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Early Management of Patients with Acute Heart Failure: State of the Art and Future Directions:

A Consensus Document from the SAEM / HFSA Acute Heart Failure Working Group

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Introduction

Heart failure (HF) afflicts nearly 6 million Americans, resulting in one million emergency department (ED) visits and over one million annual hospital discharges.[1,2] An aging population and improved survival from cardiovascular diseases is expected to further increase HF prevalence.[3] By 2030 an estimated 25% increase in HF prevalence will result in an additional 3 million affected individuals.[1,4] Of the $39.2 billion spent on HF care in the US in 2010, inpatient admissions accounted for the single largest proportion. By 2030, the amount spent on hospital care for HF will be even greater as annual total costs are expected to be close to $70 billion.

Emergency providers play a significant role in the management of patients with acute heart failure (AHF). Therapeutic and disposition decisions made by emergency providers have direct impact on morbidity, mortality, and hospital length of stay, all of which affect health care costs.[5–9] Over 80% of ED patients with AHF are admitted to the hospital, a proportion which has remained largely unchanged over the last 5 years.[2] It is crucial that emergency physicians and other providers involved in early management understand the latest developments in diagnostic testing, therapeutics and alternatives to hospitalization. Equally important are partnerships between emergency providers and heart failure specialists along with the entire interdisciplinary team caring for HF patients to streamline care from the ED to the inpatient and outpatient settings.

1. Current Approaches to Diagnosis

Although there is no universally accepted terminology to describe “acute” heart failure, for the purpose of clarity we have chosen to use AHF, defined as chronic or de novo HF with new or worsening symptoms requiring acute therapy. Patients present to the ED with signs

and symptoms, not diagnoses. While dyspnea is the most common symptom in AHF, it has a large differential diagnosis. Efficient diagnosis is critical as delays in the delivery of care for AHF are associated with increases in mortality, hospital length of stay, and treatment costs.[10–14] Thus, an understanding of the strengths and limitations of the history, physical examination, and laboratory and radiographic tests used to assist in the diagnosis of AHF is essential.

History and Physical Examination

Multiple studies suggest there is no historical or physical examination finding that achieves a sensitivity and specificity > 70% for the diagnosis of AHF. Further, only one clinical finding, the S3 gallop, achieves a likelihood ratio positive (LR+) greater than 10 and none carries a LR- less than 0.1.[14] In a meta-analysis of 18 studies,[13] prior HF was the most useful historical parameter, with a LR+ of 5.8 and LR- of 0.45, respectively. Dyspnea on exertion is the symptom with the lowest LR- at 0.48, but has a LR+ of only 1.3[13,14] while paroxysmal nocturnal dyspnea, orthopnea, and peripheral edema have the best LR+ (2/1–2.6%), but a notably poor LR- (0.64–0.70).[13,14] Notably, emergency physician clinical judgment is only modestly useful with a LR+ of 4.4 and LR- of 0.45.[13] Although the S3 has the highest LR+ (11), it has far less utility as a negative predictor (LR-, 0.88)[13] and suffers from poor inter-rater reliability.[15–18] Hepatojugular reflux (LR+, 6.4) and jugular venous distension (LR+, 5.1), are the only other examination findings with a LR+ above 5.

Chest radiography

Chest radiographs demonstrating pulmonary venous congestion, cardiomegaly, and interstitial edema are the most specific test findings for AHF (Table 1).[12,13] However, their absence cannot rule out AHF, as up to 20% of patients with AHF will have no congestion on their ED chest radiograph.[19] Particularly in late-stage HF, patients may have few radiographic signs, despite AHF symptoms and elevated pulmonary capillary wedge pressure (PCWP). [12,20,21]

Electrocardiogram

The electrocardiogram is not useful for diagnosis, but may suggest a specific cause or precipitant of AHF such as myocardial ischemia, acute myocardial infarction or arrhythmia. The presence of atrial fibrillation has a high LR+ for AHF; however, new t-wave changes are also associated with AHF (Table 1).[13] The electrocardiogram may also offer clues as to the underlying cause of chronic HF (e.g., Q waves in ischemic cardiomyopathy, low voltage in cardiac amyloid).

Biomarkers

The natriuretic peptides (NP), B-type NP (BNP), and its precursor N-terminal Pro-BNP (NTBNP), are the most established AHF diagnostic biomarkers. They add value in the setting of undifferentiated dyspnea by improving diagnostic discrimination[22,23] and correlate with cardiac filling pressures and ventricular stretch.[24] NP testing is a Class 1 (best evidence) guideline recommendation by both Heart Failure Society of America (HFSA) and American College of Cardiology Foundation / American Heart Association (ACCF/

AHA)[25,26] and may be particularly useful when the etiology of dyspnea is unclear, and have been shown to have greater utility than CXR for diagnosing AHF. [13,22] Newer markers, such as ST2 and galectin 3, have been explored for prognostic assessment and diagnosis of preclinical HF,[27,28] but their role in the ED is less clear.

