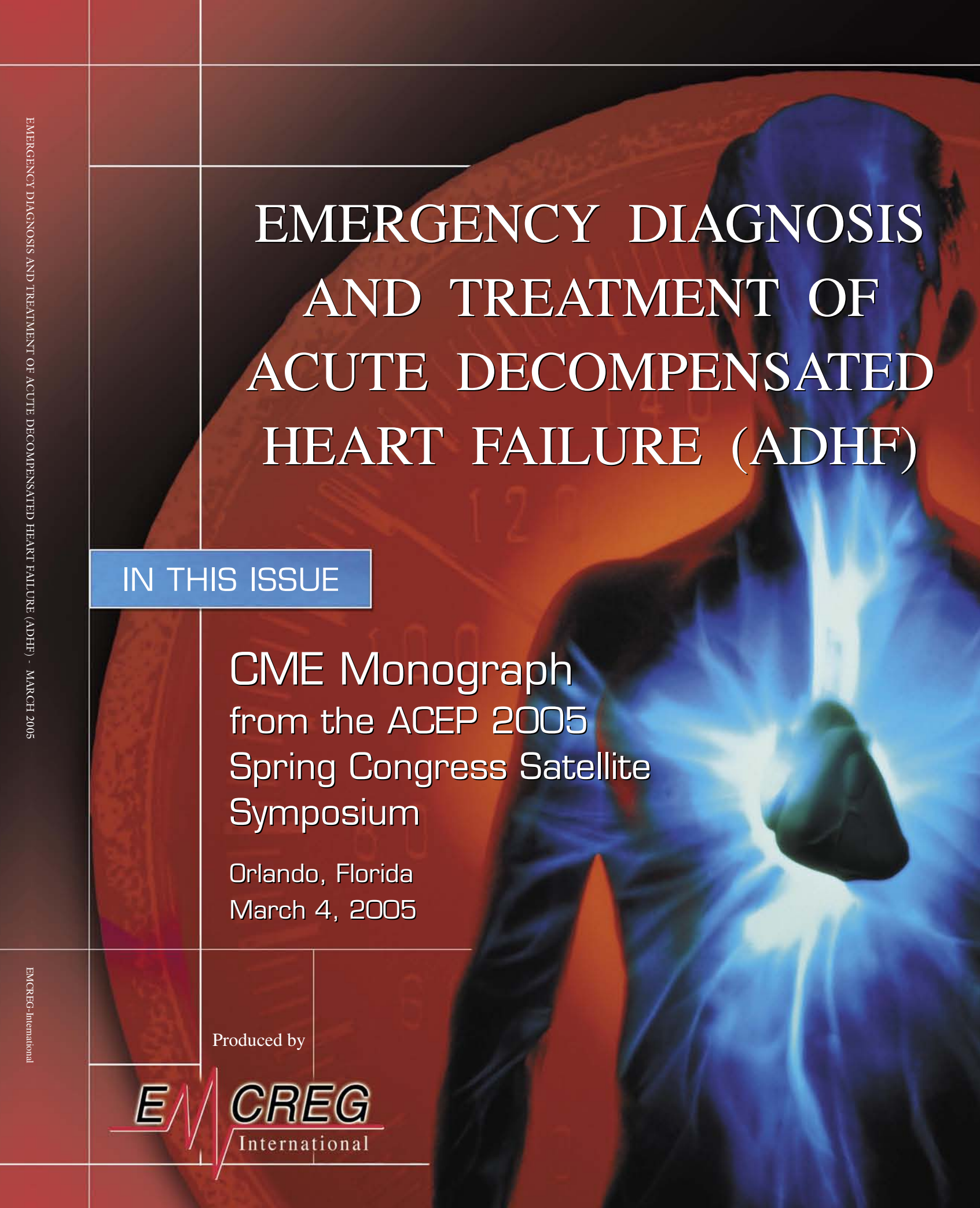
EMERGENCY DIAGNOSIS AND TREATMENT OF ACUTE DECOMPENSATED HEART FAILURE (ADHF)

IN THIS ISSUE

CME Monograph from the ACEP 2005 Spring Congress Satellite Symposium

Orlando, Florida
March 4, 2005



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Dear Colleagues:

Each year, nearly one million patients in the United States are hospitalized with acute decompensated heart failure (ADHF). In the past, there have been limited practice guidelines for the emergency management of this condition. Data from the ADHERE (the Acute Decompensated Heart Failure National Registry), indicate that ADHF patients are repeatedly hospitalized, and otherwise have a very high rate of morbidity and mortality. The management and care of this patient group remains suboptimal. This comprehensive and progressive monograph will review the latest diagnostic and therapeutic modalities for ADHF and suggest methods to improve the care for these patients at your institution. Insights and lessons from ADHERE will also be reviewed and discussed.

The Emergency Medicine Cardiac Research and Education Group-International (EMCREG) is pleased to present this educational monograph summarizing our 2005 EMCREG Symposium on the Emergency Department Diagnosis and Treatment of ADHF held in Orlando, Florida. This program is also available as an on-demand web cast on the included CD-ROM and at http://adhf.digiscript.com beginning June 2005. It is our hope that this material will provide emergency physicians with information necessary to improve and facilitate care for this unique patient population.

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Sincerely,

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DIAGNOSIS OF ACUTE DECOMPENSATED HEART FAILURE IN THE ED

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OBJECTIVES:

1. Define the use of BNP to distinguish heart failure from other etiologies of shortness of breath
2. Delineate the role of BNP for risk stratifying patients with heart failure

INTRODUCTION

As we have improved the care of patients with acute coronary syndromes (ACS), patients with cardiovascular disease are living longer than ever. Effective interventions to decrease mortality of patients with ACS have increased the incidence of heart failure. The cost of heart failure now exceeds $56 billion a year, most of which is due to hospitalization. Unfortunately, heart failure is a chronic condition and nearly half of patients admitted to the hospital are readmitted within six months. To determine optimal therapy for patients with acute decompensated heart failure (ADHF), the emergency physician must be able to confidently diagnose patients with heart failure. This requires knowledge of the diagnostic methods used to identify patients with heart failure as well as knowledge of the different etiologies of heart failure.

Sorting Out the Etiology of Heart Failure

The potential etiologies of acute heart failure are multifactorial and should be broadly divided into two categories: (1) the underlying etiology of the heart failure, and (2) the etiology of the acute precipitant that results in worsening from the chronic compensated state. For some patients, particularly those presenting for the first time, these two components may be identical. The most common etiologies of heart failure are coronary artery disease and long-standing hypertension. Other potential etiologies include dilated, hypertrophic, and restrictive cardiomyopathies; myocarditis; pericardial tamponade; valvular heart disease; and secondary effects of pulmonary diseases or metabolic disorders.

Although investigation of the underlying etiology is important to help determine whether there is a reversible component of the disease, this is usually beyond the scope of the emergency physician. There are, however, several etiologies for heart failure that the emergency physician should be aware of, as they may require modification of initial therapy. These are severe aortic stenosis, idiopathic hypertrophic subaortic stenosis or hypertrophic obstructive cardiomyopathy, and pulmonary hypertension. Identification of patients with these conditions is important because aggressive preload and afterload reduction can lead to cardiovascular collapse since these patients cannot increase their forward blood flow through the fixed mechanical lesion (such as a flow-restricted aortic valve).

The potential etiologies of acute heart failure are multifactorial and should be broadly divided into two categories: (1) the underlying etiology of the heart failure, and (2) the etiology of the acute precipitant that results in worsening from the chronic compensated state.

Reliance upon clinical impression alone leads to diagnostic uncertainty because the signs and symptoms of heart failure are relatively nonspecific.

The Breathing Not Properly Trial demonstrated that BNP is useful for the diagnosis of CHF in the ED.

Separate and distinct from the initial etiology is the cause of the acute precipitant. Congestive heart failure can be exacerbated by worsening of the underlying condition, by medication or dietary noncompliance, or by development of new or complicating medical conditions (e.g., ischemia, dysrhythmias, pulmonary embolus, or infection). Approximately 80% of patients presenting to the emergency department (ED) with heart failure have a prior diagnosis of heart failure.

Progress in the Diagnosis of Heart Failure

The diagnosis of heart failure has traditionally been challenging. Reliance upon clinical impression alone leads to diagnostic uncertainty because the signs and symptoms of heart failure are relatively nonspecific. Key symptoms such as shortness of breath are nonspecific in patients with comorbidities such as reactive airway disease. Likewise, routine laboratory tests, electrocardiograms, and radiographs cannot be relied upon to always guide an accurate and appropriate diagnosis.

Despite these challenges, diagnostic capabilities in heart failure have improved in recent years with recognition of the role that B-type natriuretic peptide (BNP) plays in the disease. In addition to being a pump, the heart is an endocrine organ that functions together with other physiological systems to control fluid volume. The myocardium produces natriuretic peptides, one of which is BNP, a hormone with diuretic, natriuretic, and vascular smooth muscle relaxing actions. BNP is a natural antagonist for the sympathetic nervous system and the renin-angiotensin-aldosterone axis. BNP is secreted in response to wall stretch, ventricular dilation and/or increased filling pressures. Measurement of endogenous BNP is thus a clinically sensible way to assess whether a particular patient has heart failure.

The Breathing Not Properly study of 1,586 patients who presented to EDs with shortness of breath showed that BNP levels alone were more accurate predictors of the presence or absence of heart failure than any historical factors, physical findings, or laboratory values.[1,2] BNP levels were much higher in patients who were subsequently diagnosed with heart failure than in those diagnosed with noncardiac dyspnea (675 pg/dL vs. 110 pg/dL). A BNP cutoff value of 100 pg/mL had a sensitivity of 90% and a specificity of 76% for differentiating heart failure from other causes of dyspnea, and a cutoff of 50 pg/mL had a negative predictive value of 96%. Without knowledge of BNP levels, emergency physicians had a 43% indecision rate in trying to make a diagnosis. BNP levels added significantly to the clinical impression, as it was found that clinical decision-making in conjunction with BNP levels could have reduced the diagnostic indecision rate to 11%. In multivariate analyses, BNP levels always contributed to the diagnosis, even after taking into account findings from the history and physical examination. Thus, the Breathing Not Properly trial demonstrated that BNP levels have significant clinical utility for both the diagnosis and risk stratification of heart failure patients in the ED.[1,2] Both diastolic and systolic dysfunction are associated with high BNP levels of more or less the same degree.[3]

BNP must be used with caution in certain populations. Although BNP can help differentiate pulmonary from cardiac etiologies of dyspnea, some types of lung disease, such as cor pulmonale and pulmonary embolism have elevated BNP levels; however BNP is not usually elevated as to as high a level as it is in patients with heart failure. In a subgroup of patients with a history of reactive airway disease in the Breathing Not Properly trial, of 417 subjects with a history of asthma or chronic obstructive pulmonary disease without a history of CHF, 21% were found to have newly discovered CHF. Only 37% were identified in the ED, while a BNP >100 pg/mL identified 93%.[4] Additionally, BNP levels >100 pg/mL provided diagnostic information beyond that obtained from individual chest radiographic indicators.[5]

There is a significant inverse relationship between body weight (body mass index) and BNP levels.[6] Thin patients with heart failure are more likely to have elevated BNP values in the absence of heart failure. Conversely, obese patients are more likely to have lower levels of BNP for any given severity of heart failure. As a result, BNP levels should be used with caution in patients with obesity, unless of course baseline BNP values are known. Then the obese patient can be followed for decompensation.

The Breathing Not Properly Trial demonstrated that BNP is useful for the diagnosis of CHF in the ED**.** The REDHOT Study suggests that BNP might also be useful to improve triage and disposition of patients who present to the ED with heart failure.[7] This trial demonstrated a "disconnect" between the physician perception of the severity of heart failure and the actual BNP value. In the first phase, 464 patients visiting EDs with complaints of breathing difficulty had BNP measurements taken on arrival. Physicians were blinded to BNP results; however inclusion in the trial required a BNP > 100 pg/ml. Patients discharged from the ED had higher BNP levels than those admitted to the hospital (976 pg/ml vs 766 pg/ml). With respect to the admitted patients, 11% had BNP levels < 200 pg/ml, which is indicative of less severe CHF. Most of these patients were perceived to have class III or IV heart failure. Mortality for these patients was 0% at 30 days and only 2% at 90 days, suggesting that patients with heart failure and low levels of BNP might have actually been safe for discharge. With respect to patients that were actually discharged, 78% had BNP levels >400 pg/mL. At 90 days, mortality was 9%. There was no mortality of those discharged with BNP levels <400 pg/mL. This suggests that use of BNP in the ED might also help determine which well appearing patients are high risk for a bad outcome over the short term (90 days).

Elevated BNP levels are useful for assessing risk stratification and prognosis in patients with heart failure. BNP levels are related to changes in limitations of physical activities and functional status. Harrison et al. followed 325 patients for 6 months after an index visit to the ED for dyspnea.[8] Higher BNP levels were associated with a progressively worse prognosis. The relative risk of 6-month CHF admission or death in patients with BNP levels >230 pg/mL was 24 times the risk of patients with levels less than 230. When combined with troponin I, both troponin I and BNP alone and in combination predict survival in CHF.[9] Both together have additive prognostic risk.

Elevations of BNP are useful for assessing risk stratification and prognosis in patients with heart failure.

The utility of BNP to diagnosis CHF is well established; however, it's ability to drive treatment is still under study. REDHOT II is a randomized controlled trial comparing treatment and outcomes of patients where therapy is guided by serial BNP measurements in the experimental group. This study should shed some light on the utility of BNP to drive treatment.

Due to the voluminous data on the clinical utility of BNP, consensus panel guidelines were recently published.[10] These recommendations state:

- Many patients presenting to emergency services with dyspnea, a history, physical examination, and a chest x-ray and ECG should be undertaken together with laboratory measurements that include BNP.
- As BNP levels rise with age and are affected by gender, comorbidity, and drug therapy, the plasma BNP measurement should not be used in isolation from the clinical context.
- If the BNP is <100 pg/mL, then heart failure is highly unlikely (negative predictive value, 90%).
- If the BNP level is >500 pg/mL, then CHF is highly likely (positive predictive value, 90%)
- For BNP levels of 100–500, one should consider the following conditions in the differential diagnosis
  a. Baseline BNP value due to stable underlying dysfunction
  b. Right ventricular failure from cor pulmonale
  c. Acute pulmonary embolism
  d. Renal failure
- Patients may present with CHF with normal BNP levels or with levels below what might one expect can occur in the following situations:
  a. Flash pulmonary edema (<1–2 hours)
  b. Heart failure up-stream from the left ventricle (i.e., acute mitral regurgitation from papillary muscle rupture)
  c. Obese patients (body mass index >30 kg/m^2)

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TREATMENT OF ACUTE DECOMPENSATED HEART FAILURE IN THE EMERGENCY DEPARTMENT

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OBJECTIVES:

1. Describe a simple two step approach to assessing the clinical status of ED patients with ADHF
2. Define the role of vasodilators as the mainstay of therapy for ADHF

INTRODUCTION

Acutely decompensated heart failure (ADHF) is a common reason for patients seeking emergency department (ED) care and the leading Medicare diagnosis for hospitalized patients over the age of 65. Hospital readmission for heart failure is common; approximately 20% of patients are readmitted within 30 days and 50% within 6 months.[1] Recent advances in the understanding of the complex pathophysiologic process that exacerbate heart failure has led to improved diagnoses and effective ED treatment of this clinical entity.

Pathophysiology and Hemodynamic Assessment

In the past decompensated heart failure was felt to be due to volume overload and impaired forward flow. Treatment was focused on maximizing cardiac output. It has now become apparent that in most ADHF/pulmonary edema there is increased systemic vascular resistance superimposed on reduced myocardial reserve (both systolic and diastolic).[2] Many variables play a role in ADHF that exacerbate left ventricular (LV) dysfunction and lead to deterioration. Low cardiac output results in decreased renal flow and stimulates neurohormonal activation, including the release of angiotensin II. Decreased cardiac output causes progressive blood volume expansion further increasing LV filling pressures and myocardial oxygen consumption. Hypotension promotes baroreceptor activation leading to increased sympathetic tone and vasoconstriction which further increases systemic vascular resistance compromising systolic performance. There is marked up-regulation of vasoconstrictors, including norepinephrine, angiotensin II and endothelin, aldosterone and arginine vasopressin rise contributing to the salt and water retention. [3,4]

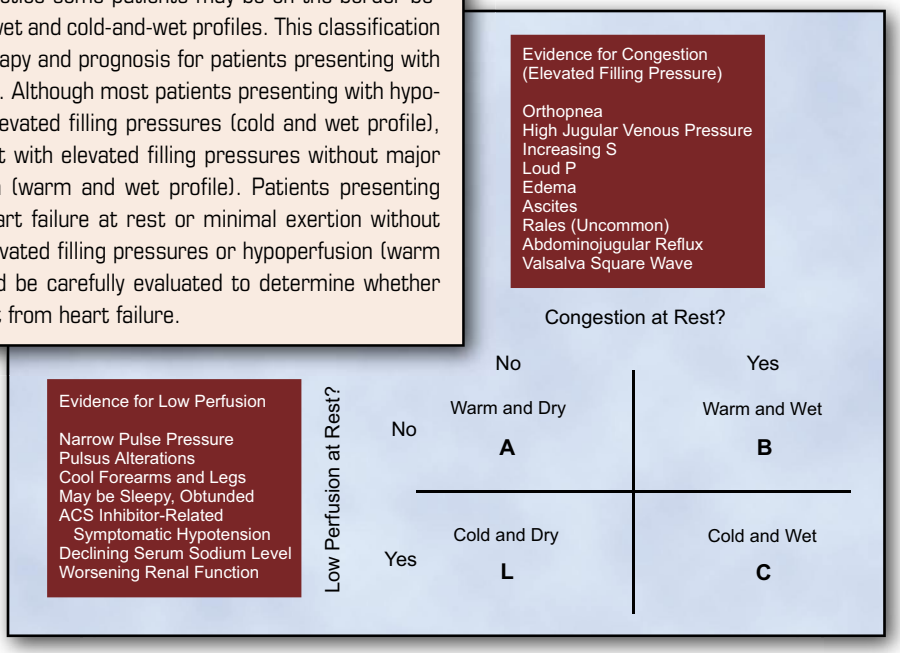
To counter-balance the effects of neurohormones, released by the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), and to maintain circulatory homeostasis, the body produces a family of vasodilator antiproliferative natriuretic peptides that play an important role in heart failure.[5] Atrial and B-type natriuretic peptides are released from the myocardium in response to increased atrial natriuretic peptide and ventricular B-type natriuretic

The release and production of stored natriuretic peptides are insufficient to balance the fluid retention of the RAAS.

