Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes

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Guideline recommendations for the prehospital and early in-hospital (first 6–12 hrs after presentation) management of acute heart failure syndromes are lacking. The American College of Cardiology/American Heart Association and European Society of Cardiology guidelines direct the management of these acute heart failure patients, but specific consensus on early management has not been published, primarily because few early management trials have been conducted. This article summarizes practical recommendations for the prehospital and early management of patients with acute heart failure syndromes; the recommendations were developed from a meeting of experts in cardiology, emergency medicine, and intensive care medicine from Europe and the United States. The recommendations are based on a unique clinical classification system considering the initial systolic blood pressure and other symptoms: 1) dyspnea and/or congestion with systolic blood pressure >140 mm Hg; 2) dyspnea and/or congestion with systolic blood pressure 100–140 mm Hg; 3) dyspnea and/or congestion with systolic blood pressure <100 mm Hg; 4) dyspnea and/or congestion with signs of acute coronary syndrome; and 5) isolated right ventricular failure. These practical recommendations are not intended to replace existing guidelines. Rather, they are meant to serve as a tool to facilitate guideline implementation where data are available and to provide suggested treatment approaches where formal guidelines and definitive evidence are lacking. (Crit Care Med 2008; 36[Suppl.]:S129–S139)

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Acute heart failure syndrome (AHFS) is defined as a gradual or rapid change in heart failure signs and symptoms resulting in the need for urgent therapy. The syndrome is complex and encompasses multiple diagnoses and etiologies (1).

Large controlled trials conducted in chronic heart failure have identified therapies that improve clinical outcomes. Mortality and morbidity can be reduced when these therapies are used properly, and practice guidelines and performance measures have been developed for chronic heart failure. In contrast, very few effective treatments are available for AHFS that improve clinical outcomes. This problem may be partially due to the fact that few large, randomized AHFS trials have been conducted over the last 2 decades. Most AHFS studies have been limited by small patient numbers or single-center enrollment. The adequately powered studies that have been conducted demonstrated either neutral or harmful effects on clinical outcomes, with the exception of REVIVE II, which showed clinical status improvement among patients randomized to levosimendan (2–5). Another potential explanation for the lack of clinical benefit is that treatments may be initiated too late in the AHFS course to be effective. For example, patients could be randomized up to 48 hrs after admission in the OPTIME-CHF trial (2).

Only recently have guidelines begun to address management of AHFS (6, 7). However, the guidelines do not specifically address early treatment. Early treatment is defined as the prehospital phase and the first 6–12 hrs after presentation (6, 7). Guideline committees are often

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reluctant to provide specific and practical recommendations regarding early treatment because of the lack of large randomized, controlled, clinical trials in this area. The Heart Failure Society of America and the European Society of Cardiology (endorsed by the European Society of Intensive Care Medicine) guidelines provide some recommendations for acute heart failure, but many of them are categorized as level of evidence C, recognizing the paucity of available clinical trial data supporting the recommendations (6, 7). Experts in cardiology, emergency medicine, and intensive care medicine from Europe and the United States convened in June 2006 to develop practical recommendations on the prehospital and early management of AHFS. The multidisciplinary and international nature of this group enhances the applicability of these recommendations. Data now exist to support the hypothesis that early and aggressive treatment in the first 6–12 hrs after presentation may result in more favorable outcomes. Thus, we believed that detailed and practical guidance on patient management during this early phase would be useful to practicing physicians. These practical recommendations are not intended to replace existing guidelines. Rather, they are meant to serve as a tool to facilitate guideline implementation where data are available and to provide suggested treatment approaches by recommendations of an expert panel where formal guidelines and definitive evidence are lacking.

Rationale for Early Treatment of AHFS

Group Recommendation

- All AHFS patients should have the appropriate, goal-directed treatment started as early as possible. In some healthcare settings, this may occur either at home or in the ambulance. There is no contraindication to this concept.

ADHERE registry data indicate that AHFS treatments are often instituted >8 hrs after presentation. The mean time to intravenous diuretics was 8.1 hrs, and the mean time to intravenous vasoactive therapy was 22.8 hrs (8, 9). The pathophysiologic mechanisms associated with AHFS, including activated neurohormones, increased filling pressure, or ischemia, may have deleterious effects on clinical outcomes (10). Early initiation of appropriate therapy may be a method to counteract these negative effects before irreversible damage has occurred.

Randomized controlled trials that compare early and delayed therapy initiation in AHFS are lacking. However, in some patients with life-threatening conditions (i.e., pulmonary edema or cardiogenic shock), the need for immediate treatment is obvious. In addition, retrospective analyses of AHFS registry databases and studies performed in other acute illnesses suggest that early treatment initiation may be associated with improved outcomes.

A retrospective analysis from ADHERE evaluated the association between clinical outcomes and time to initiation of vasoactive therapy (11, 12). The authors observed a nearly even distribution of patients who received vasoactive agents in the emergency department (ED) (n = 4,096) compared with the inpatient unit (n = 3,499). The mean time to vasoactive therapy initiation was 1–2 hrs when it was initiated in the ED compared with 20–22 hrs when it was given after admission. Early administration in the ED was associated with a shorter median hospital length of stay (4.5 days vs. 7 days, $p < .0001$) and a lower in-hospital mortality rate (4.3% vs. 10.9%, $p < .0001$) (11).