NP levels can be affected by age, gender, weight and renal function (Table 2).[29] Dyspnea not due to AHF can still be associated with NP elevation in a variety of conditions associated with myocardial stretch, (e.g. right ventricular stretch from pulmonary hypertension or pulmonary embolism, acute coronary syndromes) or decreased renal clearance. [30–32] Patients with HF with preserved left ventricular ejection fraction (HFpEF) have a smaller left ventricular radius and thicker walls compared to patients with reduced LVEF (HFrEF) resulting in proportionally lower NP levels for similar degrees of AHF, suggesting different diagnostic thresholds are needed depending on whether left ventricular ejection fraction (LVEF) is preserved or reduced.[33] Beyond clinical factors, additional variation in NP levels can arise from heritable[34] and specific genetic variants that have been shown to alter assay performance.[35] In general, changes over 50% from baseline represent worsening HF; however, significant variation in NP levels can occur within the same patient and intra-individual differences between measurements do not necessarily represent an acute clinical event. [36] Despite these limitations and a substantial ‘grey zone’ when interpreting results, NP testing remains useful and is additive to physician assessment.[37]

Point of care ultrasonography

While not a substitute for comprehensive echocardiography, point of care cardiac ultrasonography can be valuable in determining the etiology of dyspnea, providing an assessment of left ventricular function and volume status and looking for signs of pericardial effusion. Point of care ultrasonography can accurately estimate LVEF, has good inter-rater reliability, and is most likely to be of use immediately or shortly after ED arrival in those patients without a prior HF diagnosis.[20] Volume status may be assessed by inferior vena cava (IVC) diameter and its degree of change with respiratory variation. Inspiration causes the IVC to decrease in size as more blood leaves the IVC than collecting within it.[38,39] The IVC collapse index, defined as IVC diameter during expiration minus the IVC diameter during inspiration divided by IVC diameter during expiration, can help determine volume status in the setting of AHF. In AHF patients with volume overload the IVC is dilated without the normal amount of change in IVC diameter during the respiratory cycle. Thus the IVC collapse index is closer to 1, compared to patients without HF where it is typically between 0.25 and 0.75.[40]

Lung water can also be assessed with ultrasound by looking for sonographic B-lines (also called lung comets or comet tail artifacts) each of which implies thickened interstitial or fluid-filled alveoli. B-lines occur most commonly in patients with AHF and correlate with elevated PCWP and extravascular pulmonary water.[41] In the ED setting, the presence of B lines on pleural ultrasonography is associated with fluid overload, enhancing diagnostic accuracy when coupled with examination and NP measurement.[42] Several authors have shown bedside pulmonary ultrasound is accurate in detecting AHF with reported sensitivities of 86–100% and specificities of 95–98% (LR- = 0.01–0.14 and LR+ = 17.2–

49.5).[43,44] Ultrasonography has been shown to be more accurate than auscultation or chest radiography for the detection of pleural effusion, consolidation, and alveolar interstitial syndrome in the critical care setting.[45]

Other Diagnostic Technologies

Obtained using stand-alone machines or from an implanted cardiac device, impedance cardiography (ICG) may provide an additional hemodynamic measure.[46–48] However, studies evaluating the utility of externally applied ICG devices to guide acute therapy have had mixed results[49,50] and their role in the ED remains unclear. Further, while implanted devices offer extensive monitoring capabilities (heart rate, heart rate variability, activity level, thoracic impedance) for chronic HF disease management,[51] their utility in the ED is not established. Because data from indwelling devices provide important diagnostic information, they may ultimately prove useful, particularly for subtyping HF based on hemodynamic, developing tailored treatment strategies, and quantifying fluid status to aid in transition care decisions. Routine interrogation of implantable pacemakers or cardioverter-defibrillators, which provide ongoing rhythm recordings, can be used to assess for atrial and/or ventricular arrhythmias as precipitants to AHF.[52] Additional technologies to assist with non-invasive hemodynamic assessment such as finger cuff pulse-wave analysis may also be of value but their utility in the ED has yet to be determined.[53]

