure 6. *Telemetry unit length of stay (LOS) for patients with acute decompensated heart failure, for the 12 months before and 6 months after early goal-directed therapy (EGDT) implementation. DC, discharges.*



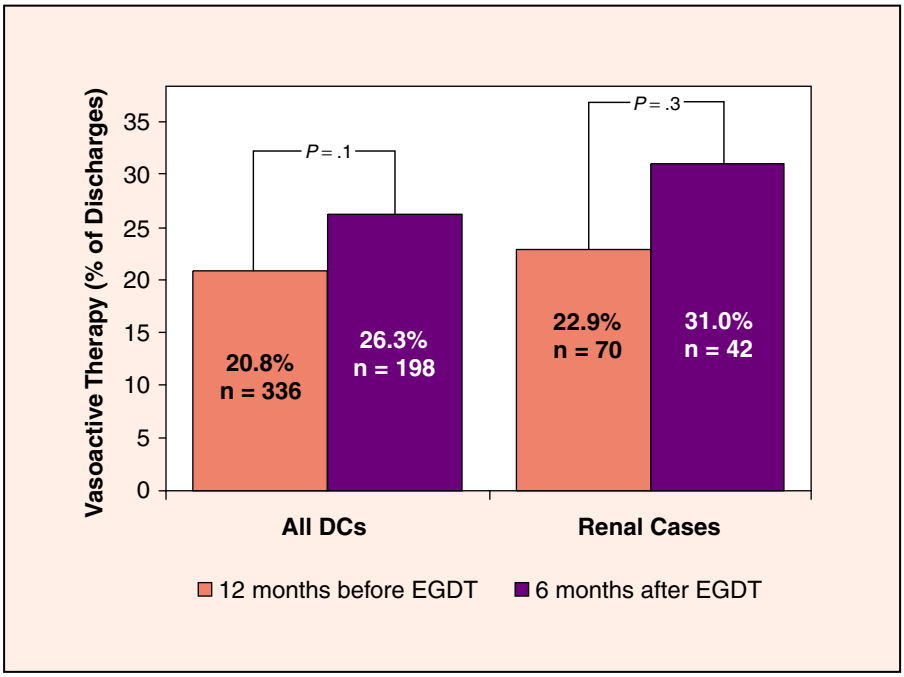
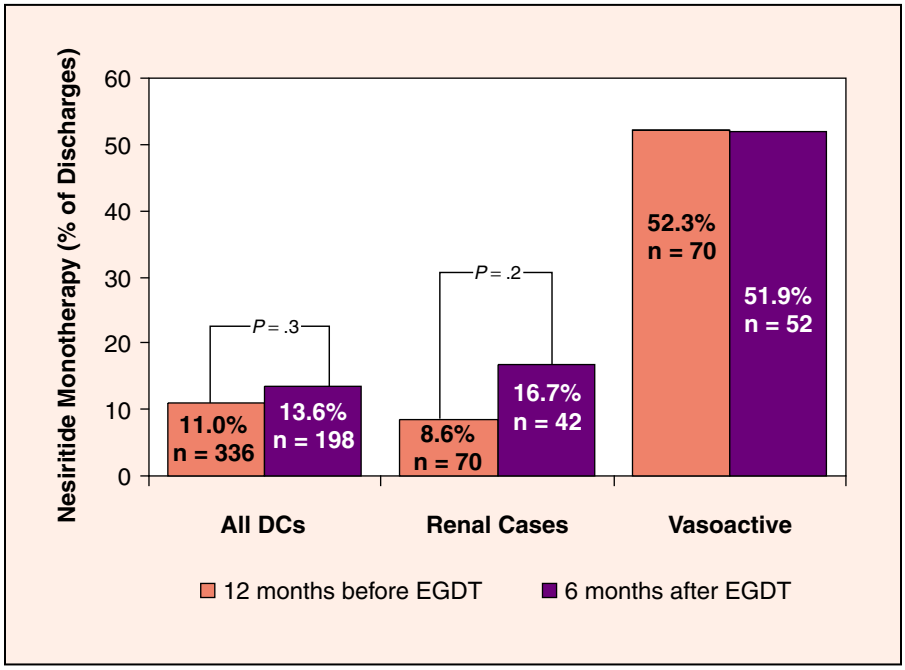