Figure 1.

Two-Minute Assessment of Hemodynamic Profile. Reproduced and reprinted with permission from Nohria A, Lewis E, Stevenson LW. JAMA 2002;287:628-640.

Diagram indicating 2 x 2 table of hemodynamic profiles for patients presenting with heart failure. Most patients can be classified in a 2-minute bedside assessment according to the signs and symptoms shown although in practice some patients may be on the border between the warm-and-wet and cold-and-wet profiles. This classification helps guide initial therapy and prognosis for patients presenting with advanced heart failure. Although most patients presenting with hypoperfusion also have elevated filling pressures (cold and wet profile), many patients present with elevated filling pressures without major reduction in perfusion (warm and wet profile). Patients presenting with symptoms of heart failure at rest or minimal exertion without clinical evidence of elevated filling pressures or hypoperfusion (warm and dry profile) should be carefully evaluated to determine whether their symptoms result from heart failure.



peptide (BNP) stress. They increase glomerular filtration rate (GFR), inhibit sodium reabsorption and reduce vascular smooth muscle tone, causing a diuresis, natriuresis and balanced arterial and venous dilation. All these effects contribute to reduced plasma volume, blood pressure and ventricular preload. BNP has lusitropic (relaxing) effects and may be antifibrotic and antiproliferative.[6] In ADHF, the release and production of stored natriuretic peptides are insufficient to balance the fluid retention of the RAAS.

Rapid bedside assessment of ADHF can be simplified by placing the patient into one of four hemodynamic profiles [Figure 1]. Two key hemodynamic parameters are the presence or absence of elevated filling pressures (wet or dry) and adequacy of perfusion (warm or cold). Congestion corresponds to elevated pulmonary capillary wedge pressure (PCWP), and impaired perfusion is suggested by a low cardiac index. Greater than 90% of patients presenting with ADHF are congested (wet). They may have adequate or reduced perfusion with the majority experiencing elevated systemic vascular resistance. Congestion (elevated filling pressure) in ADHF is represented by dyspnea and orthopnea and elevated jugular venous pressure. Rales while a helpful sign are absent in 80% of patients with chronically elevated filling pressures due to pulmonary lymphatic compensation. Peripheral edema is relatively insensitive to elevated filling pressures, and associated with many noncardiac causes. The third heart sound (S3) while a sensitive marker, is rarely appreciated. The most readily available indicator of perfusion is blood pressure and pulse pressure. This rapid assessment system allows for appropriate targeting of therapy in ADHF patients.

Determining the Etiology of Acute Decompensation and Setting Treatment Goals

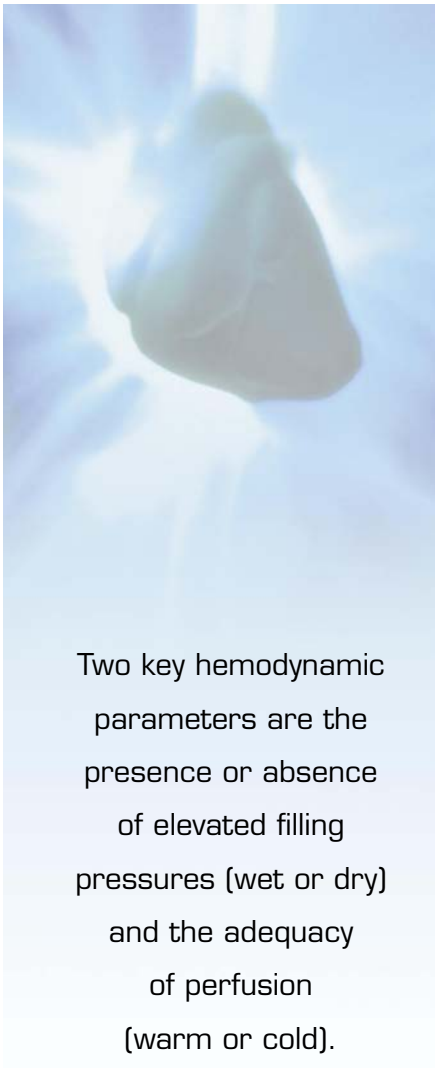
The etiologies of ADHF are multifactorial but can be divided into two categories: (1) the underlying the heart failure, and (2) the acute precipitant that results in deterioration from the chronic compensated state. In patients presenting for the first time the two components are identical. The most common causes of heart failure are coronary artery disease and long-standing hypertension. Other etiologies include dilated, hypertrophic and restrictive cardiomyopathies, myocarditis, pericardial tamponade, valvular heart disease and secondary effects of pulmonary and metabolic disorders. Understanding the underlying etiology is important in helping to determine if there is a reversible component present. The emergency physician must be aware of number of special causes of heart failure that require consideration when making therapeutic decisions. In severe aortic stenosis, idiopathic hypertrophic subaortic stenosis or hypertrophic obstructive cardiomyopathy, and pulmonary hypertension, aggressive afterload reduction can lead to cardiovascular collapse as these patients cannot increase their forward blood flow in the face of a fixed mechanical lesion.[7]

Greater than 80% of patients presenting to the ED with ADHF have a prior diagnosis of heart failure. An acute precipitant can often be identified. Exacerbation or worsening of the underlying condition can be due to medication or dietary non-compliance, or the development of a new or complicating medical condition (such as ischemia, dysrhythmia, pulmonary embolus or infection). Treatment depends on the severity of the symptoms and decompensation time course. [8,9]

Therapeutic goals in ADHF patients can be divided in three phases. The primary goal in the ED is restoration of oxygenation, organ perfusion and total body fluid balance. This is accomplished by reversing acute hemodynamic abnormalities and relieving symptoms. Intermediate goals include minimizing end-organ damage, reducing hospitalization duration and initiation of beneficial medical therapies, and should commence in the ED. Long-term goals focus on reducing readmission and improving long-term survival with treatment that decreases disease progression. This occur after the patient leaves the ED.[10] While national guidelines exist for many acute cardiovascular conditions there are no consensus guidelines for the management of ADHF. Given the lack of randomized controlled trials, consensus that incorporates evidence-based literature and expert opinion should be used as guidelines.[11]

Approach to Initial Treatment

Our improved understanding of the etiology of heart failure and its progression has identified the RAAS and neurohormonal pathways as targets of therapy, and may explain the benefits of neurohormonal blockers such as angio-converting enzyme (ACE) inhibitors, beta-blockers, aldosterone blockers (e.g., spironolactone) and supraphysiologic doses of natriuretic peptides (such as ANP and BNP) in the treatment of heart failure.

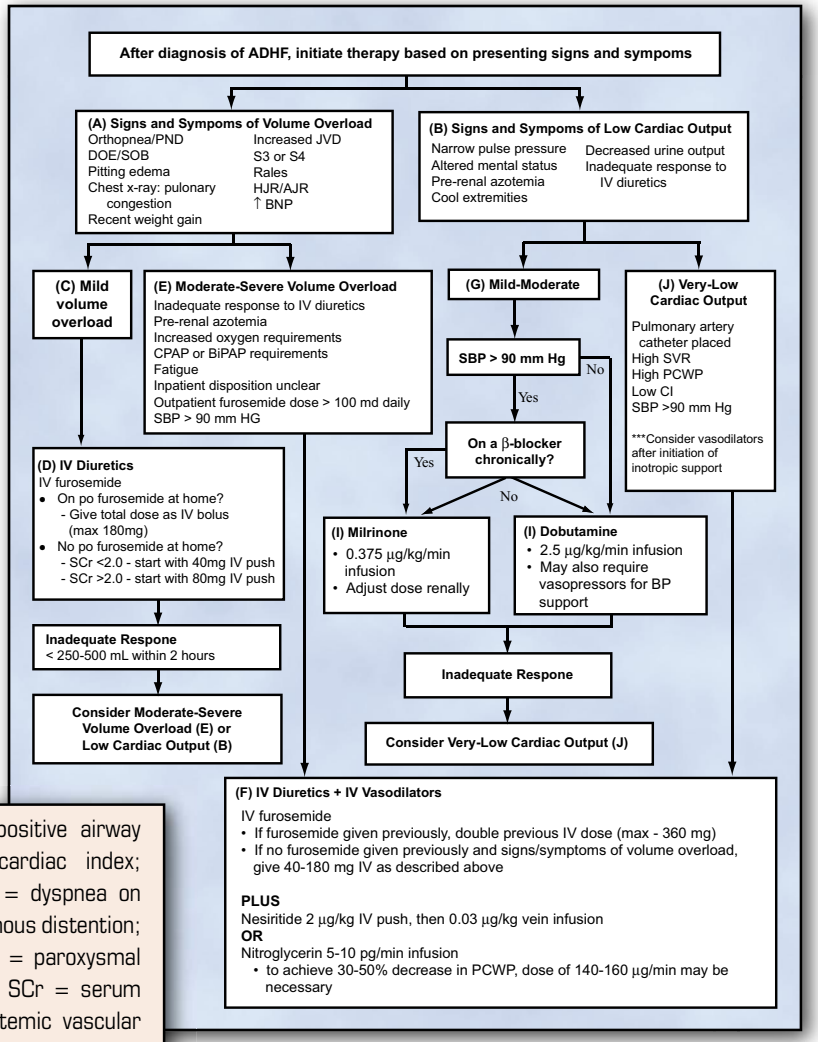


Two key hemodynamic parameters are the presence or absence of elevated filling pressures (wet or dry) and the adequacy of perfusion (warm or cold).

Initial therapy should be guided by the patient's hemodynamic profile [Figure 2].[4,11] For patients without evidence of elevated filling pressures or hypoperfusion (dry and warm), no immediate intervention is needed. Care should focus on maintaining stable volume status and preventing disease progression. These patients rarely present to the ED. In patients with elevated filling pressures but adequate perfusion (wet and warm) therapy aims to diurese. Assuming they are already receiving ACE inhibitors, the goal is to enhance their diuretic regimen. In more advanced cases the use of intravenous loop diuretics and vasodilators, such as nitroglycerin or nesiritide, can accelerate symptom resolution. The main challenge is avoiding hypotension. In this situation inotropic therapy is contraindicated. For congested (elevated filling pressure) patients with clinical hypoperfusion (wet and cold) it is usually necessary to "warm up in order to dry out". For these patients, in whom reflex responses support the failing circulation, β-blockers and ACE inhibitors may need to be withdrawn until stabilization is achieved. Low cardiac output is often associated with high systemic vascular resistance, and may improve with vasodilator therapy alone. There remains controversy about the role of inotropic-vasodilator agents such as dobutamine and milrinone, due to the increased risk for ischemic events and tachyarrhythmias. Patients with low cardiac output without evidence of elevated filling pressure (cold and dry) may be surprisingly stable and do not present with urgent symptoms. Unless they have subnormal filling pressures (volume depleted) or excessive vasodilation they often do not improve acutely. Inotropic infusion, while helping the symptoms, may lead to dependency and tachyphylaxis.

Figure 2.

Acute decompensated heart failure (ADHF) treatment algorithm. Reprinted with permission from DiDomenico et al. Ann Pharmacother. 2004;38:649-660



AJR = abdominal jugular reflex; BiPAP = bilevel positive airway pressure; BNP = b-natriuretic peptide; CI = cardiac index; CPAP = continuous positive airway pressure; DOE = dyspnea on exertion; HJR = hepatojugular reflex; JVD = jugular venous distention; PCWP = pulmonary capillary wedge pressure; PND = paroxysmal nocturnal dyspnea; SBP = systolic blood pressure; SCr = serum creatinine; SOB = shortness of breath; SVR = systemic vascular resistance.

Pharmacologic Options

An ideal agent for ADHF would be one that rapidly reduces PCW relieving symptoms and hypoxia, induces balanced arterial and venous dilation, lacks positive inotropic effects, promotes natriuresis and doesn't cause reflex neuroendocrine activation.

Diuretics are traditionally used to reduce preload thereby improving symptoms in ADHF patients. They do not have any direct myocardial benefit but activate the neurohormonal system leading to aldosterone elevation. Diuretics have been used for decades and most providers are very comfortable with them despite the fact that they lack of evidence of improved mortality. Intravenous furosemide causes a decrease in PCWP and right atrial pressure as a result of venodilation and diuresis.[12] There is a concomitant decrease in stroke volume, increase in systemic vascular resistance and pronounced spike in neurohormonal activation. Increases in the RAAS and sympathetic nervous system activation (norepinephrine levels) can be seen shortly after furosemide infusion.[13]

In one trial of high-dose loop diuretics, compared to low dose diuretics combined with intravenous vasodilators, patients treated with high-dose furosemide did significantly worse in all outcome measures.[14] A recent analysis of eight small trials found that there was greater diuresis and a better safety profile if diuretics were given as a continuous instead of bolus infusion.[15] While intravenous diuretics promote natriuresis and diuresis, they do so at the expense of neurohormonal activation and systemic vasoconstriction that prevents reduction of ventricular filling pressures. Diuretic resistance is a clinical state in which diuretic response is diminished or lost. This may be caused by prerenal azotemia, hyponatremia, sodium retention or altered diuretic pharmacokinetics. There is a cycle of low cardiac output leading to diminished renal perfusion which in turn produces volume overload and worsens heart failure. These deleterious effects are even more pronounced in patients with underlying renal insufficiency. Diuretic requirements increase as the heart failure progresses.[15]

Arginine vasopressin is a neurohormone produced by the central nervous system in response to changes in serum osmolarity, severe hypovolemia or hypotension. One approach to antagonizing vasopressin's action is to selectively block its receptor, resulting in aquaresis without electrolyte imbalances or neurohormonal stimulation. The novel compound tolvaptan is an antagonist that causes increased urine output and decreases body weight and edema. One study looked at weight reduction following 24 hours of infusion in patients with impaired ventricular function (EF <40%). There was no difference in in-hospital mortality or worsening of heart failure. This novel agent shows promise of facilitating fluid loss without adverse sequelae in patients with reduced systolic function.[16]

Inotropes have been a mainstay of therapy for ADHF because of their beneficial effects on hemodynamic parameters, namely increasing cardiac contractility, which improves cardiac output.[17] Inotropes are used infrequently in the ED due

Initial therapy should be guided by the patient's hemodynamic profile.

Diuretics have been used for decades and most providers are very comfortable with them despite the fact that they lack of evidence of improved mortality.

primarily to logistical concerns. Recent large studies demonstrated a lack of efficacy in many ADHF patients and exposed safety concerns. Inotropes increase heart rate and myocardial oxygen demand, aggravate ischemia, precipitate arrhythmias and can cause hypotension. A trial comparing dobutamine versus nesiritide, demonstrated that dobutamine increases ventricular ectopy and ventricular tachycardia.[18] Milrinone failed to demonstrate significant improvements in length of hospitalization, symptom relief or mortality, compared to placebo. It was however associated with sustained hypotension and tachyarrhythmias in the OPTIME-CHF trial.[19] Dobutamine is preferred in patients who are hypotensive (systolic BP <90 mm Hg) since it exerts its effects by stimulating β-adrenergic receptors. Higher doses are often required in patients on chronic β-blocker therapy. Milrinone is a phosphodiesterase inhibitor and its action is not impacted by concomitant β-blocker use. Milrinone doesn't increase myocardial oxygen consumption or effect heart rate to the same degree that dobutamine does. In general, given their inability to affect outcome and increased incidence of adverse effects, inotropic support should be reserved for patients with very low cardiac output. They should only be used in the ED setting on patients with symptomatic hypotension until further therapy (intra-aortic balloon pump) can be instituted.