2. Current Guideline Recommendations for AHF Therapy

The ACCF/AHA Guidelines for the Management of HF is a comprehensive document using standardized methodology to evaluate the available evidence for HF management,[26] with one section providing guidance on the hospitalized patient. While the guidelines do not provide specific recommendations on the early evaluation and management of AHF, they do suggest continuation and initiation of Guideline-Directed Medical Therapy (GDMT) for the hospitalized patient, which can be somewhat extrapolated to the ED phase of care. GDMT may include angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), beta blockers (BB), mineralocorticoid antagonists (MRA) depending on variables such as race, LVEF, and contraindications. For instance, in patients with HFrEF, it is recommended (Class I, LOE B) that, in the absence of hemodynamic instability or contraindications, GDMT be maintained and furthermore it is reasonable to consider early administration of such oral therapy in the ED. Other recommendations relevant to early care (Table 3) include initiation of intravenous loop diuretics at a dose greater than or equal to their chronic oral daily dose (Class I, LOE B), consideration of parenteral nitrates (nitroglycerin, nitroprusside) or nesiritide as adjuvant therapy for non-hypotensive patients with continued symptoms, (Class IIb, LOE A) and broad use of thromboembolism prophylaxis (Class I, LOE B).

Using methodology similar to ACCF/AHA, the HFSA published Comprehensive Practice Guidelines in 2010.[25] Section 12 of this guideline focuses on AHF and suggests that treatment start with clinical classification based on history, examination and secondary risk stratification using diagnostic adjuncts. In general, the recommendations are consistent with the ACCF/AHA (Table 3) but the HFSA guidelines specifically mention non-invasive ventilation (NIV) in patients with severe pulmonary congestion (strength of evidence [SOE]

A) and suggest that inotropic therapy (milrinone, dobutamine) be considered in patients with signs of diminished end organ perfusion, LV dilatation, reduced EF and marginal systolic blood pressure (<90mmHg), or in those who are poorly responsive to diuretics or are intolerant to vasodilators (SOE C). An update to the HFSA guideline on AHF was published in 2013,[54] and provides information on recently published trials [55–57] that have yielded important data to inform both current clinical practice and future research directions.

The European Society of Cardiology (ESC) guidelines section 12 specifically addresses the treatment of AHF.[58] Overall, the ESC Guidelines represent an approachable, clinically relevant synopsis of the available evidence in the treatment of patients with AHF (Table 3). Formatted to address clinical scenarios these guidelines provide treatment recommendations for AHF patients with pulmonary congestion, hypotension, acute coronary syndrome, atrial fibrillation with rapid ventricular response, heart block, isolated right ventricular failure, cardiorenal syndrome and adult congenital heart disease. While the recommendations are generally consistent with the ACCF/AHA and HFSA, the ESC makes a few additional pertinent recommendations. The use of intravenous opiates with antiemetics was given IIa (LOE C) recommendation for patients who are anxious, restless or distressed. When using opiates, the authors suggest close monitoring and caution regarding respiratory depression, which may be important to prevent adverse events, as suggested in a recent analysis.[58] With respect to invasive monitoring, an arterial line or a pulmonary artery catheter is recommended only in patients with refractory hypotension, in whom LV filling pressures are uncertain, or who are surgical candidates.

The American College of Emergency Physicians (ACEP) does not publish comprehensive guidelines, focusing instead on clinical policy statements targeted at critical aspects of ED care for common conditions. In 2007, ACEP produced their only clinical policy dedicated to AHF. In it, some of the more controversial and important issues confronting ED management of AHF were addressed; however, significantly more data has become available since its publication.[55,59,60]

3. Current ED therapy: applicability of recent evidence and ongoing trials

Current Approach to ED Treatment of AHF

It is noteworthy that neither the ACCF/AHA nor the HFSA guidelines include any Class I, Level A recommendations for the pharmacologic treatment of AHF.[25,26,58] ED treatment is not emphasized in the expert recommendations from the ACCF/AHA, and little has changed regarding AHF treatment in the ED since the 1970s.[26,61] This is not a reflection upon guidelines; rather it highlights the absence of robust ED clinical trial data and an ill-defined standard practice.(Table 4)

AHF Treatment: Consideration of Presenting Blood Pressure

Expert opinion, supported by smaller cohort and randomized studies, suggests our current approach should reconsider the “diuretics only” treatment paradigm, and incorporate other clinical parameters into the initial management of AHF.[12,62] While several classification schemes are proposed; none have been prospectively validated. There have been no randomized trials evaluating ED treatment strategies based on initial blood pressure. Based

on prior and recent evidence we suggest an initial treatment approach based on presenting systolic blood pressure (SBP),[63–67] dividing patients into three groups (Table 5): 1) hypertensive (SBP > 140mmHg); 2) normotensive (SBP 100–140mmHg); and 3) hypotensive (SBP < 100mmHg).[12] This approach is based on the initial BP (ambulance or ED) and not BP measurements taken several hours later, after initial ED management.