Figure 7. *Use of vasoactive therapy in patients with acute decompensated heart failure, for the 12 months before and 6 months after early goal-directed therapy (EGDT) implementation. DC, discharge.*

are followed from initial presentation through hospital discharge to document current practice. The large database that has been generated is ideal for analyzing factors that affect clinical and economic outcomes.[42]

Figure 8. *Use of nesiritide monotherapy in patients with acute decompensated heart failure, for the 12 months before and 6 months after early goal-directed therapy (EGDT) implementation. DC, discharge.*



Analysis of data from ADHERE has documented that early initiation of nesiritide in the ED significantly reduces the need for ICU and overall hospital admissions. Patients for whom nesiritide treatment was initiated in the ED had a median door-to-treatment time of 2.7 hours. Patients who were admitted to the hospital before treatment was started had a median time to treatment of 18.3 hours ($P < .0001$). Median hospital LOS was significantly shorter with early initiation of therapy (4.1 days with ED initiation vs 5.7 days with inpatient initiation, $P < .0001$). With early treatment, the percentage of patients transferred to the ICU was significantly reduced. After adjusting for other confounding risks, delay in administration of nesiritide until after admission was associated with a twofold increase in the risk of prolonged LOS.[16]

The Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor (PROACTION) trial evaluated the effects of nesiritide or placebo added to standard ED therapy for ADHF. This study demonstrated a significant benefit with early initiation of nesiritide.[43] Nesiritide treatment started in the ED was associated with an 11% reduction in hospitalization for any reason and a 21% reduction in hospitalization for HF. The 30-day readmission rate was reduced by 57% among those who were admitted initially. Despite higher drug acquisition costs, overall cost of care was found to be lower for patients treated with nesiritide, because of the decreased LOS and the reduced readmission rate associated with treatment. Early initiation of nesiritide did not increase the incidence of symptomatic hypotension, ventricular arrhythmia, or death.[43]

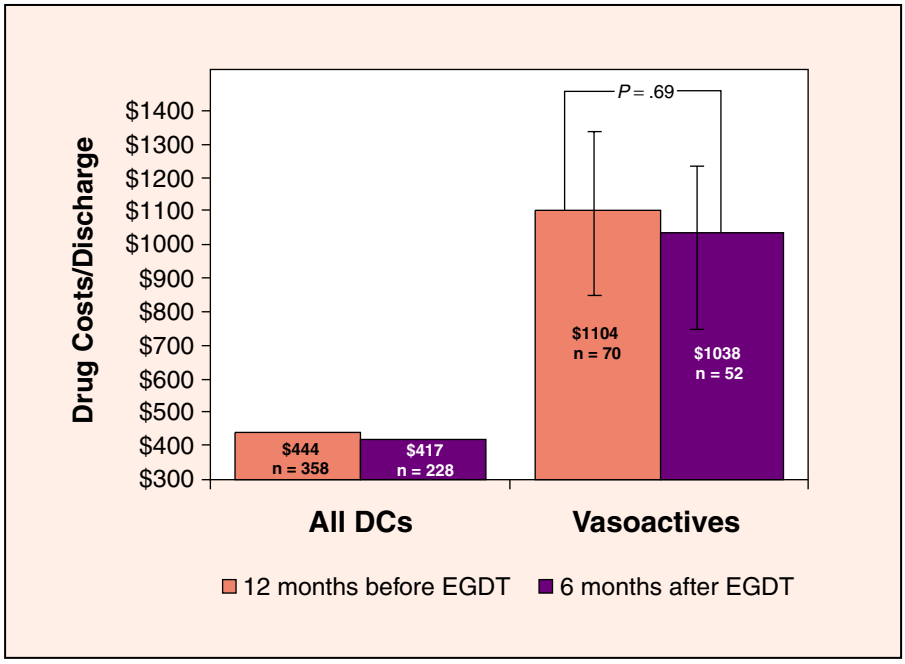


Figure 9. *Drug costs per discharge (US dollars) for patients with acute decompensated heart failure, for the 12 months before and 6 months after early goal-directed therapy (EGDT) implementation. DC, discharge.*

Conclusions

Effective treatment of ADHF requires early and critical decision making, often in the ED setting, and has been shown to decrease hospitalizations, admissions to the ICU or CCU, and readmissions, in addition to improving quality of life and reducing costs. In particular, EGDT algorithms that incorporate early administration of vasoactive medication can improve outcomes without increasing treatment costs. Data continue to indicate that early administration of vasoactive medical therapy holds the greatest promise for improving outcomes, and given the prominent role that neurohormonal activation plays in the setting of chronic and acute HF, neurohormonally active therapies (eg, nesiritide) should be considered first-line therapy in appropriate patients. ■