Calcium sensitizers such as levosimendan produce increased inotropy in a cyclic AMP-independent fashion by increasing the sensitivity of troponin C to intracellular ionized calcium, as well as peripheral vasodilation through the vascular K-ATPase channels. An effective positive inotrope, levosimendan increases in stroke volume and cardiac index and decreases PCWP, right atrial pressures, pulmonary arterial pressures and mean arterial pressures.[20] In this study, the hemodynamic effects were maintained during a 48 hour infusion and for at least 24 hours after discontinuation. When levosimendan was added to dobutamine in New York Heart Association class IV patients refractory to dobutamine and furosemide, 39% of patients getting all three agents compared to none in the standard group, experienced a 40% increase in cardiac index.[21] This exciting agent is in the early clinical trials.

Vasodilators reduce preload and afterload, enhancing ventricular function and cardiac output by improving resting hemodynamics. Vasodilators reduce ventricular filing pressures (PCWP) and preload, and over time myocardial oxygen consumption. Vasodilators also decrease systemic vascular resistance (SVR or afterload), reduce ventricular workload, increase stroke volume and improve cardiac output.[22]

Nitrates, in particular nitroglycerin, have been the first-line prehospital and ED therapy for patients with severe symptoms. Nitrates (nitroglycerin and nitroprusside) act by increasing cyclic guanosine monophosphate in the vascular smooth muscle leading to vasodilation. They improve symptoms and decrease PCWP relatively quickly. Nitroglycerin use is limited by fear of hypotension, and need for titration secondary tachyphylaxis, yet it is frequently underdosed. Nitroglycerin has direct affects on large coronary arteries and increases collateral flow, making it a useful in patients with myocardial ischemia. However, there are no trials looking at its outcome efficacy. Nitroprusside while efficacious is used infrequently due to concerns about thiocyanate toxicity (especially in the face of hepatic or renal hypoperfusion / dysfunction). It can also precipitate profound hypotension, exacerbate ischemia by inducing coronary steal, and requires invasive monitoring. Both of these agents cause reflex activation of the RAAS and sympathetic nervous system which limits their long-term use.[10]

Angiotensin-converting enzyme (ACE) inhibition blocks conversion of angiotensin I into angiotensin II, resulting in diminished systemic vascular resistance, blood pressure, preload and afterload. ACE inhibitors also block the degradation of bradykinins, a natural-

ly occurring vasodilator. ACE inhibitor therapy increases renal perfusion and decrease renal vascular resistance improving glomerular filtration rate by inducing vasodilation in both afferent and efferent arterioles. The major drawback to the use of intravenous ACE inhibitors such as enalaprilat in the acute setting is its propensity to induce hypotension. In the stable patient the agent's major limitations are renal insufficiency and angioedema. Enalaprilat has been used in the setting of ADHF secondary to uncontrolled hypertension. Oral ACE inhibitors are recommended early out for those patients not already receiving them. However, the patient must be hemodynamically stable before these agents are initiated, and this limits their aggressive up front use in the ED. Angiotensin-receptor blocker can be substituted in patients who can't tolerate ACE inhibitors.

Recent attention has been focused on the acute blockade of deleterious neurohormones. Endothelin (ET) is a vasoconstrictor peptide released from vascular endothelium and smooth muscle of the renal and pulmonary systems. Tezosentan is a highly specific and potent ET receptor antagonist. There is a dose dependent increase in cardiac index due to vasodilation and decrease in PCWP.[23] In the RITZ project, tezosentan improved hemodynamic but not clinical outcome of patients with acute heart failure. A recent trial evaluating lower doses, in hospitalized ADHF patients with dyspnea despite initial treatment, showed increased cardiac index and decreased PCWP within 6 hours at the 5 mg/hour and 25 mg/hour treatment groups, and by 24 hours in the 1 mg/hour cohort. The effect continued beyond treatment discontinuation in the 1 mg/hour group. Endothelium levels were increased in the higher dose groups, suggesting sympathetic nervous system activation, but not in the 1 mg/hour subset. Tezosentan's effect while clinically significant, is not presently appropriate for the ED given its delayed onset.[24]

The natriuretic peptide family consists of four distinct peptides. Atrial natriuretic peptides (ANP) and B-type natriuretic peptides (BNP) are structurally similar. C-type natriuretic peptides (CNP) and D-type natriuretic peptides (DNP) are less well characterized. Atrial and B-type natriuretic peptides have important central and peripheral sympathoinhibitory effects. Dampening of the baroreceptors, suppressed release of catecholamine from autonomic nerve findings and especially suppression of sympathetic outflow from the central nervous system have all been reported.[25]

The long-term continuous infusion of ANP has been shown to be clinically useful in patients with severe acute heart failure. Hemodynamic measurements evaluated by Swan-Ganz catheter significantly improved with ANP. In a recent study, hemodynamic indices characterized by decreases in right atrial pressure, mean pulmonary arterial pressure, and PCWP and an increase in cardiac index, were observed after ANP infusion. Left ventricular performance was enhanced without the development of tolerance. The activation of the RAAS promotes structural remodeling of the heart and progression of heart failure. ANP thereby improved left ventricular

Given their inability to affect outcome and increased incidence of adverse effects, inotropic support should be reserved for patients with very low cardiac output.

Patients treatment early on tend to have shorter hospital stays and better outcomes than those whose intervention was delayed.

function possibly by blunting myocardial remodeling.[26,27] While available in Asia and Europe, ANP is not approved for use in the United States.

BNP is an endogenous neurohormone, produced in the ventricles in response to increased wall stress that occurs from volume overload in ADHF patients. Nesiritide is the first natriuretic peptide (identical to endogenous BNP) to be available in the United States for the treatment of ADHF. Within minutes of administration nesiritide produces significant reductions in PCWP, right atrial pressure and systemic vascular resistance, as well as concomitant increases in stroke volume and cardiac output. Nesiritide has additional advantages over other vasodilators such as nitroglycerin, including diuresis, natriuresis and lusitropy. The beneficial coronary artery effects of nitroglycerin are also present in nesiritide. Additionally, nesiritide lacks the proarrhythmic and tachycardia seen with inotropes and many vasodilators.[25]

The Vasodilation in the Management of Acute Congestive Hear Failure (VMAC) trial compared the use of nesiritide, nitroglycerin or placebo in addition to standard therapy in 489 patients with ADHF. This safety and efficacy trial found that nesiritide reduced PCWP more than either nitroglycerin or placebo at 3 hours and 24 hours. Improvements in dyspnea and global clinical status in the nesiritide-treated patients were greater than those in the placebo recipients and similar to those in the nitroglycerin group. Nesiritide's hemodynamic effecters were long-lasting without the need for upward titration, whereas titration was necessary in order to maintain nitroglycerin's effect. This was most striking in the subset of patients with right heart catheters on a constant dose of nitroglycerin, where rapid attenuation of the desired effect and rise in PCWP was seen at 3 hours.[28]

BNP doesn't increase heart rate or provoke arrhythmias and has no inotropic effects. This lack of arrhythmogenicity is especially important in heart failure patients with atrial fibrillation and those predisposed to ventricular tachycardia. The PRECEDENT study compared the proarrhythmic effects of dobutamine versus 2 doses of nesiritide in 255 patients. Dobutamine significantly increased ventricular tachycardia events. Nesiritide did not increase heart rate despite greater reduction in blood pressure. Both agents were equally effective in improving signs and symptoms of heart failure.[19] Compared to dobutamine, nesiritide reduced 21-day hospital readmissions for heart failure and had lower 6-month mortality.[29]

In the Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor (PROACTION) study, 237 patients were randomized to standard care or at least 12 hours of nesiritide infusion in an ED observation setting. Importantly, none of these patients was subject to invasive or ICU level monitoring in the ED, yet did well. Mortality rates and complications were similar

between the two groups. Nesiritide was associated with a 57% reduction in hospital readmission within 30 days compared with standard therapy and a substantial decrease in total length of stay over the ensuing months after the index visit.[30]

In a pooled analysis from the PROACTION,[30] VMAC,[28] and NSGET[31] trials, the short term risk of death from nesiritide was investigated. As none of the studies included in the pooled analysis were powered to determine mortality differences, there is no conclusive evidence of harm. The manuscript concluded that when compared to nonionotropic based therapy, nesiritide may be associated with an increased risk of death. Further study with mortality outcomes of nesiritide compared to conventional therapy have yet to occur. As with any new therapy, the favorable attributes must be weighed against the potential risks.[32]

Early Goal Directed Therapy

Early goal directed therapy (EGDT) approach emphasizes aggressive upfront treatment, because preliminary evaluations have shown that patients treated early out tend to have shorter hospital stays and better outcomes than those whose intervention is delayed. It aims to achieve 1) hemodynamic and respiratory improvement, 2) prompt relief of symptoms, 3) enhanced decision-making in the ED with an emphasis on timely transition to inpatient care if indicated, 4) early initiation of therapy also facilitates hospital discharge and 5) avoidance of high resource utilization.[11, 33] Care needs to focus on rapid initiation of proven therapies that improve patient symptom and cardiorespiratory status without placing the patient at risk for immediate (arrhythmia, hypotension, ischemia) and delayed (worsening renal insufficiency, toxicity) adverse events. There is growing evidence that EGDT has both clinical and economic advantages over more conservative treatment approaches.

There is a subpopulation of patients, moderately sick requiring more than a few hours of care, who don't necessarily need hospital admission. The availability of an ED observation unit makes good clinical and economic sense. EGDT can be initiated and patients monitored for improvement. Patient selection is critically important in determining who will most benefit from an observation unit stay (matching acuity with available services). General selection criteria include the following;

1. adequate systemic perfusion (normal mental status),
2. evidence of reasonable hemodynamic stability (HR >50 and < 130 beats/min, systolic BP > 90 and <175 mm Hg, oxygen saturation >90%),
3. no evidence of acute cardiac ischemia by ECG or biomarkers,
4. chest x-ray findings compatible with the diagnosis of heart failure,
5. diagnosis of HF (BNP > 100 pg/mL) without other confounding morbidities.[34]

Vasodilators reduce preload and afterload, enhancing ventricular function and cardiac output by improving resting hemodynamics.

Initial treatment of ADHF is generally based on the presence or absence of pulmonary congestion (volume overload) and an assessment of perfusion (cardiac output) [Figure 3]. While treatment algorithms focus on parental therapy during the early phase, continuation of the patient's chronic heart failure medication, including ß-blockers and ACE inhibitors are important. Mild congestion improves with intravenous diuretics. Monitoring of urine output is critical. For those with normal renal function a goal of 500 ml/hr is acceptable. Patients with inadequate response to furosemide should be assessed for the presence of moderate to severe volume overload, and vasodilator therapy should be considered. Intravenous nitroglycerin or nesiritide should be started in patients with adequate blood pressure to speed relief of congestion. If nitroglycerin is used it will be necessary to up titrate the infusion frequently. Patients with evidence of poor perfusion

Figure 3.

Primary Targets of Treatment in Heart Failure.
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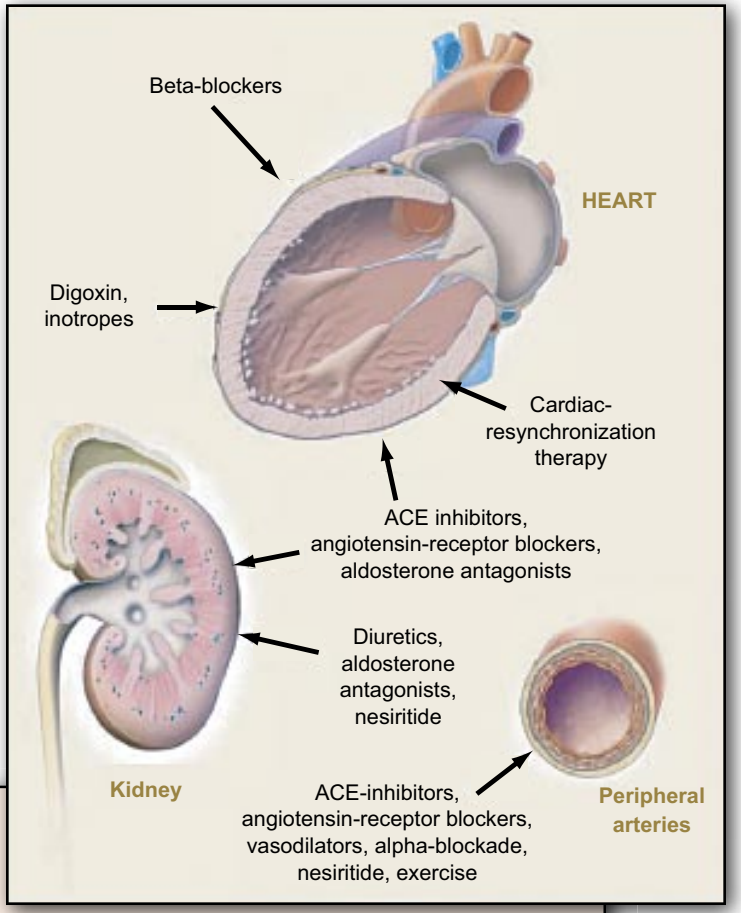

Treatment options for patients with heart failure affect the pathophysiological mechanisms that are stimulated in heart failure. Angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers decrease afterload by interfering with the renin–angiotensin–aldosterone system, resulting in peripheral vasodilatation. They also affect left ventricular hypertrophy, remodeling, and renal blood flow. Aldosterone production by the adrenal glands is increased in heart failure. It stimulates renal sodium retention and potassium excretion and promotes ventricular and vascular hypertrophy. Aldosterone antagonists counteract the many effects of aldosterone. Diuretics decrease preload by stimulating natriuresis in the kidneys. Digoxin affects the Na+/K+ –ATPase pump in the myocardial cell, increasing contractility. Inotropes such as dobutamine and milrinone increase myocardial contractility. Beta-blockers inhibit the sympathetic nervous system and adrenergic receptors. They slow the heart rate, decrease blood pressure, and have a direct beneficial effect on the myocardium, enhancing reverse remodeling. Selected agents that also block the alpha-adrenergic receptors can cause vasodilatation. Vasodilator therapy such as combination therapy with hydralazine and isosorbide dinitrate decreases afterload by counteracting peripheral vasoconstriction. Cardiac resynchronization therapy with biventricular pacing improves left ventricular function and favors reverse remodeling. Nesiritide (brain natriuretic peptide) decreases preload by stimulating diuresis and decreases afterload by vasodilatation. Exercise improves peripheral blood flow by eventually counteracting peripheral vasoconstriction. It also improves skeletal-muscle physiology.

should be considered for inotropic support. Dobutamine should be started in patients with low cardiac output and systolic blood pressure <90 mm Hg. They may require vasopressor support if hypotension develops. Patients with low cardiac output but adequate blood pressure may benefit from milrinone, especially if they are already taking beta-blockers. Those requiring inotropic support will require admission to an intensive care unit. Those receiving vasodilators can often be managed in a less acute setting (telemetry or ED observation unit). Preliminary analysis from the ADHERE registry indicated that length of stay was reduced by up to a third in patients receiving vasoactive agents (vasodilators, nesiritide or inotropes) in the ED or observation unit, compared with patients who had vasoactive therapy initiated in the hospital.[35] This early initiation of emergency department therapy is associated with lower hospital mortality, decreased frequency of invasive procedures and decreased ICU length of stay. Thus, early targeted vasoactive therapy in the ADHF patient seems to be very promising.

SUMMARY

In the majority of patients who present to the ED with ADHF, initial therapy with oxygen and diuretics will not adequately reduce filling pressures or improve cardiac output enough to improve symptoms. Inotropes improve symptoms in the short-term but are deleterious in the long-run. Vasodilators are frequently necessary as they address the primary underlying pathophysiology of heart failure. Nitroglycerin and nitroprusside are effective but their use is hampered by adverse effects and limitations. Natriuretic peptides such as nesiritide, with their neurohormonal antagonism, may offer several benefits over conventional vasodilators and inotropes for the treatment of ADHF. It has been shown that nesiritide can be used safely in the ED and upfront use can reduce hospital length of stay.

New pharmacological agents under investigation attempt to enhance our understanding of abnormal neuroendocrine function in heart failure. By specifically targeting key points such as the activation and feedback process, they may prevent disease progression and acute decompensation.[36] While we await new treatment modalities, current ED efforts must focus on the early implementation of effective strategies to improve symptoms and correct the underlying physiology.

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THE EVOLVING ROLE OF BNP IN THE DIAGNOSIS AND TREATMENT OF CHF: A SUMMARY OF THE BNP CONSENSUS PANEL REPORT

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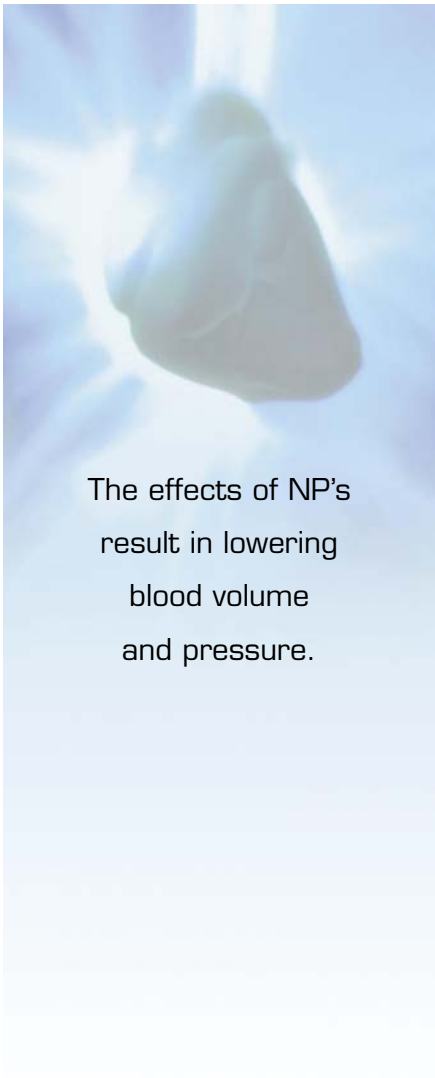
OBJECTIVES:

1. Discuss the application and limitations of BNP testing in the emergency setting
2. Describe the appropriate candidate for BNP therapy

INTRODUCTION

A BNP expert consensus panel,[1] consisting of individuals with basic, methodologic, and clinical expertise, was convened in 2004 to create a summary document to help guide the clinician on the recent explosion of natriuretic peptide (NP) data. This document contains the data from their recommendations most applicable to the emergency physician.