Elevated SBP may be an especially important target, as a sizable proportion of patients with hypertensive AHF present with volume redistribution rather than volume overload as their predominant phenotype. In such patients, congestion is due to increased afterload with rapid onset of dyspnea and flash pulmonary edema representing a classic presentation.[64] Rarely do these patients complain of symptoms days to weeks prior to presentation; rather, symptoms are abrupt and with less evidence of peripheral edema or weight gain.[68,69] While elevated systemic vascular resistance is thought to be the primary mechanism, volume mobilization from the large venous reservoir contained within the splanchnic circulation has also been proposed as a contributory mechanism.[70] For volume overload patients, IV loop diuretics remain the primary ED pharmacologic therapy, but for those with volume redistribution vasodilation may be the preferred approach to treatment. Small studies suggest safety and significant clinical benefit with nitrates or calcium channel blockers in the hypertensive AHF phenotype[63,66,67] and results from several on-going, large trials of targeted vasodilator therapy are eagerly anticipated.

This simple approach prompts greater usage of vasodilators, as approximately 50% of patients have a SBP > 140mmHg.[68] However, independent of BP, an assessment of volume status is critical as patients in any group may still require diuresis. This is particularly true for hypotensive patients as many will have a low SBP at baseline and fluid overload may still be present. Importantly, for such patients inotropes should only be used when other treatments have failed or there is clear evidence of shock or organ hypoperfusion.[25]

Clinical Trials Evidence in Acute HF: Past and Current

Hospitalizations, once viewed as episodes of fluid overload requiring intravenous diuretics in an otherwise stable chronic HF course, are now recognized as a fundamental change in the clinical trajectory of patients with HF. Whether AHF simply heralds a sicker chronic HF cohort or reflects a distinct pathophysiologic entity is unclear. Compared to outpatients with a comparable degree of cardiac dysfunction, hospitalized patients have significantly worse outcomes.[71,72] Despite an improved understanding of the pathophysiology and prognosis of patients with AHF, treatment remains primarily targeted at short-term decongestion using diuretics, and to a much lesser degree, vasodilators. Multiple Phase III clinical trials failed to show clear improvement in symptoms, survival or rehospitalization rates.[60,73–79]

Although intravenous nitroglycerin is commonly used in AHF, there are no large randomized trials evaluating its impact on long-term outcomes.[80] A recent study of low-dose dopamine and low-dose nesiritide in patients with AHF and renal dysfunction showed no impact on renal function or clinical outcomes for either agent compared to placebo.[81] In the DOSE trial, there were no significant differences in dyspnea improvement or worsening renal function between intermittent bolus or infusion of furosemide. Higher dose diuretic regimens demonstrated a nonsignificant improvement in dyspnea, and slightly higher risk of

worsening renal function, when compared to the low-dose strategy.[81] None of these studies assessed the cost-effectiveness of care and very few enrolled AHF patients in the ED.

4. Disposition Decision making – can a subset of ED patients be sent home?

The ED is increasingly being relied on to evaluate more complex patients, some of whom previously were directly admitted from an outpatient setting.[82] As a result, emergency physicians serve as major decision makers for approximately half of all US inpatient admissions for AHF.[83] However, this may present challenges as emergency physicians have a low tolerance of 'risk' in relation to ED discharge decisions. For AHF, a less than 0.5% risk of 30-day death or serious nonfatal complication (acute myocardial infarction, reperfusion therapy, respiratory failure or cardiopulmonary resuscitation) has been suggested as an emergency physician's typical threshold for ED discharge, a proportion most likely lower than for cardiologists or primary care providers.[84] Collaborative decision making coupled with capacity for close follow-up may safely change the dominant flow of patients from the ED to the inpatient setting.

Compounded by a lack of disposition recommendations from national guidelines, the absence of validated decision tools identifying patients with limited susceptibility to post-discharge events[12,85], and high rates of relapse and mortality after an ED discharge,[86,87] such risk intolerance leads to admission for more than 80% of patients treated in the ED for AHF. Consensus guidelines have addressed AHF risk stratification, but provide little objective instruction for ED disposition decision-making[26] or base recommendations on disparate studies of isolated predictors.[25,88]