Nguyen et al. (13) prospectively studied the impact of ED intervention on physiologic scores in 81 patients who presented to the ED with illnesses severe enough to warrant intensive care unit (ICU) admission. The data from this study indicated that ED intervention may have influenced the progression of critical illnesses. A similar study in patients with severe sepsis or septic shock also demonstrated improved clinical outcomes with early goal-directed therapy (14).

These data and others suggest that early initiation of treatments for AHFS may be a key factor in improving outcomes among critically ill patients (14, 15). Randomized, controlled trials are needed to fully explore this hypothesis.

Management of AHFS Primarily Based on Systolic Blood Pressure

The European Society of Cardiology guidelines were the first to classify patients with AHFS into distinct clinical conditions (7). These include a) acute decompensated heart failure, *de novo* or decompensated chronic heart failure; b) hypertensive acute heart failure; c) pulmonary edema; d) cardiogenic shock; e) high output failure; and f) right heart failure (7). However, this classification is a mixture of the clinical phenotype and disease severity on presentation, and there is significant overlap among the different conditions.

Prehospital and early ED and ICU/critical care unit (CCU) management of AHFS is primarily based on signs and symptoms. Systolic blood pressure (SBP) was recently seen as the most important predictive factor of morbidity and mortality (16, 17). We therefore proposed an algorithm primarily based on SBP at presentation and also on the existence of acute coronary syndrome (ACS) and/or right ventricular failure (Table 1).

As discussed later in this article, targeted treatment strategies differ among these clinical scenarios (Fig. 1). Thus, although AHFS is a continuum, early patient classification is a key factor in determining the most appropriate initial therapy, and it may enable patients to receive goal-directed therapy more rapidly. This classification also facilitates early risk stratification of AHFS patients.

The SBP cutoffs proposed in this document have not been definitively established, but they were chosen from a consensus among experts and based on published literature (16). At SBP of >140 mm Hg, left ventricular systolic function is likely preserved, at SBP of 100–140 mm Hg left ventricular systolic function is limited, and many patients with impaired left ventricular systolic function exhibit SBP <100 mm Hg. Indeed, clinical judgment is extremely important for the management of all patients with AHFS.

Clinical Scenario 1 (CS1): Dyspnea and/or Congestion With Elevated SBP (>140 mm Hg). In this scenario, symptoms typically develop abruptly. Dyspnea is primarily related to diffuse pulmonary edema, and minimal systemic edema is present. Patients are often systemically euvolemic or hypovolemic because of a long-lasting history of increased blood pressure and chronic treatment with diuretics. This clinical scenario is characterized by an acute elevation of filling pressures that parallels the increase in blood pressure and relatively preserved left ventricular ejection fraction in many patients (16, 18). Compared with patients with lower SBP, CS1 patients also have ischemic heart disease less often, higher levels of serum creatinine, and a better prognosis in terms of intubation rate and

Table 1. Clinical scenarios in acute heart failure syndrome

Clinical Scenario	Characteristics
CS1	SBP >140 mm Hg Symptoms develop abruptly Predominantly diffuse pulmonary edema Minimal systemic edema (patient may be euvolemic or hypovolemic) Acute elevation of filling pressure often with preserved LVEF Vascular pathophysiology
CS2	SBP 100–140 mm Hg Symptoms develop gradually, together with a gradual increase in body weight Predominantly systemic edema Minimal pulmonary edema Chronic elevation of filling pressure, including increased venous pressure and elevated pulmonary arterial pressure Manifestations of organ dysfunction (renal impairment, liver dysfunction, anemia, hypoalbuminemia)
CS3	SBP <100 mm Hg Rapid or gradual onset of symptoms Predominantly signs of hypoperfusion Minimal systemic and pulmonary edema Elevation of filling pressure Two subsets: Clear hypoperfusion or cardiogenic shock No hypoperfusion/cardiogenic shock
CS4	Symptoms and signs of acute heart failure Evidence of ACS Isolated elevation of cardiac troponin is inadequate for CS4 classification
CS5	Rapid or gradual onset No pulmonary edema Right ventricular dysfunction Signs of systemic venous congestion

SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome.

short-term mortality (16). The underlying pathophysiology is mostly related to vascular causes associated with limited left ventricular compliance or a rapidly changing pressure-volume relationship.

Clinical Scenario 2 (CS2): Dyspnea and/or Congestion With Normal SBP (100–140 mm Hg). In contrast to CS1, symptoms in patients with CS2 generally develop gradually, along with a progressive increase in body weight. The congestion is reflected by cardiopulmonary and systemic edema, although systemic edema predominates. Pulmonary congestion is generally related to high filling pressures. These patients typically have chronically elevated filling pressures, including increased venous pressure and elevated pulmonary arterial pressure. It should be noted that the lungs may be clear to auscultation. Careful auscultation for elevated pulmonary pressures should be part of the physical examination. These patients may also exhibit signs of renal dysfunction, and they often have concomitant anemia or hypoalbuminemia. These patients are likely to have chronic heart failure and may show a metabolic acidosis pattern.

Clinical Scenario 3 (CS3): Dyspnea and/or Congestion With Low SBP (<100 mm Hg). Hypoperfusion is the predominant physiologic problem in CS3. In contrast to the first two clinical scenarios, edema (especially pulmonary edema) is of less importance or totally absent. Symptoms may occur abruptly, or they may develop gradually over weeks or months. These patients also tend to have chronically elevated filling pressures. CS3 can be further classified into two subsets: patients with clear hypoperfusion or cardiogenic shock and patients without hypoperfusion or cardiogenic shock. Many of these patients have advanced or end-stage heart failure. As in CS2, a metabolic acidosis pattern may be present.