Natriuretic Peptide Physiology

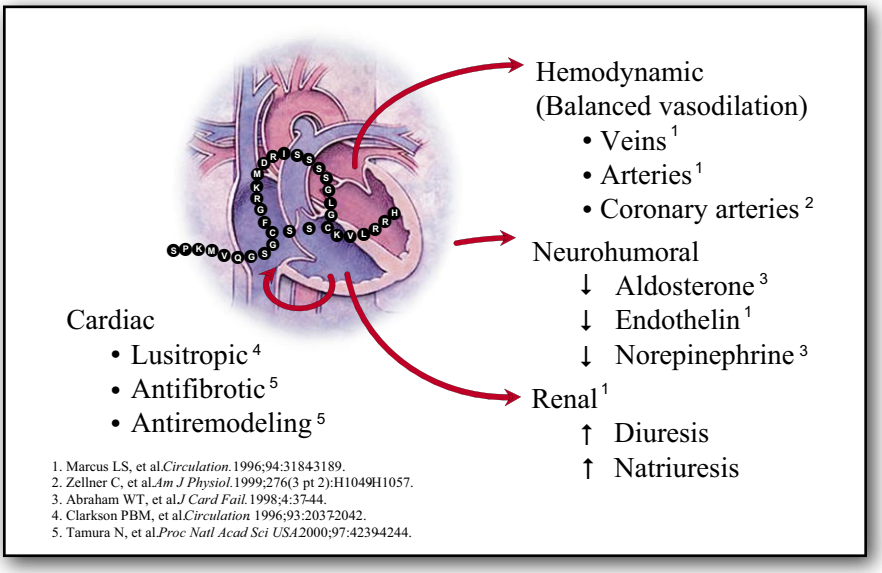
More than a pump, the heart is a critical endocrine organ functioning with other physiological systems to control fluid volume. Myocytes manufacture a family of peptide hormones, termed the NPs, represented by atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Release of the NPs is stimulated by volume overload,[2] and physiologically, they have powerful diuretic, natriuretic, and vascular smooth muscle relaxing actions. Importantly, they also serve as antagonists to the sympathetic nervous system and the renin-angiotensin-aldosterone axis (RAAS).[3,4] Release of NP's results from cardiac wall stretch, ventricular dilation, or increased pressures from circulatory volume overload. The effects of NP's result in lowering blood volume and pressure.

BNP is derived from a precursor, pre proBNP, which undergoes several cleavages. The assay relevant products are the inert N-terminal pro-BNP fragment, and physiologically active BNP. BNP's are preferentially produced and secreted by the cardiac ventricles,[5] although fluid overload may cause rapid BNP manufacture in both heart chambers.[6] The primary function of NPs is to defend against volume overload. After release into circulation, BNP actions are modulated at target sites by specific cell membrane receptors, termed A, B, and C, which mediate physiological actions by cyclic GMP.[7] Cyclic GMP has potent vasodilatory actions. BNP also causes an intravascular fluid shift, from the capillary bed into the interstitium, which contracts intravascular volume and decreases BP.[8-10] In addition, BNP is a RAAS antagonist, where it counteracts sodium conservation, vasoconstriction, and volume retention. BNP also inhibits the release of renin from kidney cells and aldosterone from adre-

nal cells. BNP is primarily metabolized by the NPR-C receptor, although some additional degradation may occur by neutral endopeptidase.[11-13] Neutral endopeptidase has a wide tissue distribution, including adipose, kidneys, lung, and brain (Figure 1).

quires 15-minutes to perform, and reports BNP levels from 5 to 5000 pg/mL. This assay is rated as moderately complex assay per Clinical Laboratory Improvement Amendments (CLIA) regulations.

Figure 1. BNP EFFECTS



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BNP for Diagnosis of Heart Failure

Despite advances in our understanding of heart failure (HF) pathophysiology, diagnosis is still difficult. While emergency department (ED) diagnosis needs to be rapid and accurate,[19] the signs and symptoms of HF are nonspecific.[20] Respiratory distress can preclude obtaining the history, and dyspnea is nonspecific in the elderly or obese.[21] Routine labs, ECG, and x-rays are also not accurate enough to always make the correct diagnosis.[22-24]

Biologic Determinants on BNP Measurements.

Blood levels of NPs are affected by a variety of factors, including circadian rhythm, age, exercise, and body posture.[14] Many drugs including diuretics, angiotensin-converting enzyme inhibitors, adrenergic agonists, sex and thyroid hormones, glucocorticoids, sodium intake, and other conditions impact levels. BNP increases with age and gender. Baseline and pathologic levels are higher in women.[15,16] The age induced BNP increase may be due to the decline in myocardial function[17] or to decreased clearance.

BNP Assay

It should be made clear that the BNP assay is not a stand-alone test. Its greatest value is when it is used with the physician's clinical judgment, and with other appropriate testing. The Triage BNP assay system is the only FDA approved point-of care assay.[18] It re-

CONSENSUS STATEMENTS: GENERAL COMMENTS.

The laboratory should perform BNP testing on a continuous 24-hour basis with a turn-around-time (TAT) of 60 minutes or less. The TAT is defined as the time from blood collection to notification of result to physician or caregiver. Either central laboratory instrumentation or point of care testing systems are acceptable.

- **In considering NP measurements, one needs to carefully consider laboratory and biologic variation, including gender, sex, obesity, and renal function.**
- **The results of natriuretic testing is dependent on the type of test you are obtaining. N terminal pro BNP and bioactive BNP are NOT interchangeable.**

The Breathing Not Properly study[25] was a large, multinational, prospective study using BNP to evaluate dyspnea in 1586 dyspneic ED patients. BNP levels were measured on arrival, and physicians assessed the probability of the patient having HF. Two cardiologists, blinded to the BNP level, reviewed all data after hospitalization to produce a "gold standard" clinical diagnosis. BNP levels alone more accurately predicted the presence or absence of HF than any other finding. The 100 pg/mL cutpoint had a 90% sensitivity and 76% specificity for a HF diagnosis. In multivariate analysis, BNP levels always contributed to the diagnosis, even after considering features of the history and physical examination.

BNP levels may also help in disposition decisions. The Rapid Emergency Department Heart Failure Outpatient (REDHOT) Trial demonstrated a "strong disconnect" between the perceived severity of HF, and illness severity as determined by BNP. On average, patients discharged from the ED had a higher BNP than those admitted, 976 pg/mL, versus 766 pg/mL, respectively. BNP also predicted outcomes of patients discharged, 78% had a BNP > 400 pg/mL, however, there was no mortality at 30 days if the BNP was less than 400 pg/mL.

The Swiss BASEL Study[26] examined cost-effectiveness of using BNP through the diagnosis and hospitalization in acute decompensated heart failure (ADHF). In 452 patients, ED measurement of BNP was associated with a 10% decrease in hospital admissions, a 3-day decline in length of stay, and an $1800 savings, with no effects on mortality or re-hospitalization rates.

CONSENSUS STATEMENT: USING BNP TO HELP TRIAGE ED PATIENTS WITH DYSPNEA.

BNP is of diagnostic utility in the evaluation of patients with acute dyspnea. Thus, in new patients presenting with dyspnea to an emergency setting, a history, physical examination, chest x-ray and ECG should be undertaken together with laboratory measurements that include BNP. Current data suggest the following guidelines:

- **As BNP rises with age and is affected by gender, comorbidity, and drug use, it should not be used in isolation from the clinical context.**
- **If the BNP is <100 pg/mL, then HF is highly unlikely (NPV = 90%).**
- **If the BNP is >500 pg/mL, then HF is highly likely (PPV = 90%).**
- **If the BNP is 100–500 pg/mL, consider: a baseline BNP elevated due to stable underlying dysfunction, right ventricular failure from cor pulmonale, acute pulmonary embolism, or renal failure.**
- **Patients may present with HF and a normal BNP, or with levels below what is expected in the following situations: flash pulmonary edema (<1–2 hours), HF up-stream from the left ventricle (such as with acute mitral regurgitation from papillary muscle rupture and obese patients (body mass index [BMI] >35).**

BNP and Renal Failure

Chronic kidney disease (CKD) influences the cut-point for BNP. In general, as CKD advances, a higher BNP cut-point is implied. A cut-point of approximately 200 pg/mL is reasonable for those with an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2. Using this approach, BNP maintains a high level of diagnostic utility, with an area under the ROC curve of >0.80 across all CKD groups.

CONSENSUS STATEMENTS: COMORBIDITIES AND SPECIAL ISSUES THAT INFLUENCE THE INTERPRETATION OF BNP LEVELS.

- **BNP is altered with chronic renal insufficiency (estimated GFR < 60 mL/min), with a recalibration of the cut off value to 200 pg/mL.**
- **BNP is helpful in the evaluation of dyspnea when it is very low or high. NT pro BNP has greater correlation with eGFR than BNP, hence levels can be elevated even with the normal age related decline of renal function in the eGFR 60-90 mL/min range.**
- **When the eGFR is below 60 mL/min, N terminal proBNP can be considerably elevated and in this setting its utility in the evaluation of HF is unknown.**
- **Baseline BNP levels might therefore be important in dialysis patients, as changes most likely reflect volume status. Thus a pre-dialysis BNP may help determine the amount of volume which should be removed.**

Cardiopulmonary Disease

Some non-HF cardiopulmonary disease may cause BNP elevations. These include cor pulmonale, lung cancer, pulmonary embolism (PE) and primary pulmonary hypertension. In these, BNP may be elevated, but not to the extent found in ADHF. In PE, BNP may be prognostic since patients with a BNP in the upper normal range or > 100 pg/mL have a higher mortality rate.[27] Although BNP is not an adequate screening test for PE, in the setting of a suspected or confirmed embolic event, a BNP elevation implies RV pressure overload and increased mortality risk. Finally, in primary pulmonary hypertension, BNP elevations parallel the extent of pulmonary hemodynamic changes and right HF.[28]

CONSENSUS STATEMENT: BNP IN PULMONARY AND ASSOCIATED CARDIAC DISEASE.

- **In approximately 20% of patients with pulmonary disease, BNP is elevated implying combined HF and lung disease, cor pulmonale, or a misdiagnosis when the true etiology of dyspnea is HF.**
- **In the setting of PE, BNP is elevated in 1/3 of cases and is associated with RV pressure overload and a higher mortality. BNP is not diagnostic for acute PE.**
- **Pulmonary disease which results in pulmonary hypertension and RV pressure or volume overload can lead to elevated BNP levels, usually in the range of 100-500 pg/mL.**

Preserved Systolic Function (PSF) Heart Failure

Diastolic myocardial dysfunction, also known as PSF, is the cause of HF in as many of 50% of cases and is also associated with high BNP.[29,30] BNP has been found to be approximately half as high in PSF as in cases of systolic dysfunction.[31]

CONSENSUS STATEMENT: BNP IN DIASTOLIC DYSFUNCTION.

- **BNP might be used to detect patients with diastolic dysfunction.**
- **BNP concentrations above age-adjusted cut-points may identify elderly patients with diastolic dysfunction.**

Obesity

Obesity is an important risk factor for coronary artery disease and HF.[32-35] Physiologically, adipose tissue is related to the natriuretic clearance receptor[36,37] and obesity can interfere with the usual diagnostic approach to HF. Mehra[38] documented an inverse relationship between Basal Metabolic Index (BMI) and BNP. Lower levels of BNP in the obese (BMI>30Kg/M2) were noted, despite similar severity of HF compared to a lean cohort, and nearly 40% of obese patients had BNP <100 pg/mL.

CONSENSUS STATEMENT: BNP IN OBESITY.

- **Since obese patients (body mass index [BMI] > 30kg/m^2) express lower levels of BNP for any given severity of HF, cautions should be exercised in interpreting BNP levels in such patients.**

BNP and Acute Coronary Syndromes (ACS)

Large studies report NP elevations in unstable angina without myocardial necrosis.[39,40] As ischemia may result in only small NP elevations, their sensitivity and specificity are inadequate as a "rule out" tool. However if present, an elevation of NP in ACS is a powerful predictor of adverse events. In 2,525 patients[41] grouped into BNP quartiles 40 hours after ACS onset, an increasing BNP was associated with higher 10-month mortality, and this relationship persisted even without evidence of HF or myocardial necrosis.

CONSENSUS STATEMENT: BNP IN SUDDEN DEATH, ACS, AND CAD.

When used together, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and ACS. Multimarker panels with BNP and troponin are now available, where each of these markers provide unique and independent outcome data.

BNP and Prognosis

BNP elevation is a powerful marker of HF prognosis. In 325 patients, followed for 6 months after an ED visit for dyspnea, the relative risk of 6-month HF admission or death, was 24 times higher if the BNP was >230 pg/mL (Figure 2).[42] This was confirmed by the Val-HeFT trial, where the lowest quartile of BNP (< 50 pg/mL) had the lowest all-cause mortality and the highest quartile (> 238 pg/mL) had the highest mortality, 32% at 30 months (Figure 2).

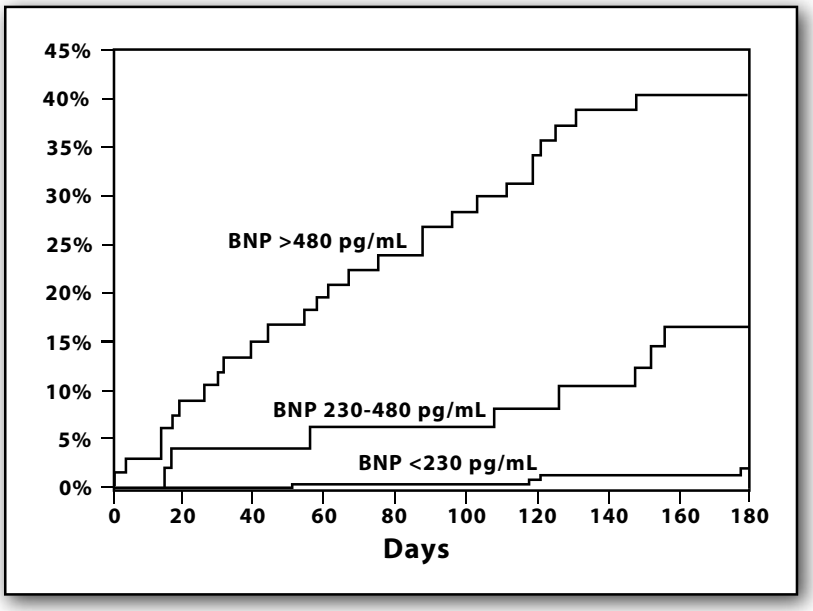

Figure 2.

Relationship of BNP determined in emergency department care to death or heart failure hospitalization. Reprinted with permission from Ann Emerg Med. 2002;39:131-138.

Giving BNP, in the form of nesiritide, can restore neurohormonal homeostasis and is associated with reduced filling pressures, decreased pulmonary vascular resistance, lowered central venous pressures, and reduction in systemic BP.

BNP as Therapy

When ADHF occurs, the balance between vasoconstrictors and endogenous vasodilators is disturbed. This forms the basis as to why exogenous BNP is given as therapy despite high endogenous levels, is analogous to giving insulin for insulin resistance. In ADHF, high levels of BNP occur as a "distress hormone", where supra-normal levels are no longer effective at maintaining the balance of vasoconstriction and vasodilation. Hence giving BNP, in the form of nesiritide, can restore neurohormonal homeostasis.

NP are much closer to ideal drugs for ADHF than other agents. The use of nesiritide is associated with reduced filling pressures, decreased pulmonary vascular resistance, lowered central venous pressures, and reduction in systemic BP. There is also increased cardiac output due to the unloading effect of vasodilatation, but without reflex tachycardia. Moreover, reducing preload and afterload without increasing heart rate is consistent with decreased myocardial oxygen consumption and a decrease in ventricular stress - a stimulus presumed to drive the neurohormonal activation of ADHF. Lastly, tolerance to these effects does not occur, and these changes in hemodynamics are present and persistent throughout the administration of nesiritide.