References

1. American Heart Association, American Stroke Association. Heart disease and stroke statistics—2004 update. American Heart Association. Available at: http://www.americanheart.org/downloadable/heart/1072969766940HSStats2004Update.pdf. Accessed September 13, 2004.
2. Kozak LJ, Owings MF, Hall MJ. National Hospital Discharge Survey: 2001 annual summary with detailed diagnosis and procedure data. *Vital Health Stat.* 2004;13:1–198.
3. Aghababian RV. Acutely decompensated heart failure: opportunities to improve care and outcomes in the emergency department. *Rev Cardiovasc Med.* 2002;3(suppl 4): S3–S9.
4. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2001;38:2101–2113.

Main Points

- The economic burden of acute decompensated heart failure (ADHF) is substantial, and any measure that optimizes care in the outpatient setting by shortening length of stay and decreasing the need for readmission is expected to improve patient quality of life and reduce costs.
- In contrast to those treated with inotropic agents and dobutamine, patients presenting to the emergency department (ED) with ADHF experienced significant benefits from early intravenous infusion of vasoactive agents, such as nesiritide, a recombinant form of B-type natriuretic peptide.
- The Midwest Heart Specialists Heart Failure Program has produced an algorithm for the early goal-directed therapy of ADHF patients; data from the 12 months before and first 6 months after algorithm implementation show that despite increased use of vasoactive medication (ie, nesiritide), overall drug costs and costs associated with vasoactive therapy were reduced.
- Analysis of data from the Acute Decompensated Heart Failure National Registry has documented that early initiation of nesiritide in the ED significantly reduces the need for ICU and overall hospital admissions.
- In hospitalized patients, treatment of ADHF with nesiritide reduces resource utilization, improves clinical outcomes, and reduces costs of care; in-hospital mortality might also be reduced with nesiritide treatment; and the higher cost of nesiritide is offset by the use of fewer resources and a significantly lower readmission rate.