Clinical Scenario 4 (CS4): Dyspnea and/or Congestion With Signs of ACS. Acute ischemia is a known precipitating factor of AHFS. Patients presenting in this category may have classic evidence of ACS with or without ST elevation. ACS is a clinical diagnosis. Isolated elevation of cardiac troponin in the absence of other evidence for ACS does not constitute ACS. Patients included in this scenario may present with clinical features of CS1, CS2, or CS3. This subgroup is defined because these patients need specific therapy for ACS.

Clinical Scenario 5 (CS5): Isolated Right Ventricular Failure. Patients presenting with CS5 have features predominantly consistent with right ventricular dysfunction. These patients do not have pulmonary edema. Symptoms may occur rapidly, or they may develop gradually (19). Pulmonary hypertension may be a contributing factor, and tricuspid regurgitation may be noted in the physical examination. These patients may have left-sided hypovolemia due to inappropriately large loop diuretic doses.

Prehospital Management of AHFS

Group Recommendation

- Rapidly establish the clinical diagnosis based on the presenting clinical scenario.
- Quickly arrange for transfer to the nearest hospital, preferably one that has a service of cardiology and CCU, with or without a cardiac catheterization laboratory.
- Establish communication between emergency medical service (EMS) personnel and the receiving hospital to provide all pertinent and available information, including history, vital signs, and, when available, laboratory and electrocardiographic (ECG) data.
- Consider use of an open system continuous positive airway pressure (CPAP) where available in the EMS setting.

EMS systems differ around the world. The available personnel include emergency medical technicians, paramedics, nurses, and physicians. The training level of personnel, availability of diagnostic equipment, and ability to administer treatments also vary among countries. These recommendations should be applied according to the locally available resources.

The initial step in the prehospital management of AHFS is to establish the clinical diagnosis and to define the patient's clinical scenario based on presentation characteristics. The clinical assessment should include risk factor evaluation, past and recent medical history, current medications, symptoms, and physical examination. All personnel should be able to assess blood pressure, heart rate, and respiratory rate.