To date, nesiritide is the only natriuretic peptide available in the US for IV therapy. Colucci et al.[43], in the Efficacy Trial, showed that nesiritide causes a dose-related decrease in PCWP, systemic vascular resistance, mean right arterial pressure, dyspnea, fatigue, a significant increase in cardiac index, and an improvement in global status. The most common side effect was dose-related hypotension. The Comparative Trial[44] evaluated nesiritide versus many other cardiovascular agents, including dobutamine, milrinone, nitroglycerin, dopamine, and amrinone. Global clinical status, fatigue, and dyspnea improved in all groups, with no significant differences between nesiritide and standard therapy. The most common side-effects were bradycardia and dose-related hypotension.

In 1998, Burger et al,[45] conducted the PRECEDENT study. Its primary objective was to compare heart rate and arrhythmias with two doses of nesiritide (0.015 or 0.03 µg/kg/min) to dobutamine. They concluded that although inotropic HF therapies, including dobutamine and milrinone, are associated with favorable hemodynamic and symptomatic effects, they cause arrhythmias and tachycardia which may increase myocardial oxygen demand, ischemia, and mortality. They demonstrated fewer arrhythmias and no heart rate increase with nesiritide. Furthermore, the rates of 21-day readmission and 6-month mortality were higher with dobutamine. The authors concluded that nesiritide is safer than dobutamine for short-term ADHF management.

The VMAC trial[46] was a safety and efficacy study of intravenous nesiritide versus intravenous nitroglycerin or placebo in 489 ADHF patients with dyspnea at rest. Swan Ganz catheterization was performed in roughly half, at the physician's choice. Patients were randomized into four blinded groups, each receiving standard therapy and: fixed dose nesiritide, titratable nesiritide, titratable nitro-

glycerin, or placebo. Nesiritide had a faster onset and greater reduction in PCWP than nitroglycerin. The improvement in clinical status and dyspnea was similar in both groups (Figure 3). They concluded that when added to standard care, nesiritide improves hemodynamic function more effectively than IV nitroglycerin or placebo.

In another evaluation, a risk adjusted comparison of outcomes from the ADHERE registry of more than 100,000 ADHF patients found improved survival with vasodilators compared to inotropes. When comparing vasodilators, there are similar outcomes between nesiritide and nitroglycerin.

The current approved use of nesiritide is for ADHF. Although guideline statements are lacking, the totality of diagnostic and therapeutic data regarding nesiritide yield an intuitive rationale and a reasonable evidence-based approach for ADHF assessment and management. One of the most valuable findings is that beginning vasoactive therapy in the ED is associated with a 3.1-day reduction in hospital length of stay compared to therapies not initiated until after admission. This suggests that the choice of therapy in the ED may critically impact the course of the patient.[47]

INTEGRATING BNP LEVELS INTO A RATIONAL USE OF NESIRITIDE

While BNP is approved by the FDA for HF diagnosis, its usefulness to monitor treatment is still under study. However, some suggestions can be made. We believe that one can stratify patients to the high-risk category in part by using BNP levels. Fonorow[48] recently analyzed the ADHERE database and found that high BUN levels provide a poor prognosis for patients in ADHF. Thus,

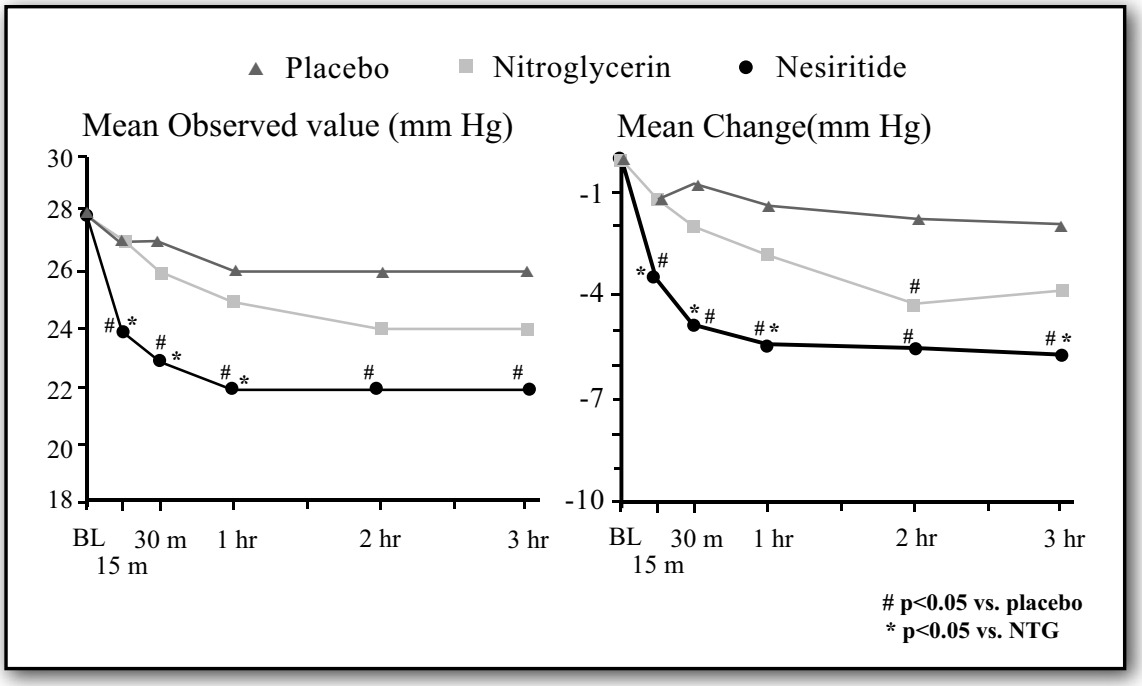

Figure 3.

Vasodilation in the Management of Acute CHF (VMAC) trial: Primary end point is pulmonary capillary wedge pressure changes over 3 hours.[46]

the combination of high BNP and poor renal function identifies high-risk patients (Figure 4).

If patients are admitted with BNP levels <500 pg/mL and BUN levels are <40 (lower risk), one can often start treatment with parenteral diuretics. Subsequently, they can be reclassified into low- or high-risk groups based on their response over the next 6–12 hours. Those with an adequate diuresis, a fall in BNP, and no deterioration in renal function may be candidates for continued diuretics/vasodilators until euvolemia is reached. Hopefully this will lead to a BNP level <400 pg/mL in these patients. In one study, patients whose discharge BNP levels were < 430 pg/mL had a reasonable likelihood of not being readmitted within the following 30 days.[49] If the BNP level was > 400 pg/mL, the volume status required re-evaluation. If the patient is not yet euvolemic, nesiritide might be considered for 24 hours.

If patients after receiving 6–12 hours of intravenous diuretics have an inadequate diuresis, no change or an increase in BNP, and worsening renal function, they should be considered at high risk. If their systolic BP is at least 90 mm Hg, they can be given 1–2 days of nesiritide with iv diuretics. BNP can then be checked 6 hours after cessation of nesiritide and oral vasodilators and diuretics can be used until euvolemia is achieved.

Patients with systolic BPs <90 mm Hg often need vasopressors and/or inotropes, sometimes under Swan-Ganz guidance. In our experience at the Cleveland Clinic, if these individuals show improvement in BP and symptoms, we will then transition their therapy to nesiritide. If there is no improvement on inotropes or pressors, further invasive strategies should be considered. Finally, it is conceivable that in patients who are admitted with very high BNP levels, or have impaired renal function, nesiritide might be started immediately.

SUMMARY

In summary, the BNP Consensus Panel of 2004 has provided consensus approaches for the use of BNP for the diagnosis and treatment of HF. Ideally, the use of these recommendations will improve the care of your patients.

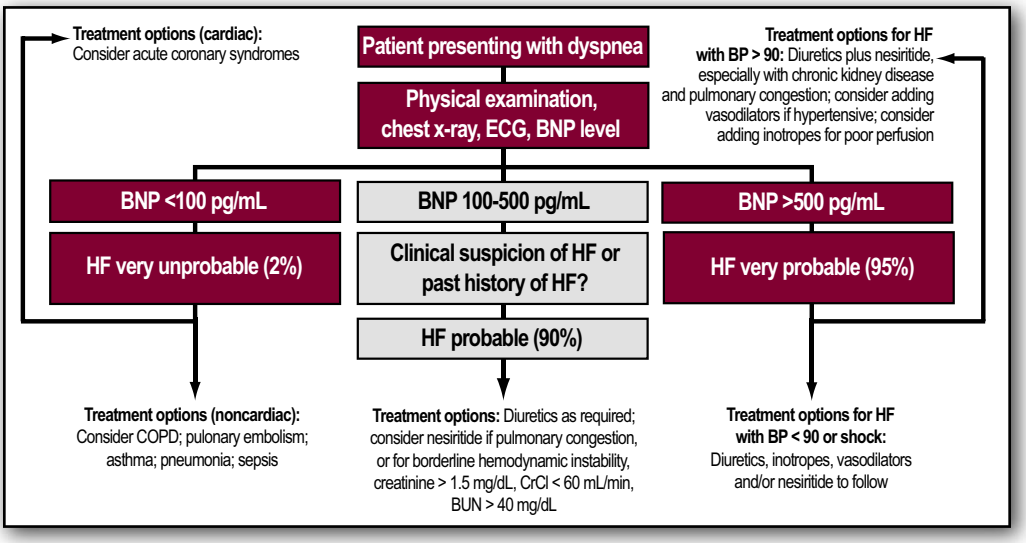

Figure 4.

BNP Consensus Algorithm

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BACKGROUND AND FINDINGS FROM THE ADHERE NATIONAL REGISTRY

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OBJECTIVES:

1. Describe the methods and process of the ADHERE registry
2. Describe how findings of the ADHERE registry can be used to direct and improve care for ADHF patients

INTRODUCTION

Acute decompensated heart failure (ADHF) represents a major public health problem. In the United States, there are approximately 1 million hospitalizations annually with a primary discharge diagnosis of ADHF. Nearly twice as many hospitalizations are associated with heart failure, as a secondary diagnosis. These numbers are expected to increase over the next two decades.[1-3] Heart failure takes a particularly high toll on the elderly. Since the early 1990s, ADHF has been the leading cause of hospitalization in persons over the age of 65 years. Reported death rates appear excessive both during and after hospitalization and high readmission rates suggest that inpatient care does not result in effective long-term management.[4,5] The enormous direct costs associated with treating the 5 million Americans with chronic heart failure are mostly attributable to the inpatient management of episodes of decompensation.[6] It has been proposed that these dismal statistics exist, in part, due to a poor understanding of the characteristics of patients admitted with ADHF and how to treat them. In this regard, most information about ADHF is derived from clinical trials that are small (hundreds of patients) and poorly representative of patients hospitalized for ADHF, due to the many inclusion and exclusion of such trials.

A few registries have been developed to evaluate chronic heart failure in the outpatient community setting.[7-9] The Acute Decompensated Heart Failure National Registry (ADHERE) was developed to provide a large, national database describing the clinical characteristics, physician practice and treatment patterns, and outcomes of patients hospitalized with ADHF.

The Acute Decompensated Heart Failure National Registry (ADHERE) was developed to provide a large, national database describing the clinical characteristics, physician practice and treatment patterns, and outcomes of patients hospitalized with ADHF.

Methodology of ADHERE

ADHERE is a large, multicenter registry designed to amass a large clinical database on the clinical characteristics, management, and outcomes of patients hospitalized for ADHF across the United States. Data are collected on the episode of hospitalization beginning with the point of initial care and ending with the patient's discharge, transfer out of the hospital, or in-hospital death. ADHERE is sponsored by Scios, Inc. (Fremont,

California). The specific objectives of ADHERE are (1) to describe the demographic and clinical characteristics of patients who are hospitalized with ADHF, including specific subgroups of interest; (2) to characterize the initial emergency department evaluation and subsequent inpatient management of patients hospitalized with ADHF; (3) to identify patient characteristics and medical care practices associated with improved health outcomes in patients hospitalized with ADHF; (4) to characterize trends over time in the management of ADHF; and (5) to assist hospitals in evaluating and improving quality of care for patients hospitalized with heart failure. Additional goals of ADHERE include development of predictive models for mortality, complications, and length of hospital stay and to link with de-identified data on longitudinal trends in the clinical care and outcomes of registry patients. Aggregate data from the ADHERE database is also used for the observational study of treatment effects.

Sites were selected to represent the "real world" of ADHF. Sites included both academic (84 hospitals) and nonacademic (190 hospitals) hospitals and were geographically diverse including 46 hospitals in the Northeastern United States, 86 hospitals in the South, 66 hospitals in the Midwest, 22 hospitals in the West, and 54 hospitals in the Mid-Atlantic region. Some of the largest acute care hospitals in the United States are participating but sites are diverse in size, ranging from 72 to 1610 beds. Sites are reimbursed a nominal fee for each completed case report form.

For the purpose of this registry, ADHF is defined as either new-onset heart failure or decompensation of chronic, established heart failure with symptoms sufficient to warrant hospitalization. Patients are identified for inclusion in the registry from admissions given a discharge diagnosis of heart failure based on International Classification of Diseases, Ninth Revision (ICD-9) coding. Eligibility is not contingent on the use of any particular therapeutic agent or regimen. Patients may be male or female and must be at least 18 years old at the time of hospital admission. The registry is accumulating data on individual hospitalizations, not individual patients, and it is possible that some patients may be enrolled in the registry more than once. The goal of the registry is to enroll a representative patient sample. Sites are encouraged to enroll admissions meeting entry criteria as consecutively as possible. Hospitals with more than 75 eligible patients in a month are allowed to enroll a random sample of these consecutive admissions using a Joint Commission for Accreditation of Healthcare Organizations (JCAHO)–approved sampling method (Specifications Manual for National Implementation of Hospital Core Measures, JCAHO, 2003, section 4).

Data are collected by chart review and entered using a web-based electronic data capture (EDC) system designed by Phase Forward (Waltham, Mass) and licensed by the study contract research organization, PharmaLink FHI (Research Triangle, NC). Data are recorded concerning demographics, medical history, non-intravenous and intravenous cardiovascular medications, initial evaluation (at site hospital), chronic infusion therapy, hospital course, disposition, and procedures. Information related to four specific aspects of the JCAHO quality improvement initiative for heart failure are also captured: (1) patient instruction on diet, weight, and medication management at discharge; (2) assessment of left ventricular systolic function documented or scheduled; (3) angiotensin-converting enzyme (ACE) inhibitor use at discharge in patients considered candidates for this therapy based on accepted clinical criteria; and (4) counseling on smoking cessation in current smokers. Human subjects considerations, patient confidentiality, site monitoring, and other specific methodological issues have been previously outlined in detail, elsewhere.[10]

Insights from ADHERE

From October 2001 through December 2004, 150,745 heart failure discharges were enrolled in ADHERE. The mean age of patients was 72.5 years and 52% were women. Most patients were white (74%) or black (21%) and were covered by Medicare or Medicaid (79%). Seventy-six percent of patients enrolled had a prior history of heart failure and one-third had a history of admission for ADHF within the prior 6 months. A history of hypertension was common (74%), as was coronary artery disease (57%) and diabetes (44%). Other important or common co-morbid conditions included history of atrial fibrillation (31%), chronic obstructive pulmonary disease or asthma (31%), and chronic renal insufficiency (30%). Most patients (89%) presented with dyspnea. Rales and peripheral edema were present in 67% and 65% of the cases, respectively. Of patients with documented left ventricular ejection fraction prior to admission, 42% had preserved or only mildly depressed systolic function. The characteristics of patients enrolled in ADHERE are very different from those of patients included in clinical trials [Table 1].

Table 1.

Comparison of Patients Enrolled in Randomized Controlled Trials of ADHF Versus ADHERE.

Characteristic	Clinical Trials	ADHERE
Average Age (years)	55-65	72.5
Gender (% Women)	20-25	52
Ischemic Etiology (%)	50	60
Renal Insufficiency (%)	Usually excluded	30
Preserved LV Systolic Function (%)	Usually excluded	42
Atrial Fibrillation (%)	< 25	31
Diabetes (%)	25-30	44

The median length of stay for all hospitalized patients was 4.3 days (mean 5.8 days. The in-hospital mortality rate was 3.9% (10.6% for patients who received treatment in an intensive care unit (ICU). Registry data on the JCAHO quality of care indicators showed that only 32% of patients were given instruction on diet, weight monitoring, activity level, worsening symptoms, follow-up appointments, and medication management at discharge. Assessment of left ventricular systolic function was either documented or scheduled in 83% of patients. A total of 66% of the patients judged eligible to receive an ACE inhibitor by standard clinical criteria were discharged on this medication. Counseling on smoking cessation for current smokers was given to 40% of eligible patients.

ADHERE Mortality Analyses

To date, two primary analyses of mortality have been performed on ADHERE. These include a classification and regression tree (CART) analysis in all patients to define covariate adjusted odds ratios of death (11) and a multivariable regression and propensity analysis in patients receiving IV vasoactive medications to define covariate adjusted probability of treatment (12). The former analysis allows the development and validation of a predictive model for in-hospital mortality, based on patient characteristics discerned at the time

of presentation. That is, the CART analysis provides – for the first time – a way to stratify patients for risk of in-hospital mortality. The latter analysis permits the comparison of treatment choice on outcome. Specifically, the covariate and propensity score adjusted risk of in-patient mortality was evaluated by treatment status comparing intravenous dobutamine, milrinone, nesiritide, and nitroglycerine.