5. Fonarow GC. Introduction: clinical update on the use of natriuretic peptides in the treatment of heart failure. *Rev Cardiovasc Med*. 2003;4 (suppl 7):S1–S2.
6. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol*. 2001; 37:379–385.
7. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA*. 1989;261:884–888.
8. Peacock WF. Rapid optimization: strategies for optimal care of decompensated congestive heart-failure patients in the emergency department. *Rev Cardiovasc Med*. 2002;3(suppl 4):S41–S48.
9. Maisel AS, McCord J, Nowak RM, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction: Results from the Breathing Not Properly Multinational Study. *J Am Coll Cardiol*. 2003;41:2010–2017.
10. Felker GM, Adams KF Jr, Konstam MA, et al. The problem of decompensated heart failure: nomenclature, classification, and risk stratification. *Am Heart J*. 2003;145(2 suppl):S18–S25.
11. Cuffe MS, Califf RM, Adams KFJ, et al, for the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–1547.
12. Burger AJ, Elkayam U, Neibaur MT, et al. Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy. *Am J Cardiol*. 2001;88:35–39.
13. Burger AJ, Horton DP, LeJemtel T, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: The PRECEDENT Study. *Am Heart J*. 2002;144:1102–1108.
14. Emerman CL. Treatment of the acute decompensation of heart failure: efficacy and pharmacoeconomics of early initiation of therapy in the emergency department. *Rev Cardiovasc Med*. 2003;4(suppl 7):S13–S20.
15. Peacock F, Emerman CL, Costanzo MR, et al, for the ADHERE Scientific Advisory Committee and Investigators. Early initiation of intravenous vasoactive therapy improves heart failure outcomes: an analysis from the ADHERE registry database [abstract 92]. *Ann Emerg Med*. 2003;42 (4 suppl):S26.
16. Peacock WF, Emerman CL, Wynne J, for the ADHERE Scientific Advisory Committee and Investigators, and the ADHERE Study Group. Early use of nesiritide in the emergency department is associated with improved outcome: an ADHERE registry analysis. *Ann Emerg Med*. 2004;44(suppl): S78.
17. Mills RM, Hobbs RE, Young JB. "BNP" for heart failure: role of nesiritide in cardiovascular therapeutics. *Congest Heart Fail*. 2002;8:270–273.
18. Hobbs RE, Mills RM, Young JB. An update on nesiritide for treatment of decompensated heart failure. *Expert Opin Investig Drugs*. 2001;10:935–942.
19. Protter AA, Wallace AM, Ferraris VA, Weishaar RE. Relaxant effect of human brain natriuretic peptide on human artery and vein tissue. *Am J Hypertens*. 1996;9: 432–436.
20. Boerrigter G, Burnett JC Jr. Recent advances in natriuretic peptides in congestive heart failure. *Expert Opin Investig Drugs*. 2004;13: 643–652.
21. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: A double-blind, placebo-controlled, randomized crossover trial. *Circulation*. 1996;94: 3184–3189.
22. Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. *J Card Fail*. 1998;4:37–44.
23. Brunner-La Rocca HP, Kaye DM, Woods RL, et al. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. *J Am Coll Cardiol*. 2001;37:1221–1227.
24. Aronson D, Burger AJ. Intravenous nesiritide (human B-type natriuretic peptide) reduces plasma endothelin-1 levels in patients with decompensated congestive heart failure. *Am J Cardiol*. 2002;90:435–438.
25. Yoshimura M, Yasue H, Morita E, et al. Hemodynamic, renal, and hormonal responses to brain natriuretic peptide infusion in patients with congestive heart failure. *Circulation*. 1991;84:1581–1588.
26. Holmes SJ, Espiner EA, Richards AM, et al. Renal, endocrine, and hemodynamic effects of human brain natriuretic peptide in normal man. *J Clin Endocrinol Metab*. 1993; 76:91–96.
27. Burger AJ, Aronson D. Effect of vasoactive therapy on heart rate variability in patients with acutely decompensated congestive heart failure. *Am J Cardiol*. 1999;84:476–478.
28. Colucci WS. Nesiritide for the treatment of decompensated heart failure. *J Card Fail*. 2001;7:92–100.
29. Publication Committee for the VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531–1540.
30. Colucci WS, Elkayam U, Horton DP, et al, for the Nesiritide Study Group. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med*. 2000;343: 246–253.
31. Emerman CL. Safety and efficacy of nesiritide for the treatment of decompensated heart failure. *Rev Cardiovasc Med*. 2002; 3(suppl 4):S28–S34.
32. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. *J Am Coll Cardiol*. 2002;39: 798–803.
33. Lenz TL, Foral PA, Malesker MA, et al. Impact of nesiritide on health care resource utilization and complications in patients with decompensated heart failure. *Pharmacotherapy*. 2004;24:1137–1146.
34. Abraham WT, Adams KF, Fonarow GC, et al, for the ADHERE Scientific Advisory Committee and Investigators. Comparison of in-hospital mortality in patients treated with nesiritide vs other parenteral vasoactive medications for acutely decompensated heart failure: an analysis from a large prospective registry database [abstract 298]. *J Card Fail*. 2003;9(suppl 1):S81.
35. de Lissovoy G, Stier DM, Ciesla G, et al. Economic implications of nesiritide versus dobutamine in the treatment of patients with acutely decompensated congestive heart failure. *Am J Cardiol*. 2003;92:631–633.
36. Lewis DA, Gurram NR, Abraham WT, Akers WS. Effect of nesiritide versus milrinone in the treatment of acute decompensated heart failure. *Am J Health Syst Pharm*. 2003;60(suppl 4):S16–S20.
37. DiDomenico RJ, Park HY, Southworth MR, et al. Guidelines for acute decompensated heart failure treatment. *Ann Pharmacother*. 2004;38:649–660.
38. Costanzo MR, Saltzberg MT, Gupta V. Early goal-directed therapy in the management of acute heart failure. Available at: http://medicalmedia.net/pdf/241.pdf. Accessed July 26, 2004.
39. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67.
40. Lee DS, Austin PC, Rouleau JL, et al. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA*. 2003;290: 2581–2587.
41. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail*. 2003;9:13–25.
42. Fonarow GC, for the ADHERE Scientific Advisory Committee. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med*. 2003;4(suppl 7):S21–S30.
43. Peacock WF, Emerman CL, on behalf of the PROACTION Study Group. Safety and efficacy of nesiritide in the treatment of decompensated heart failure in observation patients [abstract 1027-89]. *J Am Coll Cardiol*. 2003;41(suppl A):336A.