Where available, oxygen saturation should be determined. In some locations,

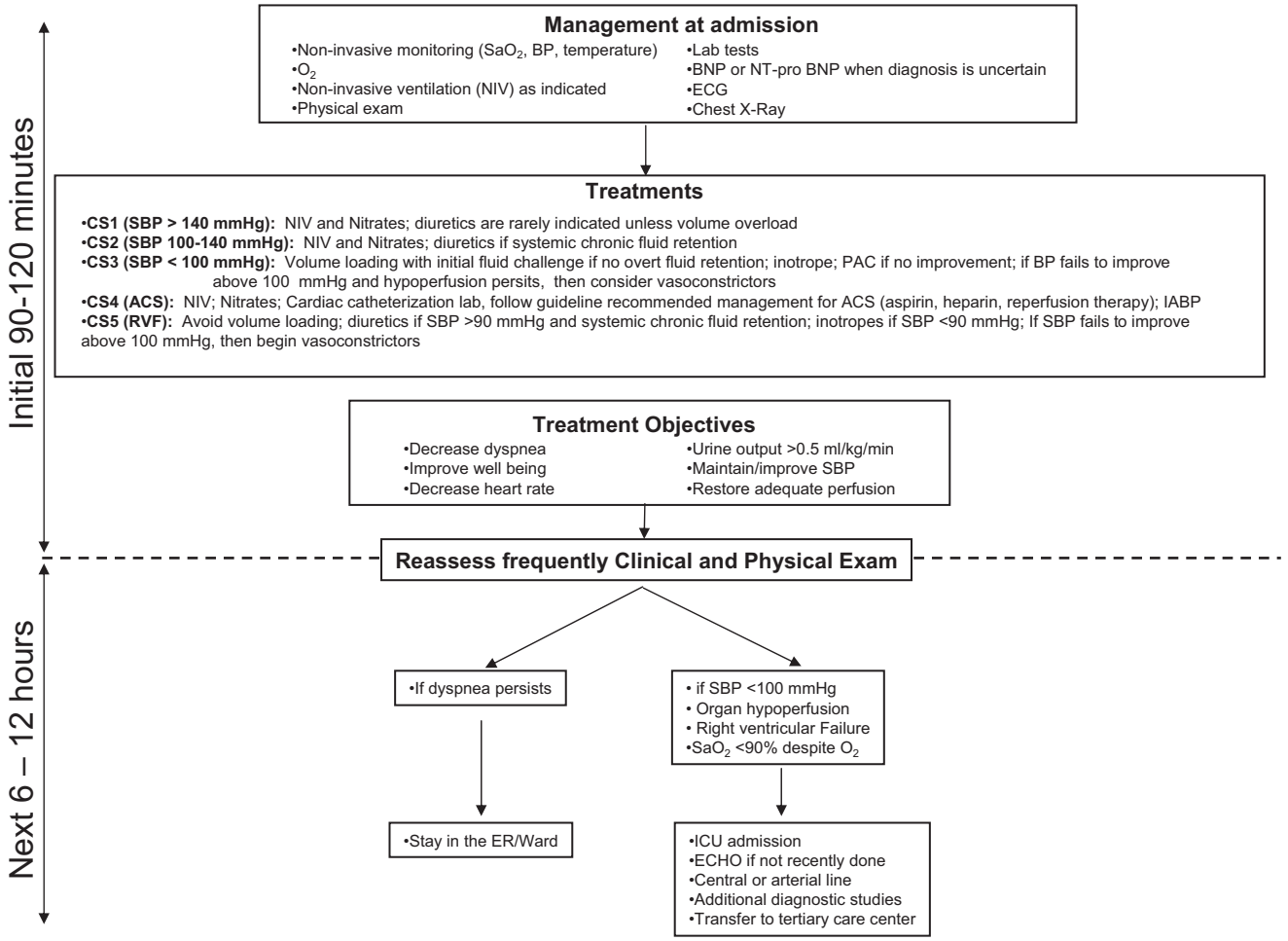

Figure 1. Proposed algorithm for the prehospital and early in-hospital management of patients with acute heart failure syndromes. *SaO_2*, arterial oxyhemoglobin saturation; *BP*, blood pressure; *BNP*, B-type natriuretic peptide; *NT-proBNP*, N terminal pro-BNP; *ECG*, electrocardiogram; *NIV*, noninvasive ventilation; *PAC*, pulmonary artery catheter; *ACS*, acute coronary syndrome; *IABP*, intraaortic balloon pump; *ER*, emergency room; *ICU*, intensive care unit; *ECHO*, echocardiography.

more detailed communications may be available, including central telemetry, in which ECG data can be obtained in the ambulance and transmitted to the receiving hospital. This evaluation tool may be particularly critical for patients with CS4. Ambulances should be equipped with cardiac defibrillators during transport. In some countries, portable point-of-care devices are available to analyze B-type natriuretic peptide (BNP), troponin, creatine kinase myocardial band, electrolytes, or blood gases. Handheld ultrasound devices may also become a tool that can be used in EMS settings (20–23).

In conjunction with establishing the clinical diagnosis, arrangements should be made to transport the patient to the nearest hospital with a cardiology service and a CCU. Cardiac catheterization laboratory facilities are also desirable for patients with an ACS. However, in some countries, EMS regulations require that the patient be transported to the nearest hospital, regardless of the available services. The consensus group discourages this practice and suggests that whenever possible, patients with heart failure and ACS should be immediately transported to a hospital with adequate intensive care facilities.

Diagnostic Assessments and Vital Sign/Hemodynamic Monitoring

Group Recommendation

- Noninvasive monitoring, including arterial oxyhemoglobin saturation, blood pressure, respiratory rate, and continuous ECG, should be started within minutes of admission or in the ambulance if possible.
- Urine output should be measured as frequently as possible; no catheter is needed.
- ECG data should be gathered at admission for all patients.
- Radiograph should be performed at admission for all patients.
- Echocardiography should be performed at the earliest appropriate time according to the clinical scenario and individual patient need.
- Monitoring of cardiac output and filling pressures, for instance with a pulmonary artery catheter, is suggested in hemodynamically unstable patients who are not responding in a predictable fashion to traditional treatments or who are refractory to initial therapy, who have a combination of congestion and hypoperfusion, whose volume status and cardiac filling pressures are unclear, or who have clinically significant hypotension and worsening renal function during therapy (6, 7).

Symptomatic improvement is the focus on treatment during the first few hours after AHFS presentation. Therapy should be based on the specific clinical scenario. Because early treatments are symptom focused, invasive monitoring usually is not necessary within the first hours. In CS3 patients, if symptomatic treatments fail to restore SBP and perfusion within 90 mins, invasive monitoring and CCU/ICU admission is usually indicated. Patients presenting with concomitant acute coronary syndrome (CS4) should receive early treatments for ACS as indicated.

Admission Laboratory Analysis

Group Recommendation

The following laboratory assessments should be performed at admission in AHFS patients:

- Sodium
- Potassium
- Glucose
- Blood urea nitrogen or urea
- Serum creatinine
- Creatine kinase myocardial band and/or troponin T or I
- Complete blood count
- Venous blood gases, if a central catheter is available (24)

The following assessments should be performed at admission in patients with CS1 or CS2:

- BNP or N terminal-pro-BNP can improve the diagnostic accuracy of AHFS and rule out pulmonary causes when added to standard clinical judgment.

In a patient presenting with dyspnea, BNP <100 pg/mL or NT-pro-BNP <300 pg/mL decreases the likelihood of an AHFS diagnosis, while BNP >500 pg/mL (25) or NT-pro-BNP >450 pg/mL in patients <50 yrs of age, >900 pg/mL in patients 50–75 yrs of age, and >1800 pg/mL if age is >75 yrs (26) are likely indicators of AHFS.

Noninvasive Ventilation (NIV)

Group Recommendation

- NIV should be used as early as possible in all AHFS patients when dyspnea, respiratory distress, and/or pulmonary edema are present to prevent the need for intubation and its subsequent complications and, potentially, to reduce the risk of mortality.
- NIV should never be used when there is a need for emergent intubation.
- A positive pressure of 5–7.5 cm H_2O and titrating to clinical response is the most appropriate initial therapy when CPAP is used.
- CPAP by face mask is inexpensive, and it has minimal adverse effects or complications. Therefore, an adequate number of CPAP devices to cover patient volume should be available in any ED, ICU, CCU, or cardiac ward.

Noninvasive respiratory support can be instituted early in AHFS, and it can be provided by either CPAP or bilevel ventilation (both inspiratory and expiratory support, BiPAP). These respiratory support methods are collectively known as NIV.