In order to develop a practical user-friendly bedside tool for risk stratification for patients hospitalized with ADHF, CART analysis of the ADHERE database was performed using the first 65,235 discharges enrolled.[11] The first 33,046 hospitalizations (from October 2001 through February 2003) served as the derivation cohort and were analyzed to develop the risk prediction model. Then, the validity of the model was prospectively tested using data from 32,229 subsequent hospitalizations (validation cohort) enrolled in ADHERE from March 2003 through July 2003. In-hospital mortality was similar in the derivation (4.2%) and validation (4.0%) cohorts. Recursive partitioning of the derivation cohort for 39 variables indicated that the best single predictor for mortality was high admission levels of blood urea nitrogen (≥ 43 mg/dL), followed by low admission systolic blood pressure (< 115 mm Hg), and then by high levels of serum creatinine (≥ 2.75 mg/dL). A simple risk tree identified patient groups with mortality ranging from 2.1% to 21.9% (Figure 1). The odds ratio for mortality between patients identified as high and low risk was 12.9 (95% confidence interval, 10.4-15.9) and similar results were seen when this risk stratification was applied prospectively to the validation cohort. These results suggest that ADHF patients at low, intermediate, and high risk for in-hospital mortality can be easily identified using vital sign and laboratory data obtained on hospital admission. The ADHERE risk assessment tool provides clinicians with a validated, practical bedside instrument for mortality risk stratification. Similar to the contemporary approach to the triage and management of chest pain patients based on risk assessment at presentation, the ADHERE CART analysis may ultimately help direct the placement and therapy of patients presenting with ADHF.

To compare in-hospital mortality of ADHF patients receiving parenteral treatment with one of four intravenous vasoactive medications, a retrospective analysis of data from ADHERE was performed.[12] Data

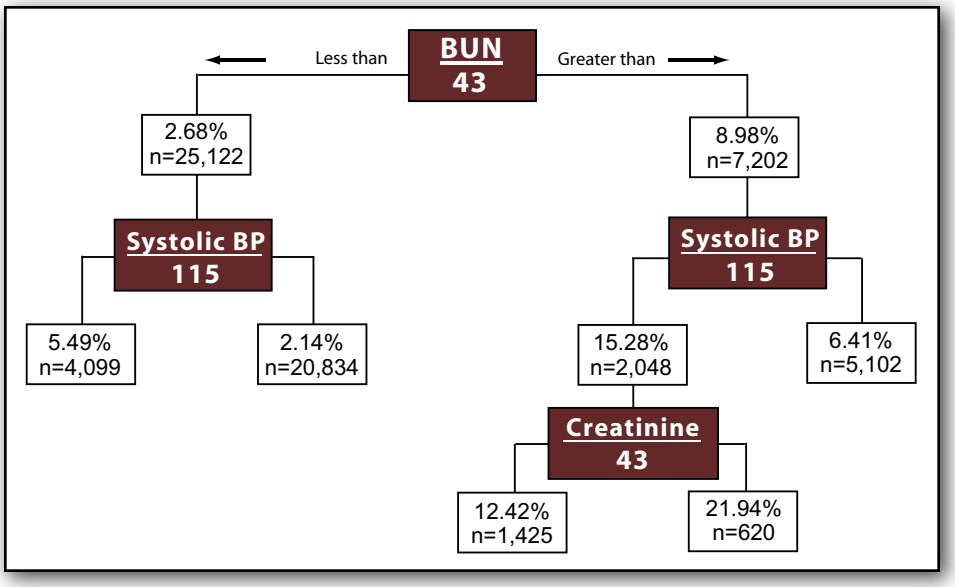


Figure 1.

ADHERE Risk Assessment Tree from CART Analysis. Adapted from Fonarow et al, JAMA. 2005;293:572-580 with permission from the American Medical Association.

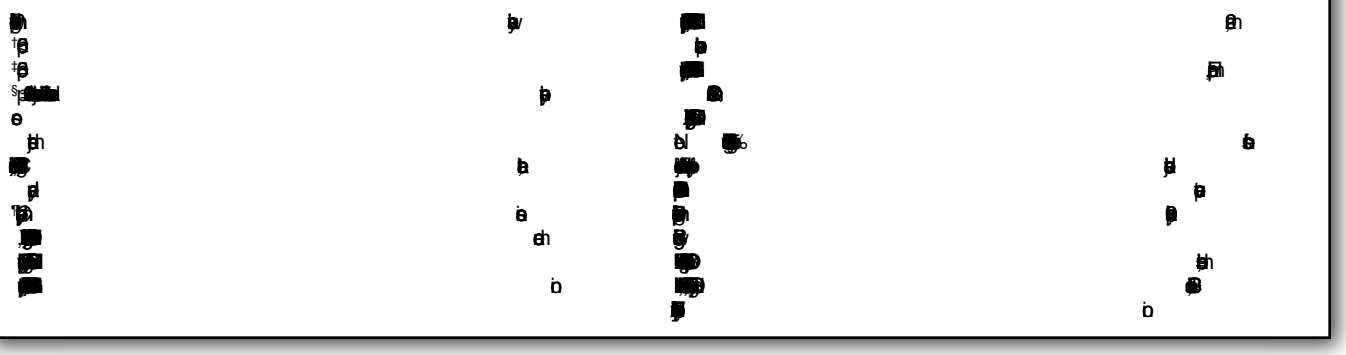
from the first 65,180 patient episodes (from October 2001 through July 2003) were included in this analysis. Cases in which patients received nitroglycerin, nesiritide, milrinone, or dobutamine were identified and reviewed (n = 15,230), to determine if the choice of intravenous vasoactive therapy affected in-hospital mortality. Since the choice of therapy was not directed by a protocol but by clinician judgment or preference, proper adjustment based on factors influencing treatment decision (using adjustment for covariates and propensity scoring) were made. Risk factor and propensity score-adjusted odds ratios (ORs) for in-hospital mortality were calculated.

Patients who received intravenous nitroglycerin or nesiritide had lower in-hospital mortality than those treated with dobutamine or milrinone. The risk factor and propensity score-adjusted ORs for nitroglycerin were 0.69 (95% confidence interval [CI]: 0.53–0.89, p ≤0.005) and 0.46 (0.37–0.57, p ≤0.005) compared with milrinone and dobutamine, respectively. The corresponding values for nesiritide compared with milrinone and dobutamine were 0.59 (0.48–0.73, p ≤0.005) and 0.47 (0.39–0.56, p ≤0.005), respectively. The adjusted OR for nesiritide compared with nitroglycerin was 0.94 (0.77–1.16, p = 0.58). Thus, therapy with either a natriuretic peptide or vasodilator was associated with significantly lower in-hospital mortality than positive inotropic therapy in hospitalized ADHF patients in ADHERE. The risk of in-hospital mortality was similar for nesiritide and nitroglycerin (Table 2). These observations are consistent with findings from randomized controlled trials and support the use of vasodilators (nesiritide or nitroglycerin) as first-line intravenous agents for the treatment of ADHF. The selection of a specific intravenous vasodilator may be guided by the results of randomized controlled trials.[13] Of course, inotropes may still play a role for those who present in or in impending cardiogenic shock.

Table 2.

Mortality Odds Ratios in Pair-Wise Treatment Comparisons in the ADHERE Registry.
Reprinted with permission from Abraham et al, JACC 2005 (In Press).

Analysis*	NTG (n = 6055) vs. MIL (n = 1660)	NTG (n = 5713) vs. DOB (n = 3478)	NES (n = 4663) vs. MIL (n = 1534)	NES (n = 4270) vs. DOB (n = 3301)	NES (n = 4402) vs. NTG (n = 5668)	DOB (n = 3656) vs. MIL (n = 1496)
Unadjusted	0.34 (0.28-0.41)†	0.24 (0.20-0.28)†	0.53 (0.44-0.64)†	0.37 (0.32-0.44)†	1.64 (1.38-1.94)†	1.39 (1.15-1.68)†
Adjusted for covariates‖	0.69 (0.54-0.88)†	0.46 (0.38-0.57)†	0.59 (0.48-0.73)†	0.47 (0.39-0.56)†	0.95 (0.78-1.16)‡	1.27 (1.04-1.56)§
Adjusted for covariates and propensity score¶	0.69 (0.53-0.89)†	0.46 (0.37-0.57)†	0.59 (0.48-0.73)†	0.47 (0.39-0.56)†	0.94 (0.77-1.16)‡	1.24 (1.03-1.55)§



SUMMARY

Registries such as ADHERE may provide insights that cannot be discerned from randomized controlled trials. Heart failure patients enrolled in clinical trials are very different than heart failure patients in the community, as demonstrated by the characteristics of more than 150,000 discharges for ADHF in ADHERE. The ADHERE registry provides important insights into ADHF treatment and outcomes that may favorably impact future care. Specifically, it provides us with a valuable risk-assessment tool and with insights into the effects of treatment selection on outcomes in ADHF patients.

Acknowledgments

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DISEASE MANAGEMENT OF ACUTE DECOMPENSATED HEART FAILURE: THE ADHERE EMERGENCY MEDICINE MODULE

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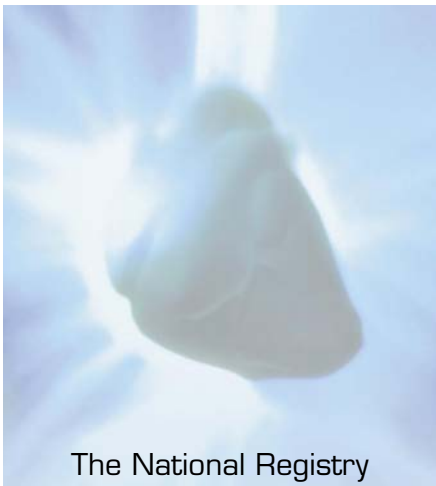
OBJECTIVES:

1. Review the necessary elements and process required for a well-orchestrated disease management program
2. Discuss the objectives, design and logistics of the ADHERE Emergency Medicine Module

INTRODUCTION

A major factor limiting the long-term efficacy of current congestive heart failure (CHF) treatment strategies is a lack of compelling data confirming which approaches and therapies work best in most clinical situations. Studies have shown that the care given to CHF patients varies widely, based on the location where patients receive treatment and the specialty of the physician who treats them. In the absence of any established standards or best-practice guidelines, physicians have little evidence on which to base treatment decisions. Because of this lack of consensus standards, many CHF patients receive less than optimal care. The National Registry ADHERE is the first national registry that prospectively collects observational data from across the United States in order to track and study the medical management of patients hospitalized with acute decompensated heart failure (ADHF).[1] ADHERE is sponsored by Scios and overseen by an independent scientific advisory committee of nationally recognized heart failure experts. To date, more than 275 hospitals and more than 100,000 patient cases have been entered into the ADHERE registry, making it the largest, most extensive registry of its kind.



The National Registry ADHERE is the first national registry that prospectively collects observational data from across the United States in order to track and study the medical management of patients hospitalized with acute decompensated heart failure (ADHF).

The original registry is referred to as the Core Registry. As interest in the long-term outcomes of these patients emerged, the Longitudinal Module was developed to follow the course of these patients beyond the immediate hospitalization and into the outpatient setting. More recently, the ADHERE Disease Management Quality Initiative for Care Beginning in the Emergency Department Module (ADHERE ED DM) was initiated to give insight into the treatment patterns and overall quality of disease management (DM) of ADHF in the emergency setting.

Disease Management

Traditional approaches to the treatment of disease have been a "component-based management model" whereby selected portions of the disease are managed by certain specialists that address specific aspects of the patient's illness. In this system, the internist or cardiologist focuses on the long-term management of CHF whereas the emergency physician is concerned with the acute stabilization of a decompensated state. The newer concepts of disease management incorporate the entire spectrum of patient care and include the full use of ancillary health

care and social services. Because ADHF patients have a combination of both an acute and chronic condition it is important to begin to consider the longitudinal course of their management even as we begin the stabilization process in the emergency department (ED). This consideration has become more important in recent years as the ED has become the safety-net and primary care provider for many of these patients. It is not uncommon for ADHF patients to become frequent patients in our emergency departments. By default, the emergency physician then becomes responsible for their overall care and must consider issues such as access to outpatient medications, the ramifications of their inpatient management and the longitudinal impact of early treatment decisions within the emergency setting.[2-4] There is considerable evidence to suggest that the treatment plan initiated by the emergency physician has a significant impact on the long-term outcomes of other common disease processes such as pneumonia and acute coronary syndromes. It is reasonable to expect that the same would be true in the treatment of ADHF.[2-4] There are typically three common elements to any well-orchestrated disease management program:

1. Identify patients at elevated risk of adverse outcomes
2. Intervention to reduce those risks
3. Systematic evaluation to assess the impact of the intervention

Good disease management practice also requires the physician to think about the patient's pathology from both the short-term and long-term management perspectives. This is particularly important when treating chronic diseases such as CHF due to the differences in the pathophysiologic mechanisms involved in the acute and chronic presentations. CHF in its acutely decompensated form is primarily a problem of plumbing. Within the vascular conduits involved in ADHF, there is a mismatch in the pressures, resistances and fluid volumes required to maintain blood flow or cardiac output which further results in a congestive state that limits oxygenation by the lungs. This condition has the potential for positive feedback and can rapidly spiral to an unstable state. Traditional therapies such as nitroglycerin, morphine and diuretics can ameliorate the congestion by manipulation of the acute plumbing derangement. The result is a dramatic change in the immediate clinical situation and the patient often appears almost back to normal in terms of symptoms. However, despite this illusion of stability, the chronic pathophysiology of CHF and the underlying cause of the decompensation is still present.[5,6] The congestion and fluid retention of the heart failure state is a natural physiologic adjustment to a dysfunctional Starling-Venous Return relationship and is necessary to bring cardiac output back to normal (Figure 1).[5,6] The cost of this adjustment is

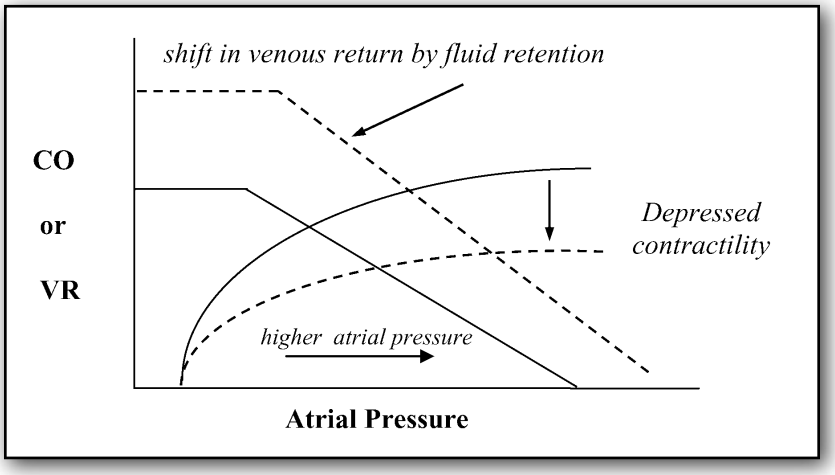


Figure 1.

The congestion and fluid retention of the heart failure state is a natural physiologic adjustment to a dysfunctional Starling-Venous Return relationship. CO = cardiac output. VR = venous return

higher atrial pressures that can lead to pulmonary edema and dyspnea which brings the patient acutely to the ED. If this mechanism is not taken into consideration in the disposition of stabilized ADHF patient then there is tremendous potential for overall treatment failure. Proper disease management also requires a global perspective of all aspects of the patient's pathophysiology to be successful.

In the past few decades we saw an emphasis on an evidence-based approach to DM with a focus on utilizing results from clinical trials to dictate the best treatment options for patients with specific disease states or presentations. More recently we have begun to realize the necessity of balancing this population-based probabilistic view of treatment with a scientific-oriented analysis of the physiologic nuances of the individual patient in a goal directed approach to management.[7] ADHF DM is especially amenable to this notion since there is little current trials-based information and the pathophysiologic spectrum of disease presentation is varied. However, as we develop an emergency medicine ADHF DM strategy it is important that we look at the process as a whole and the impact of treatment plans on outcomes.[8]

For all these reasons a registry that tracks the course of patients with ADHF from the emergency medicine perspective can be instrumental in defining the best practices for future DM.

ADHERE Emergency Medicine Module

The ADHERE Emergency Medicine Module is expected to be the vehicle through which a comprehensive disease management process is developed from the unique perspective of emergency medicine as a specialty. Building on prior ADHERE programs, this module was designed by emergency physicians with the intention of answering specific questions of interest to those managing ADHF patients that present to the ED and follows their hospital course and outcomes.

Program Objectives

The main objectives of AHERE ED DM are:

1. Develop a large clinical ADHF database from acute care hospitals across the United States
2. Examine the current national state of medical management of patients presenting to the ED for ADHF
3. Compare pre/post outcomes of implementation of a Disease Management program for ED presentations of ADHF

Some of the secondary objectives include:

1. Assist hospitals in evaluating and improving quality of care by
   a. tracking quality indicators
   b. providing monthly and quarterly site specific and United States benchmark data
2. Characterize trends over time in the management of ADHF

As we develop an emergency medicine ADHF DM strategy it is important that we look at the process as a whole and the impact of treatment plans on outcomes.