Prediction of Low Risk

There have been many investigations of high-risk physiologic markers in ED patients with AHF (Table 6), but most were retrospective, involved hospitalized patients, lacked a measurement of additive value to clinical assessment, and did not use a rigorous AHF diagnostic standard.[89,90] These limitations notwithstanding, renal dysfunction, low blood pressure, low serum sodium, and elevated cardiac biomarkers (troponin or NP) have been consistently associated with an increased risk of morbidity and mortality.[91] As the majority of patients are already admitted to the hospital, characterizing AHF clinical profiles safe for either ED discharge, or discharge after a brief period of treatment and observation, would be of even greater utility. Unfortunately, risk-prediction instruments in AHF have been largely unsuccessful when attempting to define a cohort of patients safe for early discharge and at low-risk of 30-day mortality and readmission.[92,93] More importantly, risk tools have not been implemented in the ED to determine how they augment, or detract from, clinician judgment. As a result, published tools have had little impact on ED disposition decision making. Those patients with high-risk features or significant comorbidities need, and often benefit from, inpatient admission. However, up to 50% of hospital admissions may not be necessary and should be the focus of future research.[94,95]

Previous studies have defined 30-day AHF readmission rates of 15–20% and mortality rates of less than 1% as "low-risk" characteristics in ED patients.[84,95–98] A rule derived and validated in two separate AHF datasets identified a subset of 19.2% of patients who would be considered low-risk for 30-day morbidity and mortality.[10,99] However, its additive value on top of clinical judgment has yet to be prospectively tested. An evaluation of four AHF prediction rules suggests they would have limited utility to help emergency providers identify patients safe for discharge.[100]

In a Canadian study of over 12,000 patients, a prediction rule for 7-day mortality was derived and validated. Their model (Table 7) suggests several ED variables can be used to categorize patients at low-risk of 7-day mortality. However, this study had several limitations including retrospective patient identification, excluding early readmission for AHF as an outcome in the model, a lack of prospective testing compared to clinician judgment, and a practice environment not reflective of the United States.[88]

Current Challenges in ED Disposition Decisions

What remains elusive from the ED standpoint is defining who, despite a reassuring clinical profile, is at risk for early readmission, cardiovascular events, or death after discharge home. Compared to a group with worsening renal and cardiac biomarker profiles, as well as an increased risk of 180-day mortality, those with more reassuring biomarker profiles and a decreased risk of mortality unfortunately have a similar risk for readmission.[56,101]

Multidimensional criteria, such as McKesson Interqual[102] or Milliman Care Guidelines,[103] are widely used by hospital utilization management to guide and justify level of care (e.g discharge, observation, inpatient floor, or ICU). Their purpose is to help healthcare organizations assess the clinical appropriateness and safety of patient services across the continuum of care, whether prospectively, concurrently, or retrospectively. While they may serve as a useful tool for real-time risk stratification of AHF patients, the small amount of evidence evaluating the accuracy of such criteria in determining appropriate ED disposition for AHF suggests they are limited.[104]

Among patients stable for discharge, early follow-up is critical and has been associated [105] with a decreased risk of readmission. Collaborative post discharge follow-up involving cardiology and primary care has also been associated with better guideline adherence and lower mortality.[106] Further, disease management programs providing close monitoring and follow-up have lowered readmission rates.[107] Connecting low-risk patients to these programs represents an opportunity that should be systematically evaluated. Unfortunately, assurance of follow-up post-ED care is challenging and even the best risk prediction tool may not be able to influence physician or patient behavior and facilitate discharge after initial management in the ED.[8,84]

Beyond Physiologic Risk Predictors

Social, behavioral, and environmental factors strongly influence one's ability to implement the lifestyle changes required to optimally manage a chronic illness.[108,109] Furthermore, patient self-care, and implementing strategies to overcome barriers to successful self-care, are associated with optimal outpatient management and reduced readmissions.[110–114]

Unfortunately, emergency physicians have largely avoided the complex social, environmental, and behavioral aspects of chronic HF care. Attempts to address these issues in the ED are often thwarted by the lack of the necessary resources or time. Factors unrelated to acute treatment (e.g. health literacy and numeracy, disease knowledge, symptom monitoring, transportation) result in patients being admitted for further management of AHF, despite objective evidence of stability. Combining future risk prediction instruments with clinicians' judgment as well as obtaining and addressing patients' self-care barriers may provide the tools necessary to change physicians' practice patterns.[85]

Recommendations

To augment clinical judgment when making disposition decisions, we suggest ED patients with AHF be divided into 3 broad categories (Figure 1). Those at high-risk for mortality or serious adverse events should be admitted to the hospital, with an ICU admission needed in those who require invasive monitoring, ventilator support or other ICU level treatment. Those without high-risk features should be further risk-stratified based on active comorbidities, response to initial therapy, and their ability to manage their illness as an outpatient. Those with active comorbidities or significant self-care barriers may be better suited for inpatient management. Those without active comorbidities who have an incomplete response to initial therapy may be ideal candidates for an observation unit (OU). Candidates for ED discharge are those with adequate response to ED therapy and no high-risk markers, significant comorbidities, or self-care barriers.