NIV has a number of theoretical advantages, making it an attractive therapy for the early treatment of AHFS. It augments cardiac output, decreases left ventricular afterload, increases functional residual capacity and respiratory mechanics, and can reduce the work of breathing.

A total of 23 clinical trials have assessed the comparison between either CPAP and standard therapy (27–38), BiPAP and standard therapy (28, 33, 34, 39–42), or CPAP and BiPAP (28, 33, 34, 43–49). Two meta-analyses of these studies have recently been published and showed similar results. The first revealed that both CPAP and BiPAP reduce the need of intubation, but only CPAP reduces mortality in patients with acute cardiogenic pulmonary edema (50). The second showed that CPAP reduced the need for mechanical ventilation and mortality when compared with standard therapy (51). BiPAP led to a reduction in the need for mechanical ventilation and a nonsignificant reduction in mortality when compared with standard therapy. Similar findings were reported in another meta-analysis by Winck et al. (52). In this analysis, CPAP was associated with a 22% absolute risk reduction in the need for intubation and a 13% absolute risk reduction in mortality. Some risk factors for intubation have been described in patients treated with conventional therapy: severe acidosis (pH <7.25), hypercapnia, acute myocardial infarction, low blood pressure, and severely depressed ventricular function (24).

Based on these data, early use of NIV should be considered for the early management of all AHFS patients. NIV requires minimal nursing resources; however, patient cooperation is necessary. Generous use of morphine together with clear instructions may enhance patient adaptation to the technique. Hospitals should have an adequate number of devices available to meet the needs of their AHFS patient volume. The typical inclusion criteria for NIV in clinical trials are severe acute respiratory failure, Pa_{O_2}/F_{IO_2} <250 mm Hg, sudden-onset dyspnea with respiratory rate >30 breaths/min, and typical physical signs of pulmonary edema. Exclusion criteria may be an immediate need for endotracheal intubation, coma or severe sensorial impairment, shock, ventricular arrhythmia, progressive life-threatening hypoxia (arterial oxyhemoglobin saturation <80% with oxygen), pneumothorax, recent upper gastrointestinal operation, claustrophobia, and facial deformities.

Diuretics

Group Recommendation

- Aggressive diuretic monotherapy is not necessary in the majority of patients.
- Diuretics should only be given when there is evidence of systemic volume overload.
- Diuretics are not the ideal first-line therapy for most patients with CS1.
- Diuretics may be helpful in addition to vasodilators (nitrates) in CS1, but they are ineffective as monotherapy. In general, nitrates should be administered first, and volume status and blood pressure should be monitored. Patients who experience a decrease in blood pressure of 30–40 mm Hg after an appropriate dose of nitrate therapy will generally improve symptomatically without diuretic therapy. If volume overload is present, diuretics should be given. The jugular venous pressure should be carefully assessed to determine volume.
- Diuretics may be used as first-line therapy in CS2 and CS5 with evi-

dence of gradual onset of dyspnea and gradual increase of body weight because of the likelihood of high filling pressure and systemic edema. The recommended initial dose is furosemide 20–40 mg intravenously at admission. The dose should be up-titrated according to renal function, SBP, and history of chronic diuretic use. However, high doses are not recommended because they may be detrimental to renal function and decrease patient tolerability of angiotensin-converting enzyme (ACE) inhibitors.

- Continuous infusion should be considered in CS2 after the initial intravenous bolus.
- Patients receiving diuretics should be reevaluated in 30 mins to 1 hr. Therapeutic targets include symptomatic improvement, improvement in physical findings, hemodynamic improvement, oxygen saturation, and diuresis. Gradual diuresis is the goal, not sudden production of large volumes of urine.
- Electrolytes should be monitored closely.

Surveys indicate that loop diuretics are the first-line agent around the world for the treatment of patients with AHFS. Furosemide is the most common loop diuretic used in clinical practice.

It is important to recognize two key points related to diuretic therapy. First, the widespread use of diuretics is largely based on bedside observation of short-term effects by individual physicians. Only a few studies have evaluated short- and long-term clinical outcomes. Second, the most frequent clinical scenario of patients admitted with AHFS is CS1. Patients are often systemically euvolemic or hypovolemic because of a long-lasting history of increased blood pressure and chronic treatment with diuretics. High-dose diuretics in these patients may be detrimental.

Appropriate early diuretic use may differ depending on the characteristics of AHFS. Patients with fluid redistribution (CS1) should be considered differently from patients with worsening chronic fluid overload (CS2). The separation between these two profiles is not rigid, but this categorization may help provide a framework for diuretic therapy. This classification can be made based on the patient's history, clinical examination (signs of congestion), symptom severity (moderate decompensation, pulmonary edema, or cardiogenic shock), and blood pressure. The pathophysiology and therapeutic goals differ between these classifications. Thus, recognizing the appropriate patient profile is important, and it will help to guide the physician's early management strategy.

Diuretic prescription is primarily anecdotal. Only a few trials have studied the appropriateness of diuretic doses and methods of administration. These data suggest that low-dose furosemide (20–40 mg or ~0.25–0.5 mg/kg intravenously) is a reasonable initial therapy for most patients (53–55). However, patients with hypotension and/or cardiogenic shock may require less aggressive diuresis. Patients with chronic heart failure on high-dose diuretic therapy (CS2), patients with primarily right-sided heart failure (CS5), or patients with renal dysfunction may require higher doses or continuous diuretic infusion. Metolazone is also an option in patients with renal dysfunction owing to its additional, synergistic action on the proximal tubule (56).