Components of the ED DM program include:

1. Treatment algorithms
2. Order Sets
3. Physician/RN education
4. Patient Education
5. Discharge Instructions
6. Feedback loop (data monitoring tools)

3. For the ADHF patient in an ED setting
   a. Describe demographic and clinical characteristics of ADHF
   b. Characterize the initial ED evaluation & subsequent management
   c. Identify characteristics and medical care associated with improved outcomes

Program Design

Overview: The study design is that of a multi-center, continuous, observational, quality improvement initiative focusing on the management of patients treated in the hospital for ADHF in the United States with an emphasis on emergency medical care. It is expected that there will approximately 150 hospitals participating, continuously enrolling patients for about 18 months or up to 60,000 patient episodes. Sites are eligible to participate if they are a current ADHERE site or if they are in the top 1,700 largest United States acute care hospitals with a median number of annual HF discharges of ~300 patients. Selected academic and community hospitals will be equally distributed along the spectrum of HF patient volume and geography. Components of the ED DM program include:

1. Treatment algorithms[8]
2. Order Sets
3. Physician/RN education
4. Patient Education
5. Discharge Instructions
6. Feedback loop (data monitoring tools)

Patient population: Patient eligibility is not linked to a specific therapeutic agent or regimen. Patients eligible for entry into the ADHERE Registry include those over the age of 18 admitted to an acute care hospital and treated actively for ADHF, either as a new onset with decompensation or as chronic heart failure with decompensation. This would include those patients who receive a principal ED or hospital discharge diagnosis of ADHF or is diagnosed clinically and is documented in the DRG codes. Patients are excluded if ADHF is a co–morbid condition, but is not a principal focus of diagnosis or treatment during the ED or hospital episode.

Staff and Institutional requirements:

1. Sites must commit to utilizing a DM strategy and will be required to implement at least three of five components listed below.
2. Each site must have:
   - One ED Physician as the Principal or Co-principal investigator
   - One dedicated Registry Coordinator
     a. Requires access to all ED and hospital chart data
     b. Can perform electronic data capture (EDC) entry
   - Inpatient physicians (such as cardiologists)
     a. Encouraged to participate as a Co-principal investigator to facilitate a fully integrated DM Quality Improvement program
   - ED HF algorithm
   - HF admission orders

- Patient discharge instructions
- Physician HF education
- Patient HF education

Data Collection: The ADHERE Registry is a large database of primary clinical information collected from hospital records of patients at select institutions nationwide. No prior registry has conducted research at this level on the clinical care of patients with ADHF. Using medical records, data are collected from the point of initial care through patient discharge from the hospital. The registry is completely confidential, and all patient data are kept anonymous through encrypted treatment. Data include:

- Demographics
- EMS data
- Medical history
- Initial medical evaluation
- Hospital course
- Medications
- Procedures
- Disposition

The program is designed to collect data surrounding the episode of hospital care that begins in the ED as the point of initial care and ends with ED or hospital discharge, transfer or death. If the institution is also a part of the ADHERE core the patient may tracked up to 90 days after admission. Data are collected through an Internet-based EDC system. Participating institutions enter data using a standard web browser connected to an EDC system customized for the ADHERE registry. The system has been fully tested and is compliant with federal regulations:

- 21 CFR 11, Guidance on Computerized Systems used in Clinical Trials, and ICH GCP guidelines
- All site staff will be trained on these regulations
- EDC system access is controlled by the data coordination center and system entry is limited by username/password–protected logon procedures.
- Hospitals will be prevented from accessing electronic case report forms or aggregate data from any hospital other than their own.

To follow the patient across recurring visits the Longitudinal Unique Identifier (LUID) system will be utilized for confidentiality:

- Computer generated unique identifier
  a. LUID encryption uses the US Federal Standard SHA-1.
  b. The LUID algorithm will be independently validated by Booz Allen, Homeland Security - Information Assurance, Civil Business Segment.
- With a given set of variables, a LUID is generated that cannot be related back to an individual.
- Patient level variables used to construct the LUID are not stored in the system, and this information cannot be de-encrypted from the LUID stored in the database.
- The LUID is stored in the database along with patient data and allows for longitudinal tracking of hospital readmissions and patient outcomes.

Endpoints: In order to meet the overall objectives of the Program, a number of specific endpoints are targeted from within the data collection process. The most important of these areas of focus include:

Impact of Disease Management Tools on Outcomes
- Length of stay, symptomatology
- Recidivism, time to treatment

Disposition of Patient
- based on presentation parameters (i.e. Cr > 2.0)

Impact of diuretics relative to outcomes
- Dose and timing
- Defining which patients are responders.

BiPAP & CPAP
- Impact on drug therapy
- Impact on symptoms & outcomes
- Oxygen Saturations

Resource utilization
- Benefit of observation units

Treating Physicians
- Primary Care, Specialists and Consultants

Quality Initiative: The ADHERE Registry issues a Benchmark Report each quarter to participating clinics and hospitals. These reports summarize registry data collected on acute heart failure treatment during the previous year. The reports also make available institution-specific, regional, and national statistics (such as quality indicators) to participating hospitals in order to help them evaluate and improve the care they provide to patients. The goal is for the individual hospital to utilize this information to effect change in order to optimize overall disease management.

SUMMARY:

ADHF is expected to become on the most difficult medical and financial problems facing our healthcare systems. Preliminary evidence from the ADHERE Core Registry and a number of other clinical trials indicate that the emergency department should be the focal point for the disease management process of ADHF. The ADHERE ED DM program presents a real opportunity for the emergency medicine community to better understand the issues surrounding this disease state and to objectively outline the best course for overall disease management.

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ACUTE DECOMPENSATED HEART FAILURE DISEASE MANAGEMENT TOOLS

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OBJECTIVES:

1. Discuss components of emergency department heart failure disease management tools
2. To understand how disease management tools could improve the care of emergency department patients with heart failure

INTRODUCTION

The rising prevalence and cost of care for heart failure is staggering. Almost 5 million Americans have heart failure, with 550,000 new cases diagnosed each year at a total cost of $27.9 billion.[1] The incidence is expected to continue to increase dramatically due to our aging population (9.8% prevalence of heart failure in individuals over age 74), improved survival from acute coronary syndromes (ACS), and management advances in cardiovascular diseases.[2-4] Hospitalization accounts for over 60% of heart failure costs.[5] Over half of patients older than 65 years with congestive heart failure (CHF) are readmitted within 6 months of hospital discharge.[6]

While medical risk factors are well know to be associated with hospital readmission (age, increased length-of-stay and number of comorbidities),[7,8] often overlooked social factors (such as single marital status, readiness for discharge, medication and dietary noncompliance) also influence the chance of CHF readmission.[8-10] Heart failure disease management (DM) programs are designed to target social risk factors resulting in decreased recidivism.

Heart Failure Disease Management

Heart failure DM programs have proven to be effective at reducing subsequent readmissions in those discharged after a CHF admission.[6, 11, 12] It has been suggested that DM programs are nearly as effective as that seen with angiotensin-converting enzyme inhibitors, beta-blockers or digoxin.[13] DM programs stress the need for coordinated, comprehensive care both during hospitalization and after discharge. They generally consist of a multi-faceted approach including patient education and teaching, dietary assessment, medication analysis and social services consultation. These processes have traditionally occurred once the patient is hospitalized.

Why Disease Management in the ED?

Because the emergency department (ED) is the portal for 80% of hospital admissions for heart failure, it represents an ideal place to begin a DM program. CHF patients discharged directly from the ED have a high rate of recidivism, and disease management may help avoid unnecessary readmissions.[14,9] Those pa-

Heart failure DM programs have proven to be effective at reducing subsequent readmissions in those discharged after a CHF admission.

tients managed in an observation unit (OU) receive definitive care, including medication adjustment and follow-up arrangements, and DM has been suggested to impact recidivism in these patients.[15, 16] Whether it is initiation of CHF standardized orders for an inpatient admission, or comprehensive education, and teaching in the patient discharged from the ED or OU, disease management can be potentially initiated on every ED patient with CHF.

The impact of early ED intervention and treatment has been seen in other disease processes such as pneumonia and ACS. The CRUSADE initiative has suggested that, those patients with non ST-segment elevation myocardial infarction (NSTEMI) that receive treatment with glycoprotein (GP) IIb/IIIa inhibitors within 24 hours of hospital admission have a decreased likelihood of in-hospital morbidity and mortality compared with those patients that receive treatment after 24 hours (p<0.0001) (Table 1).[17,18] Patients with pneumonia that receive antibiotics within 4 hours of hospital arrival have a reduced hospital length-of-stay (LOS) and in-hospital mortality (Table 2).[19] A separate analysis found that after adjustment for clinical and demographic variables, initial antibiotic administration in the ED, and door-to-needle time was associated with reduced LOS.[20]

Table 1.

In-hospital outcomes stratified by time to IIb/IIIa inhibitor treatment.

	GPIIB/IIIA < 24h (n=17,355)	No GP IIb/IIIa < 24h (n=32,023)	P
Death (%)	2.7	4.7	< 0.001
(Re)-Infarction (%)	3.0	3.0	0.67
Cardiogenic Shock (%)	2.9	2.2	< 0.001
CHF (%)	6.3	9.4	< 0.001
RBC transfusion (%)	12.0	13.0	< 0.001

Table 2.

Antibiotic administration within 4 hours of arrival and patient outcomes stratified by risk classes*

Outcome Measures	Antibiotic Within 4 h, % (95% CI)	Antibiotic After 4 h, % (95% CI)	Adjusted‡ AOR (95% CI)	Adjusted‡ P Value
All patients				
30-d mortality	11.6 (10.9-12.3)	12.7 (11.8-13.6)	0.85 (0.76-0.95)	.005
In-hospital mortality	6.8 (6.3-7.3)	7.4 (6.7-8.1)	0.85 (0.74-0.98)	.03
Length of stay ~5 d	42.1 (41.0-43.2)	45.1 (43.8-46.5)	0.90 (0.83-0.96)	.003
30-d readmission	13.1 (12.4-13.9)	13.9 (12.9-14.9)	0.95 (0.85-1.06)	.34
PSI risk classes II and III				
30-d mortality	2.1 (1.5-2.7)	3.4 (2.6-4.4)	0.62 (0.42-0.93)	.02
In-hospital mortality	0.9 (0.6-1.4)	1.2 (0.7-1.9)	0.77 (0.42-1.44)	.42
Length of stay ~5 d	31.2 (29.4-33.1)	35.3 (32.9-37.7)	0.86 (0.75-0.99)	.03
30-d readmission	9.4 (8.3-10.6)	10.9 (9.4-12.6)	0.87 (0.70-1.07)	.19
PSI risk classes IV and V				
30-d mortality	15.5 (14.6-16.4)	16.5 (15.4-17.7)	0.87 (0.78-0.98)	.03
In-hospital mortality	9.2 (8.4-9.9)	9.9 (9.0-10.9)	0.86 (0.74-1.00)	.04
Length of stay ~5 d	46.5 (45.3-47.8)	49.2 (47.6-50.8)	0.92 (0.84-1.00)	.04
30-d readmission	14.7 (13.8-15.7)	15.2 (14.0-16.5)	0.99 (0.88-1.12)	.89

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; PSI, Pneumonia Severity Index.
*Patients without prehospital antibiotic treatment.
†Univariate analysis comparing the antibiotic timing subgroups "within 4 h" vs "after 4 h."
‡Multivariate analysis comparing the antibiotic timing subgroups "within 4 h" vs "after 4 h" using logistic regression. The logistic regression model included the timing of initial antibiotic, PSI, admission to the intensive care unit, census regions of hospitalization, race/ethnicity, and other processes of care (oxygenation assessment, blood culture within 24 hours, and initial antibiotic consistent with current guidelines). Adapted and reprinted with permission from Houck et al. Arch Intern Med. 2004;164:637-644.

ED Heart Failure Disease Management Tools

There are several aspects to ED disease management. The first component is implementing an ED heart failure treatment algorithm (Figure 1). Categorizing a patient based on their perfusion status (warm versus cold), fluid status (hypervolemic, euvolemic, hypovolemic) and level of disease severity will help dictate initial therapy. The majority of patients will be hypervolemic and well-perfused and will respond to diuretics and vasodilators.

The second component of DM is the introduction of ED CHF admission orders. Admission orders ensure continuity of care from the ED to the inpatient ward with regard to medications, labs, and ancillary tests. It also ensures that the patient that spends several hours in the ED waiting for an inpatient bed is appropriately managed while care

Because the emergency department is the portal for 80% of hospital admissions for heart failure, it represents an ideal place to initiate a DM program.

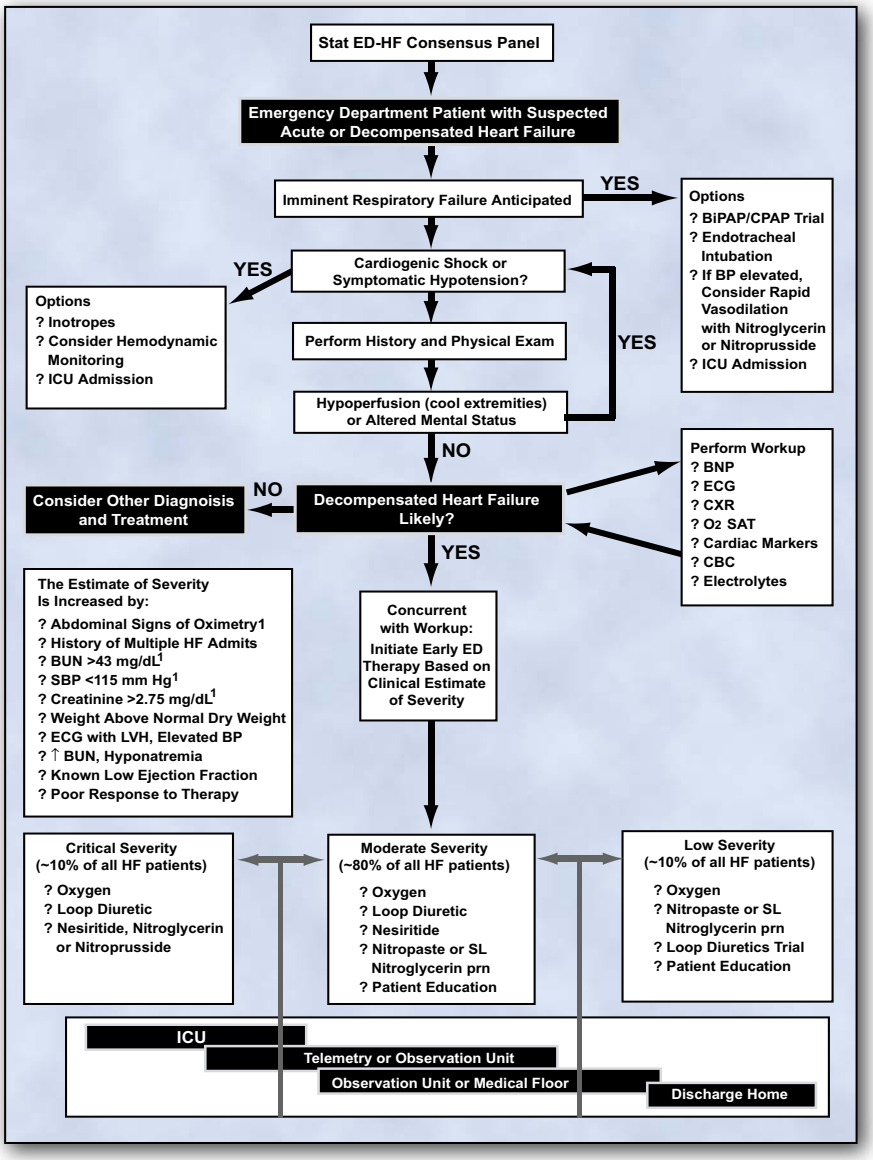


Figure 1.

ADHF Treatment Algorithm. Guidelines for the early stabilization and disposition of acute decompensated heart failure in the emergency department.

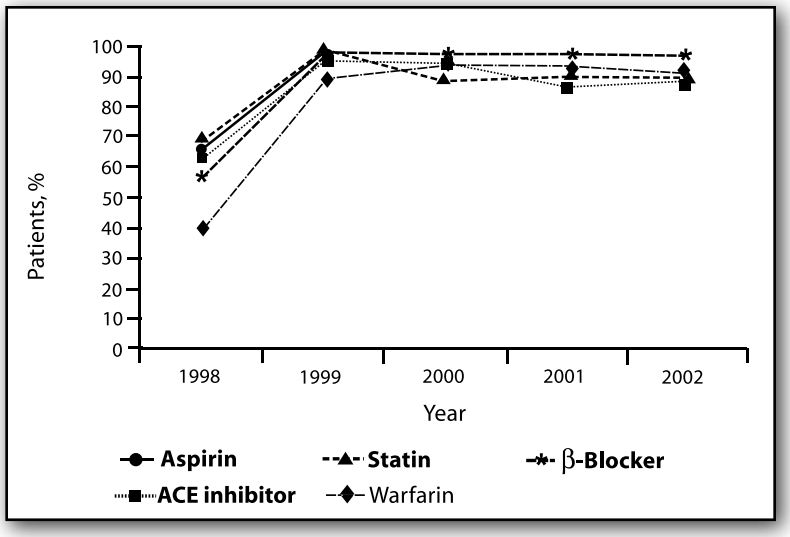
is transitioning from the emergency physician to the admitting team. There are other advantages to standardized orders. The amount of evolving literature is overwhelming- in 1995 there were 10,000 randomized controlled trials published.[21] Standing orders ensure guideline compliance from the literature, yet allow physicians some autonomy by allowing for individual patient adjustments.