5. Observation Units and Observation Services- their role in ED Patients with AHF

The pathway from ED to inpatient for AHF patients may not be the best use of resources, as relatively few require intensive acute care, mechanical ventilation, mechanical or pharmacologic circulatory support, or undergo invasive diagnostic or therapeutic interventions.[115,116] The majority of AHF patients require intravenous diuresis in a monitored setting until symptoms subjectively improve. These patients, especially if they do not require a prolonged hospital stay, may best be ideal candidates for observation services.

Observation Services

Observation is a billing status indicating a patient is still an outpatient, although they may be receiving care in a hospital or ED-based setting. The rules governing observation status, as generated by the Center for Medicare and Medicaid Services (CMS) and generally followed by private payers, have undergone many changes since their inception in the 1990s. However, CMS has been consistent in that observation services should not span more than 48 hours, and generally should necessitate 24 hours or less. Despite this, the mean length of stay for adult general medical patients in observation status is 41.1 hours, with 26% of stays lasting greater than 48 hours.[117]

Observation status is independent of the actual location of care delivery. The most common, and likely least efficient approach involves intermixing observation patients amongst the

general medical population. [118] While this approach requires the least in terms of infrastructure and resources, it frequently results in lengths of stay beyond the typical 24 to 48 hours. Generally, patients appropriate for observation care will be less ill; they will require less intensive monitoring than higher acuity inpatients on the same service or hospital unit. A more efficient model is to geographically cluster observation patients in a unit that is designed explicitly to deliver care to the short stay population by inpatient specialists,[119] hospitalists,[120,121] or emergency providers (representing 56% of all dedicated OUs).[118] This placement may facilitated the goals of providing frequent reassessment, adjustment of treatment needs based on response to therapy, and ready access to adjunctive diagnostic studies so the decision to discharge or admit the patient can be made within 24 hours of presentation.

AHF and Observation Care

Many patients with AHF may be ideal for management in an observation setting. Frequent reassessment, diuresis, afterload reduction, and targeted patient education can be accomplished in a relatively short time. In consultation with cardiology or primary care providers, outpatient medication regimens can be adjusted, and where available, patients can be linked with specialty HF programs upon discharge. While prospective, randomized, controlled trials evaluating this strategy are lacking, preliminary evidence suggests AHF patients managed in an OU setting have similar outcomes and improved resource utilization compared to a risk-matched group of admitted patients.[122,123]

The Society for Cardiovascular Patient Care (formerly the Society of Chest Pain Centers) published evidence- and consensus-based guidelines for patient selection and management in the observation setting,[124] which were later externally validated in an independent data set (Table 8).[95] However, the evidence base behind such recommendations is still not robust. As suggested previously, the absence of high risk does not equate to being low risk. Therefore, it may be easier to define who is not appropriate for short stay / OU care. In addition to those measures in Table 7, patients requiring acute critical care measures such as aggressive titration of parenteral vasoactive medications or ongoing non-invasive positive pressure ventilation (NIPPV) after initial stabilization are candidates for a critical care unit, not an OU. Patients with minimally elevated troponin levels may still be candidates for observation management, especially if serial troponin measurements are followed to exclude ACS. However, patients with a mildly elevated troponin are at increased risk for “failing” observation care and requiring inpatient management.[97] Likewise, patients with complex psychosocial needs, such as end stage HF or lack of social support necessitating consideration of skilled nursing facility (SNF) placement, frequently need inpatient resources. Conversely, simpler social barriers, such as medication availability, lack of follow up care, or patient education may be addressed in an observation setting.

6. Unanswered Questions and Future Research Agenda

While the need to alter the current course of research related to AHF is widely recognized, there is a lack of clarity on the specifics of a new agenda. [54] For new therapies, does lack of clinical trial success reflect an absence of drug efficacy, suboptimal study design, or both? Indeed many trials may appear unsuccessful due to the heterogeneous nature of the AHF

population. Targeting therapy to more specific patient characteristics and avoidance of a one-size-fits all approach is an important alternative to explore. However, it is unclear what agents are best for a given phenotypic variant and precisely when they should be administered during the course of treatment. Evolving data suggest that early interruption of acute pathophysiology may be a critical consideration, but it can take time for certain perturbations to manifest, and intervention before adequate information has been obtained may increase the potential for therapeutic misalignment. The hypothesis that early treatment with effective novel agents may limit organ damage and improve outcomes has gained momentum in recent years but study of this concept is just beginning.[56,63,101,125]