Variables for adjusting diuretic therapy have not been established. In general, the lowest dose should be used that produces the desired clinical effect. In chronic heart failure, diuretic therapy is titrated according to fluid balance and the resolution of signs and symptoms. These targets may be insensitive estimates of volume status during the initial management period for AHFS, especially in obese patients or those with other comorbidities.

The onset of diuresis may not occur until 30–120 mins after administration; thus, urine output alone is not an ideal therapeutic target. Dyspnea, global patient status, respiratory rate, oxygen saturation, and need for intubation are better targets, especially in critically ill patients. Diuretic resistance and diuretic adaptation are important problems in patients with chronic heart failure, but their significance is limited in the initial management of AHFS patients. Patients with diuretic resistance may require higher diuretic doses or combination diuretics with different mechanisms of action. Loop diuretics may increase the neurohormonal cascade, which is detrimental to heart failure patients (57).

Vasodilators

Group Recommendation

- Nitrate therapy is recommended in CS1, CS2, and CS4 if SBP is >110 mm Hg. The blood pressure below which nitrates should not be used varies among patients and clinical settings.
- If available, it is recommended to administer nitroglycerin spray sublingually before admission (prehospital) or in the ED.
- The initial recommended dose of intravenous nitroglycerin is 10–20 μg/min, increased in increments of 5–10 μg/min every 3–5 mins as needed.
- Slow titration of intravenous nitrates and frequent blood pressure measurement is recommended to avoid large decreases in SBP.
- An arterial catheter is not required for monitoring nitrate therapy.
- Vasodilators are not recommended as first-line therapy in CS3.
- Nesiritide can decrease pulmonary artery occlusion pressure and improve dyspnea in acute heart failure, but it is currently a second-line agent due to concerns about deleterious effects on renal function and outcome.
- Calcium antagonists are not recommended in AHFS during the first 0–12 hrs.

Based on registry data, the majority of AHFS patients present with increased left ventricular filling pressure and high or normal blood pressure (CS1 and CS2); only a minority present with low blood pressure or cardiogenic shock (CS3) (17, 58, 59). Patients with CS1 or CS2 are ideal candidates for early initiation of vasodilator therapy. Acute therapy with vasodilators can improve both hemodynamics and symptoms.

Vasodilators are usually given in conjunction with diuretics, although much of the acute effect of loop diuretics may be due to venodilation (60). One small randomized study suggested that high-dose nitrates plus low-dose furosemide

were more effective than low-dose nitrates plus high-dose furosemide in acute pulmonary edema (53). Currently available vasodilators include nitrates, nitroprusside, and nesiritide.

Nitrates include nitroglycerin, isosorbide mononitrate, and isosorbide dinitrate. Nitrates relieve pulmonary congestion primarily through direct venodilation. At higher doses, coronary artery dilation and increased collateral blood flow may decrease ischemia, an effect that is often desirable given the high incidence of coronary artery disease in heart failure patients. In AHFS, intravenous nitroglycerin is preferred. The initial recommended dose is 10–20 μg/min, and it is increased in increments of 5 μg/min every 3–5 mins as needed. Frequent titration should be used to achieve goals rapidly without lowering blood pressure too precipitously. Tachyphylaxis is common, necessitating incremental dosing. The major adverse effects of nitrates are hypotension (mean blood pressure should remain >70 mm Hg) and headache.

Nitroprusside is a balanced arterial and venous vasodilator with a very short half-life, facilitating rapid titration. Afterload reduction lowers blood pressure and can increase stroke volume. Nitroprusside may be used in patients not responding to nitroglycerin. Nitroprusside is given by continuous intravenous infusion, starting at 0.1–0.2 μg/kg/min and increased every 5 mins to achieve hemodynamic goals (blood pressure control or 20% to 50% decrease in occlusion pressure and/or 20% to 40% increase in cardiac output). Coronary steal is a concern in patients with ischemia, and nitroglycerin is preferred in these patients. Nitroprusside has been associated with increased mortality in AMI patients who received it within the first 9 hrs after the AMI (61). Thus, nitroprusside should be avoided in CS4. The major complication of nitroprusside therapy is hypotension. Toxicity may also occur from accumulation of cyanide or thiocyanate, usually in patients with renal insufficiency receiving high doses for ≥24 hrs.

Nesiritide, a recombinant form of human B-type natriuretic peptide, is a venous and arterial vasodilator that may also potentiate the effect of diuretics. It is given intravenously as a 2-μg/kg bolus followed by a 0.01-μg/kg/min infusion. In the VMAC trial, nesiritide lowered pulmonary artery occlusion pressure significantly more than either intravenous nitroglycerin or placebo at the 3-hr time point, and it improved dyspnea compared with placebo (4). However, the doses of nitroglycerin reached in the VMAC trial were lower than those typically used in clinical practice. Although nesiritide has natriuretic effects, it has not been shown to improve either glomerular filtration rate or renal plasma flow (62). Hypotension is the most common side effect. In addition, meta-analyses of data from VMAC and other trials have suggested that nesiritide may worsen renal function and decrease survival at 30 days compared with conventional therapies (63, 64). Resolution of these concerns awaits completion of appropriately powered prospective clinical trials. In contrast to other agents, blood levels of nesiritide do not rapidly decrease after drug discontinuation. Intravenous ACE inhibitors are not recommended in the early AHFS setting, particularly in patients with ischemic chest pain (65).