The third component of DM is the completion of a patient discharge checklist. This checklist is a method of ensuring those patients that meet criteria for specific interventions (medications, smoking cessation, cardiac rehabilitation) are given the appropriate medications and instructions upon discharge. The institution of a discharge medication program at 10 hospitals in Utah was associated with dramatic improvements in appropriate discharge prescriptions and the relative risk of death and readmission at 30-days and 1-year after hospital discharge (Figures 2 and 3).[22] This program focused on nursing-initiated documentation of appropriate medications upon discharge from the hospital. When an appropriate medicine was not prescribed at discharge, the discharge-planning nurse contacted the attending physician or resident directly, after which the missing medication could be added to the discharge list if there were no contraindications.

The final component of DM is patient education. Unlike other acute inpatient disease process such as pneumonia and pyelonephritis, acute CHF exacerbations are treated until the subject is back to their baseline *compensated state*- the underlying disease process is never completely cured. As a result, patient behavior after hospitalization may have a tremendous influence on the progression of their disease process, and subsequent morbidity and mortality. It has been suggested that over 50% of readmissions are possibly or probably preventable, and that medication and dietary noncompliance, inadequate discharge planning or follow-up, failed social support, and not recognizing symptom recurrence were a big contributor to these preventable readmissions. [9] A DM program that empowers the patient with knowledge about their disease process, appropriate follow-up, and signs of decompensation, increases the likelihood of avoiding readmissions.

Figure 2.

Proportion of patients receiving the appropriate discharge prescriptions. The 5 targeted medications were given as indicated to patients without documented contraindications before and more than 3 years after implementation of the discharge medication program (1998 and 2002, respectively). Data for 1998 and 2002 were collected through the same process. ACE = angiotensin-converting enzyme. Reprinted with permission from Lappe et al. Ann Intern Med 2004; 141(6):446.



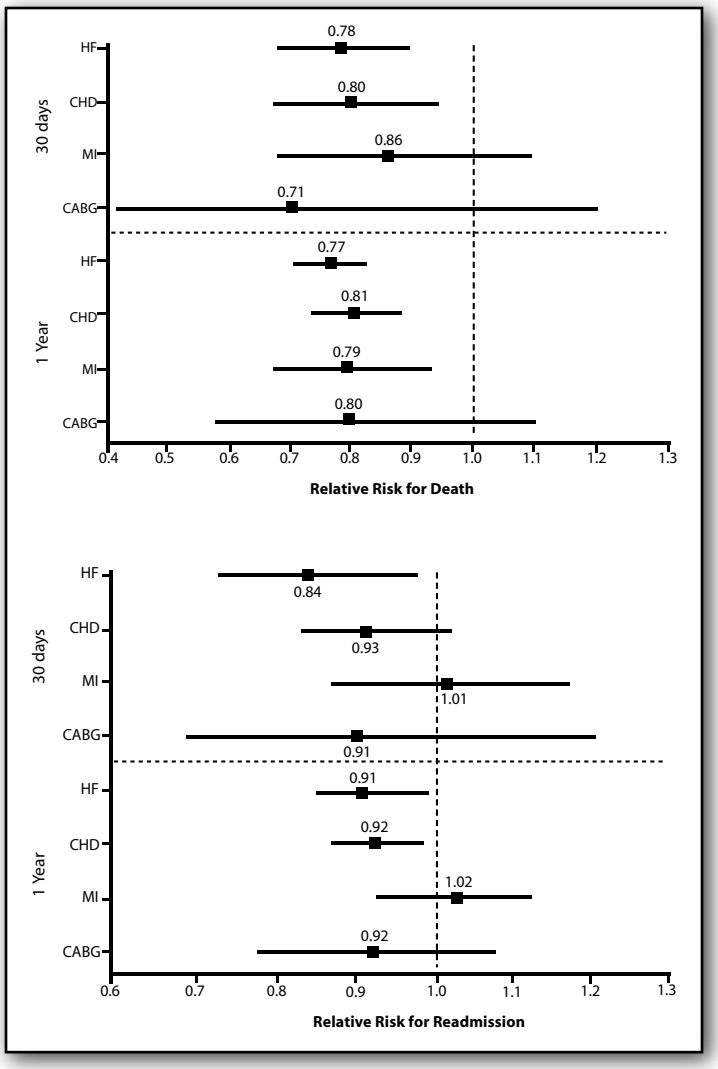


Figure 3.

Adjusted relative risk for Death and Readmission at 30 days and 1 year for patients before and after implementation of the discharge medication program. Reproduced and reprinted with permission from Lappe et al. Ann Intern Med 2004; 141(6):446.

These results testify to the fundamental contribution a DM program can make to the management of the heart failure patient; in this preliminary study, charges were halved by not admitting a patient, and an average of one bed-day was saved per observational unit patient.

A Practical Example: Disease Management in the Observation Unit

In January 2002, the University of Cincinnati Department of Emergency Medicine initiated an acute decompensated heart failure observation unit (OU) protocol. The protocol selects non-high-risk patients for management over a 23-hour period. During this time patients receive vasodilators and diuretics as well as further evaluation including echocardiography and ACS risk stratification evaluation (serial cardiac markers with the option for rest ischemia imaging) (Figure 4). An educational video has been developed that instructs the patients about their disease process, diet, medications, and warning signs that their heart failure may be worsening. Discharge planning occurs through a combination of cardiology nurse practitioner evaluation, as well as follow-up in the heart failure and general internal medicine clinic.

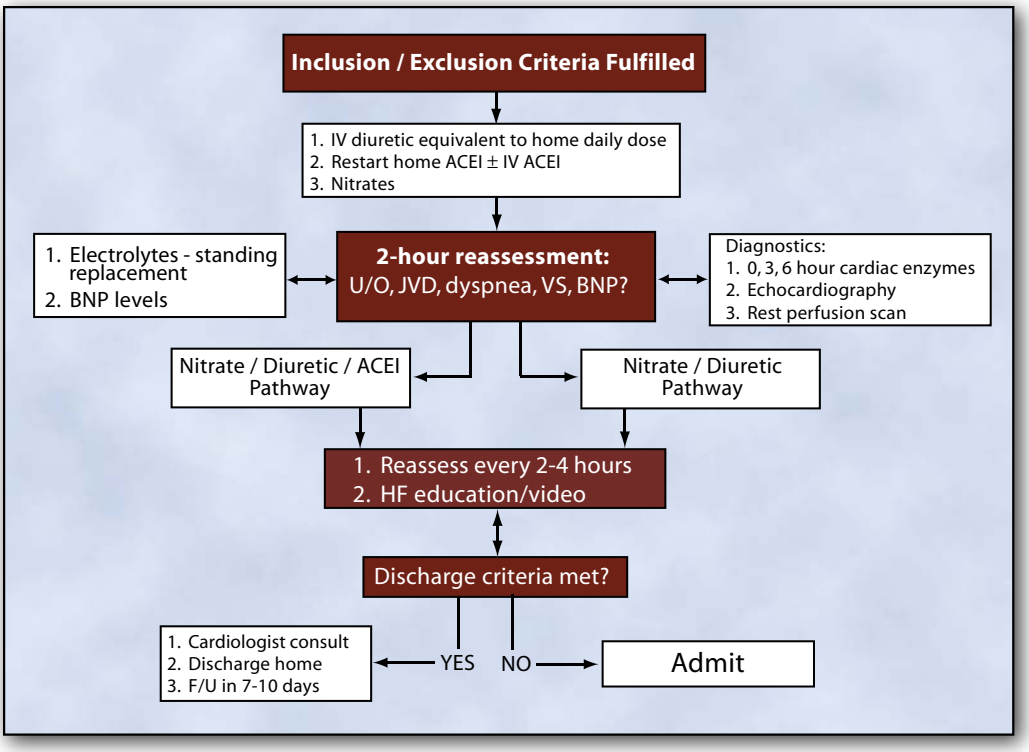


Figure 4.
University of Cincinnati ADHF pathway.

We evaluated the effectiveness of the OU protocol by comparing patients managed in the OU with a similar risk-matched cohort of inpatients.[23] Overall, 59 patients who were being admitted to the hospital with presumed decompensated heart failure were enrolled in the study. All patients had a history of heart failure and satisfied two major, or one major and two minor modified Framingham Criteria. Inclusion and exclusion criteria were selected based upon prior risk studies so as to identify what current practice indicates is a low to moderate risk patient. Patients currently believed to be at high risk and patients with new onset heart failure were not included.

One patient was found to have no prior history of heart failure, and two patients left the inpatient setting against medical advice. Inclusion of these subjects may affect the data but this represents the clinical scenario and it is important to include these sources of error in outcomes analysis. Thirty-two patients were admitted to hospital while 27 were placed in the observation unit. Eight (29.6%) OU patients required subsequent admission.

Outcomes measured in this study included readmissions for CHF, repeat visits to the ED for heart failure, and death. There were 6 events among admitted patients (18.8%) and 4 events among OU patients (14.8%). Any difference was not significant (p=0.482). All events included a readmission for heart failure. All but one event included a heart failure-related ED visit. We also compared crude estimates of bed-hours and costs between the two groups. Use of the OU avoided admission in 70.4% of cases. Median time from triage to discharge for OU patients was 26.5 hours (range 13.8 – 108.6 hours) while patients admitted directly from the ED had a median length of stay of 58.1 hours (range 22.8 – 173.0 hours). The length of hospital stay was significantly shorter for OU patients than for admitted patients (p<0.001).

Charges for the two groups of patients were obtained, categorized by the source of the charge. Figure 5 shows the source of charges for admitted and OU patients (outliers not shown).

The total charge was significantly lower for the OU patients (Median $4203, Range $2518 – $17485) than for admitted patients (Median $8398, range $4283 – $34604) (P=0.001). Inpatient charges and pharmacy charges were different between the two groups (P<0.001 and P=0.042, respectively). These results testify to the fundamental contribution a DM program can make to the management of the heart failure patient; in this preliminary study, charges were halved by not admitting a patient, and an average of 1 bed-day was saved per OU patient. A combination of a treatment pathway, patient education and discharge planning are integral components in making OU treatment successful.

SUMMARY

Disease management is an integral component in the comprehensive care of heart failure patients, and has been shown to reduce readmissions and the overall cost of care.[11] The ED acts as a major portal for heart failure admissions and because of this, emergency physicians have the potential to significantly impact the care of HF patients. The majority of ED patients, whether admitted, managed in an OU, or discharged home, will likely benefit from one or more of the components of DM.

The majority of ED patients, whether admitted, managed in an OU, or discharged home, will likely benefit from one or more of the components of DM.

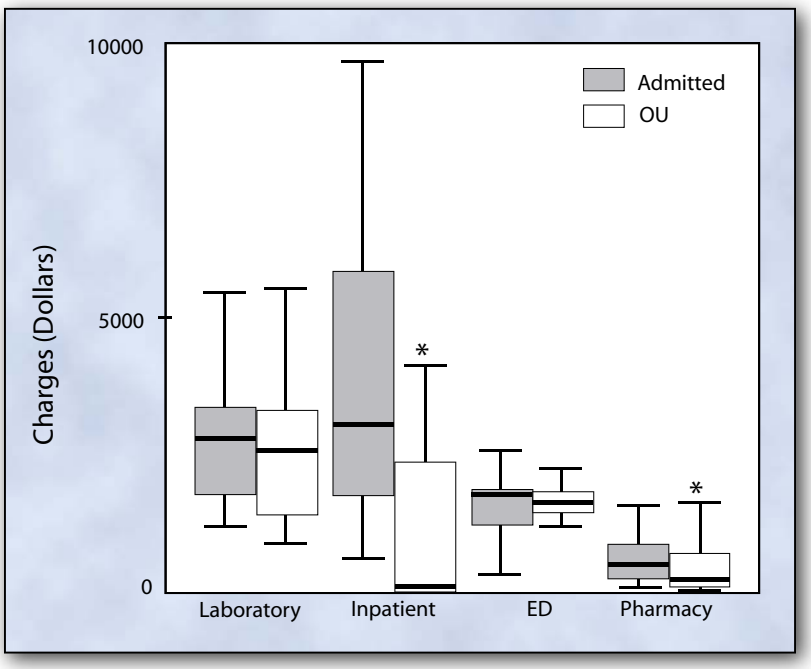


Figure 5.
Boxplots showing the source and amount of charges for observation unit and admitted patients. (* indicates a significant difference)

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Continuing Medical Education Post-Test

Based on the information presented in this monograph, please choose one correct response for each of the following questions or statements. **Record your answers on the answer sheet on page 48**. To receive Category I credit, complete the post-test and record your responses on the answer sheet. Mail in the return envelope no later than June 1, 2006. A passing grade of 80% is needed. A certificate will be sent to you upon your successful completion of the post-test.

Diagnosis of Acute Decompensated Heart Failure in the ED

1) A 61-year-old male tobacco smoker with a history of asthma presents to the emergency department with shortness of breath of 3 days' duration. He has exertional dyspnea, orthopnea and hears some wheezing when he is breathing. Physical examination reveals scant crackles at the bases bilaterally with 9 cm of jugular venous distention, an S4 heart sound, and no murmur. Which of the following best supports a diagnosis of congestive heart failure?
   a) Cardiomegaly on chest radiography
   b) A BNP level of 1200 pg/dL
   c) Normal chest radiography
   d) A BNP level of 311 pg/dL

2) Which of the following diseases can result in low grade BNP elevations (<500 pg/dl)?
   a) Right ventricular failure from cor pulmonale
   b) Acute pulmonary embolism
   c) CHF in an obese patient
   d) CHF in a patient with normal body mass index
   e) All of the above

Treatment of Acute Decompensated Heart Failure in the Emergency Department

3) The patients clinical status can be determined by assessing then for which of the following?
   a) Degree of cardiac perfusion and presence of congestion
   b) Degree of cardiac perfusion and blood pressure
   c) Blood pressure and presence of congestion
   d) Renal function and volume status
   e) Renal function and peripheral edema

4) Which of the following is not true about the role of vasodilators in acutely decompensated heart?
   a) They reduce preload and afterload
   b) Myocardial oxygen consumption is often increased
   c) They increase stroke volume and improve cardiac output
   d) They may cause hypotension
   e) The best hemodynamic indicator of vasodilator therapy response is a drop in the pulmonary capillary wedge pressure

Pertinent BNP Consensus Panel Recommendations

5) In an analysis of more than 46,000 patients enrolled in the ADHERE registry, the ED use of vasoactive therapy, as compared to delayed usage on the inpatient unit, was associated with which of the following:
   a) decreased mortality
   b) lower ICU admission rate
   c) shorter hospitalizations
   d) fewer invasive procedures
   e) all of the above

6) An elevated troponin, in the setting of acute decompensated heart failure is associated with:
   a) longer ICU hospitalization
   b) increased mortality
   c) longer hospitalization
   d) a higher rate of intubation and balloon pump usage
   e) all of the above

Continuing Medical Education Post-Test (cont.)

Background and Findings from the ADHERE National Registry

7) When describing the patient population in the ADHERE registry in comparison to other ADHF trials, all of the following are true EXCEPT:
   a. Patients in ADHERE tend to be older.
   b. About half the patients in ADHERE are women.
   c. Renal insufficiency patients are excluded from ADHERE.
   d. The ADHERE population includes academic and community center.
   e. All of the above are true.

8) In the ADHERE intravenous vasoactive mortality analysis, which of the following statements are true:
   a. Patients who received in-hospital nitroglycerin had lower in-hospital mortality.
   b. Patients who received intravenous nesiritide had lower in hospital morality.
   c. Patients treated with dobutamine or milrinone had higher in-hospital mortality.
   d. A and C are correct
   e. A, B, and C are correct

Disease Management of Acute Decompensated Heart Failure: The ADHERE Emergency Medicine Module

9) Which of the following are required for a successful point-of-care program?
   a. Quality control
   b. Education of physicians
   c. Laboratory accreditation and regulation
   d. Defined and regulated testing procedures
   e. All of the above

10) Factors that should be considered in the cost analysis of a point-of-care testing program include all of the following EXCEPT:
   a. Laboratory result turn-around-time (TAT)
   b. Time to disposition
   c. Patient and physician (consumer) demand
   d. Cost of testing platform and reagents
   e. All of the above are correct.

Acute Decompensated Heart Failure Disease Management Tools

11) The components of disease management include all of the following except:
   a. Treatment algorithm
   b. Admission orders
   c. Patient discharge checklist
   d. Patient education
   e. All of the above

12) Patient education and a discharge checklist are two disease management tools that are used to improve medication and dietary compliance in an effort to decrease 30-day hospital readmission. The current 30-day readmission rate for heart failure patients discharged from the hospital is approximately:
   a. <10%
   b. 20%
   c. 45%
   d. 70%

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

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1.	a	b	c	d	
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9.	a	b	c	d	e
10.	a	b	c	d	e
11.	a	b	c	d	e
12.	a	b	c	d	

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