In addition to therapeutic considerations, there is a need to better define clinically meaningful end-points of acute intervention. Dyspnea resolution remains the most common goal of treatment and is undoubtedly an important patient-centric outcome, but its subjective nature has made standardization challenging. Moreover, dyspnea correlates poorly with in-hospital worsening HF and post-discharge events (e.g., readmission and mortality) making it difficult to rely on as the sole measure of improvement.[126–129] Maneuvers that illicit cardiac stress through provocation with position change (i.e., seated to supine) or physical exertion (i.e., walk-tests) may help delineate more subtle effects of AHF on dyspnea and thus serve as more definitive measures of clinical improvement, but have yet to be tested in prospective trials.[130] Further, other HF symptoms, such as fatigue and body swelling, may be as meaningful as dyspnea to patients and important patient-centered endpoints to explore.[131] The assessment of frailty, especially in older patients, has also recently evolved as an important marker of risk and prognosis and may become a routine part of the pre-discharge “bundle”.[132]

Testing Novel Approaches to Therapeutic Decision-Making

To address such unanswered questions and help shape the future research agenda for AHF, new approaches to therapeutic decision-making must be developed. To better understand potential confounders and identify the ideal target population, therapeutic trials are increasingly looking towards timing of intervention and targeted phenotypic groups. Understanding the ED has an active role in the initial management and disposition of AHF patients, many of these trials have focused on inclusion of emergency physicians, both as part of trial design and as principal investigators. Highly successful for acute myocardial infarction trials, such a collaborative approach offers promise for early patient identification and more comprehensive recruitment.

While commonly available parameters such as blood pressure and measures of renal function and myocardial injury are currently used to define patient subgroups, there is growing interest in the utility of biomarkers to enhance phenotypic granularity. Although inclusion and exclusion criteria often consider biomarker profiles, targeting a specific therapy to one biomarker has yet to be implemented in a large-scale study. Trials aimed at administration of a specific drug to a biomarker which identifies patients most likely to benefit are under consideration. Quite unique, this approach would represent a further departure from the one-size-fits-all methodology and facilitate truly tailored therapy. Lastly, the use of implantable hemodynamic monitors to assess intracardiac filling pressures and

guide outpatient therapy may reduce the burden of AHF on the department, but require more study.[133]

Testing Novel Approaches to Disposition Decision-Making

With increasing pressure to avoid unnecessary hospitalizations, there is tremendous interest in improving upon the process of patient disposition. While much research has focused on risk stratification for AHF patients with development of pathways for disposition based on presence or absence of clearly defined variables, little attention has been directed towards the determination of when sufficient cardiac unloading has occurred. Improvement in dyspnea is typically used to demonstrate treatment effectiveness, but there is often no uniform means to determine this beyond patient self-report, making it difficult to quantify differences from one patient to another. As noted above, novel implantable hemodynamic monitors or non-invasive hemodynamic tools may allow clinicians to assess change in filling pressures and optimize timing of discharge and early follow-up.[134]

Basing disposition on the absence of dyspnea post-provocation would be a novel approach to help ensure symptoms have fully resolved. Studies to test this endpoint are clearly needed. However, even after several days of in-hospital treatment, residual dyspnea is common[129] and additional measures to evaluate the effect of treatment on myocardial stress would be beneficial. Although NP levels are strongly associated with cardiac dysfunction, studies of NP guided management have yielded mixed results.[9,135] Other biomarkers may be useful for this purpose but to date, none have been clearly identified. Finally, alternative endpoints should be explored. Total days alive out of the hospital, or total hospital days, over a 30-day period, may be more useful than 30-day readmission rates when evaluating the impact of a novel diagnostic or therapeutic investigation on AHF care.

Conclusions

With the rising prevalence of HF and the ED serving as the primary entry point for the majority of AHF admissions, emergency providers will continue to play a critical role in AHF management. Early AHF treatment has begun to evolve from largely a diuretic-only strategy to one that also considers blood pressure management as part of the initial approach. Clinical trials must be conducted in the ED in order to improve the evidence base and drive optimal initial therapy for AHF. Should ongoing and future studies suggest early phenotype-driven therapy improves in-hospital and post-discharge outcomes, ED treatment decisions will need to evolve accordingly. The potential impact of future studies which incorporate risk-stratification into ED disposition decisions cannot be underestimated. Predictive instruments that identify a cohort of patients safe for ED discharge, while simultaneously addressing barriers to successful outpatient management, has the potential to significantly impact quality of life and resource expenditures.