Cardiac Enhancers and Vasoconstrictors

Group Recommendations

- Inotropes are used in a small number of patients, mainly with CS3. They are not recommended in CS1 and should be used in selected patients with CS2 or CS4.
- Traditional inotropes (dobutamine, milrinone) or the new inodilator levosimendan (where available) may be used early in patients with evidence of poor organ perfusion (patient is cold, clammy, or vasoconstricted or the patient has renal impairment, liver dysfunction, or impaired mentation) and low cardiac output, low SBP, and high filling pressures (as detected by physical examination and symptoms) who are not responding to other therapies.
- If no improvement in perfusion is observed, then advanced hemodynamic monitoring should be used. If blood pressure remains low (<100 mm Hg), then a vasoconstrictor should be considered after optimizing preload. Norepinephrine is the recommended vasoconstrictor in AHFS.

Traditional Inotropes. Inotropes are a traditional component of the AHFS treatment strategy. The most common inotropes in clinical practice include dobutamine and milrinone, but dopamine is also available. Traditional inotropes are no longer recognized as first-line, acute therapy for the majority of AHFS patients, and data from ADHERE, OPTIMIZE, and Euro Heart Failure Survey II indicate that traditional inotropes are used in approximately 10% of AHFS admissions (1, 9, 66). The OPTIME-CHF study found no benefit for milrinone in 949 patients hospitalized for worsening heart failure (2). A higher risk of arrhythmias was observed, and patients with ischemic etiology who were randomized to milrinone had worse outcomes (67, 68). Patients were excluded if they required inotropic therapy; thus, the OPTIME-CHF population did not include low-output/hypoperfused patients. A retrospective analysis from the ADHERE registry also suggested that inotropes should be avoided in the majority of AHFS patients. In this analysis of >65,180 patient cases, patients treated with either dobutamine or milrinone had significantly increased risk of in-hospital mortality compared with nitroglycerin or nesiritide after adjustment for covariates and propensity score (9).

Early use of inotropic therapy may be appropriate in patients presenting in cardiogenic shock or with evidence of low output who are not responding to other therapies (7). These patients may include those with SBP <85–90 mm Hg or evidence of organ hypoperfusion, including patients who are cold, clammy, or vasoconstricted. Renal impairment, liver dysfunction, and impaired mentation are also possible signs of hypoperfusion. As discussed, these patients account for the minority of AHFS hospitalizations. Inotropes may stabilize patients at risk of progressive hemodynamic collapse or serve as a life-sustaining bridge to more definitive therapy, such as mechanical circulatory support, ventricular assist devices, or cardiac transplant.

Levosimendan. Levosimendan is a novel calcium sensitizer that improves cardiac contractility by binding to troponin-C in cardiomyocytes. The significant vasodilatory properties of levosimendan are mediated through adenosine triphosphate-sensitive potassium channels, causing peripheral arterial and venous dilation and increasing coronary flow reserve (69). Levosimendan has beneficial hemodynamic and clinical effects in patients with AHFS, and it is safe in ACS (3, 70, 71). In the REVIVE trial, levosi-

mendan significantly improved a composite of clinical signs and symptoms of AHFS compared with placebo over 5 days as assessed by patients and their physicians (5). In the SURVIVE study comparing levosimendan and dobutamine, a statistically significant improvement in survival for levosimendan-treated patients was seen early, especially in patients chronically treated with a β-blocker and in patients with prior heart failure, but it was not evident in 180-day survival (3).

In countries where it is available, early levosimendan infusion can be considered for patients who remain symptomatic with dyspnea at rest despite initial therapy, particularly those chronically treated with β-blockers. Levosimendan may be initiated in patients with SBP >100 mm Hg with a bolus infusion dose of 6–12 μg/kg for 10 mins. This bolus dose should be lowered in patients with less pronounced fluid overload, such as those with *de novo*, new-onset AHFS. The initial rate of continuous infusion is typically 0.1 μg/kg/min. In patients with SBP >85 and <100 mm Hg, the infusion should be started without a bolus dose to avoid hypotension. Levosimendan is not recommended for patients with SBP <85 mm Hg, although it has been used in combination with vasopressors, most often norepinephrine, in selected patients (3).

Vasoconstrictors. Norepinephrine is recommended alone or in combination with an inotrope or cardiac enhancer in CS3 and CS6 in order to increase SBP in the situation of persistent organ hypoperfusion (e.g., low urine output clearly related to low blood pressure). The recommended dose is 0.2–1.0 μg/kg/min. It may be started on a peripheral catheter, but a central catheter should be placed for its infusion as soon as feasible. Epinephrine is not recommended as first-line therapy, even in CS3. It is used as rescue therapy in cardiac arrest. There is no evidence of a renal benefit with low-dose dopamine.

Device Therapy

Group Recommendations

- Device therapy should only be recommended when there is potential for myocardial recovery with or without intervention.
- Initiate the transfer process within the first 12 hrs in patients who have an indication for device therapy if device resources are not locally available.
- Consider early mechanical intervention in the following situations: blood pressure is not sustained >80 mm Hg in spite of inotropes; urine output is <30 mL/hr (or <0.5 mL/kg/min); skin is cool and mottled; oxygen saturation is dropping; there is ongoing ischemia.
- Intraaortic balloon pump is the first-line intervention.
- Ultrafiltration may be considered in patients who fail to respond to diuretic therapy

Early mechanical device therapy may be useful in patients who have not responded to other therapies during the first 6–12 hrs after presentation. Patients who may be candidates for device therapy include those with severe and persistent hypotension or hypoperfusion despite the use of inotropes, urine output <30 mL/hr, decreasing oxygen saturation, persistent ischemia, or cold or mottled skin. When implemented early, the use of these devices may promote recovery in some patients.

IABP is the first-line device for these patients. It can be rapidly placed in the cardiac catheterization laboratory or in the CCU/ICU. It is associated with some risks, including compromised blood flow to the leg and dissection (particularly in patients with peripheral vascular disease). IABP only provides a temporary solution for AHFS. IABP may be implemented more quickly in patients with suspected ongoing ischemia.

Left ventricular assist devices will not generally be used within the first 6–12 hrs of an AHFS presentation. Data from ADHERE indicate that <1% of patients hospitalized for AHFS receive left ventricular assist devices during the entire hospital stay; thus, their utility during the early phase is relatively low and should be further defined.

Managing Comorbidities

The majority of patients with AHFS have multiple comorbidities. These conditions may contribute to the development of AHFS, and they should be controlled as soon as possible after presentation. Examples include atrial fibrillation with rapid ventricular response, ventricular arrhythmias, bradycardia, severe anemia, and infection. In addition, concomitant medications can exacerbate heart failure and precipitate AHFS. These medications should be stopped immediately after presentation. Examples include nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, thiazelinediones, sympathomimetics, tricyclic antidepressants, class I and III antiarrhythmics (except amiodarone), and nondihydropyridine calcium channel blockers.

Management of Chronic Heart Failure Medications During AHFS Episode

Group Recommendations

- Beta-blockers, ACE inhibitors, angiotensin receptor blockers, and/or aldosterone antagonists should be continued at the highest tolerated dose unless the patient has symptomatic hypotension (SBP <90 mm Hg), is in cardiogenic shock, or has significant hyperkalemia (ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists) (K >5 mmol/L).

Time Course for Symptomatic Improvement in AHFS

Few data are available for CS1, but a clinical goal is to improve dyspnea by 3–6 hrs. The majority of data are from patients with CS2 (VMAC, REVIVE) (4, 5). In these studies, dyspnea began to improve at 3 hrs, and it continued to improve until 48 hrs. Most patients (>70%) improved within the first 24 hrs. In these studies, patient global assessment (well-being) roughly matched dyspnea improvement. Symptomatic improvement in patients with CS3 and CS5 generally occurs after 48 hrs. However, in the more critically ill patients or in the patients with CS4, efficacy markers other than symptomatic improvement are needed. For example, the symptomatic improvement in CS4 primarily depends on percutaneous intervention results.

The average hospital length of stay for patients with CS1 is approximately 4 days in the United States and 9–11 days in Europe. Most registries involved patients who would fit into the CS1 category, so little information on length of stay is available for the other clinical scenarios. However, the EFICA registry enrolled a

sicker population who would most likely be classified as CS2 or CS3. Length of stay in EFICA ranged from 14.5 to 15.1 days, depending on the presence of cardiogenic shock (1, 5, 17, 58, 59, 66).

Regulatory View on Studies in the Early Management of AHFS

The basic regulatory requirements for a drug in AHFS are to demonstrate predictable favorable hemodynamic effects and a clear clinical benefit, with no short- or long-term safety concerns. The immediate treatment objectives for AHFS are to relieve symptoms and to improve the hemodynamic condition. These short-term benefits should also be accompanied by favorable effects on longer term outcomes.

Hemodynamic improvement has traditionally been the efficacy marker for AHFS therapies. However, most therapies tested have not targeted the initial 6–12 hrs after presentation (72). Dyspnea is the dominant symptom in AHFS, and dyspnea improvement should be observed in conjunction with hemodynamic improvement. Patients with AHFS have a very poor prognosis. In addition to acute symptomatic and hemodynamic improvement, an effective drug for AHFS should also provide longer term benefit. From a regulatory perspective, total mortality is the preferred primary efficacy end point. Dyspnea improvement with reduction in pulmonary artery occlusion pressure, from either one or several studies, would also be considered acceptable evidence for efficacy provided deleterious effects on mortality and morbidity, both immediate and delayed, are ruled out. Hemodynamic findings are useful and needed, but they are not enough to form the sole basis for drug approval (72).

Potential safety issues related to AHFS therapies include life-threatening arrhythmias, hypotension, myocardial ischemia, renal dysfunction, and sudden death. Increased short- or medium-term mortality has been reported with several agents (72). Therefore, 6-month mortality data are required to exclude the possibility of a deleterious effect, even if the claim is only made for symptomatic benefit.

SUMMARY

Patients presenting with AHFS are a complex and heterogenous population at high risk of short-term morbidity and mortality. Early classification of patients according to their clinical presentation is a key step in determining the appropriate initial treatment. We proposed five clinical scenarios that physicians can use to identify an initial therapeutic approach. These categories identify patients according to the primary pathophysiologic problem, so that early, goal-directed therapy can be implemented. Early initiation of diagnostic and goal-directed treatment strategies may be a key factor in improving patient outcomes. Early and frequent reassessment is also imperative so that adjustments in the initial therapeutic approach can be made as clinically indicated. These recommendations may serve as a stimulus for much-needed research on early treatment initiation in patients with AHFS. The rapid treatment approach may prove to be an effective intervention for the management of AHFS.

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