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Highlights

- ED treatment of AHF has evolved from a diuretic only strategy to one that considers early use of vasodilators
- ED AHF management lacks a strong evidence base
- Ongoing and future clinical trial collaborations between ED and heart failure physicians should be conducted in the ED to improve this evidence base

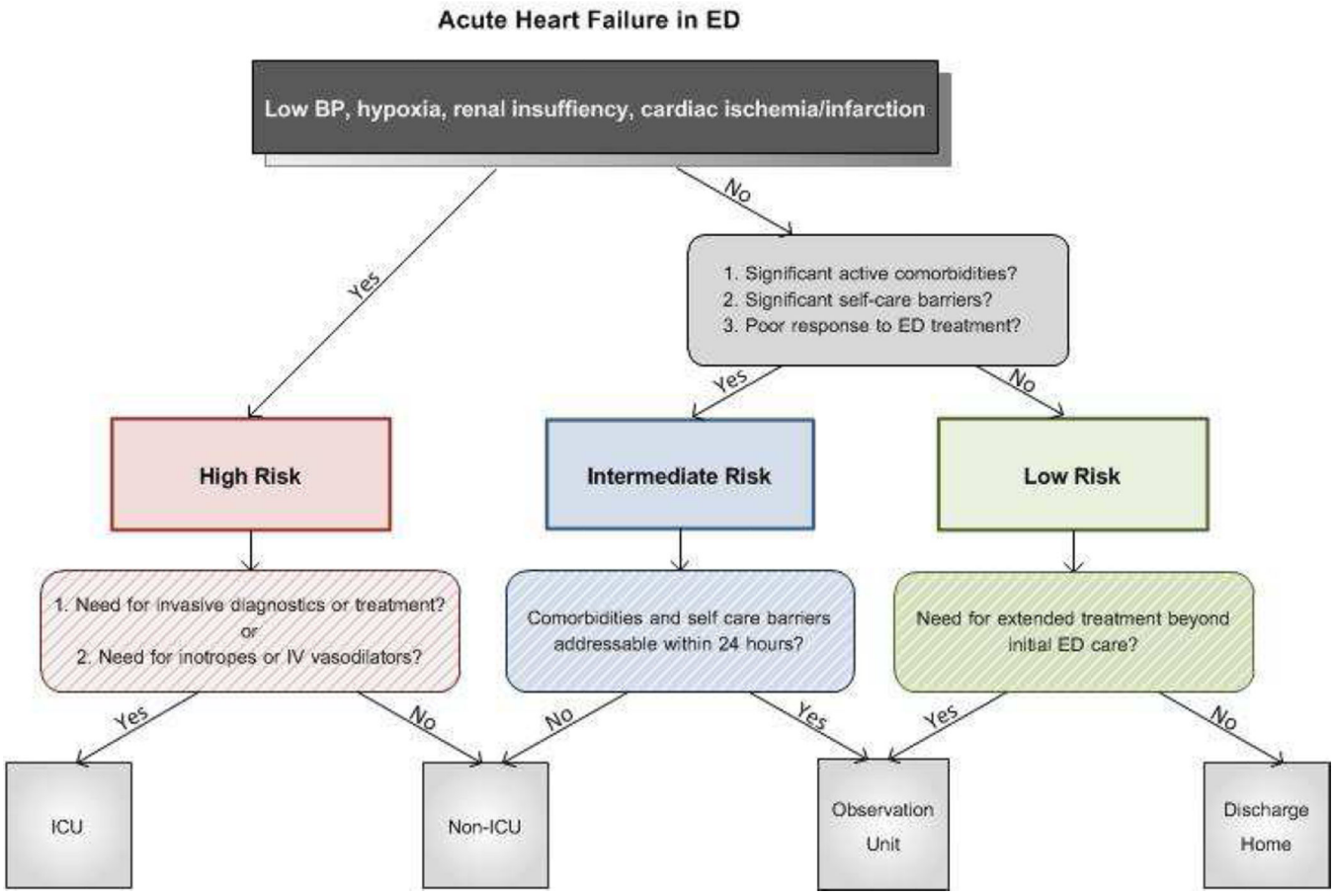

Figure 1.

A conceptual model of AHF risk stratification in the ED based upon known predictors of risk for mortality or serious adverse events, presence of absence of comorbidities, and self-care issues. Such an algorithm may augment clinical judgment in disposition decisions.

Table 1

Summary of Diagnostic Accuracy of Findings on Chest Radiograph and Electrocardiogram for AHF in ED Patients presenting with Dyspnea

Finding		Pooled		Summary LR (95% CI)	
		Sensitivity	Specificity	Positive	Negative
Chest Radiograph	Pulm Venous Congestion	0.54	0.96	12.0 (6.8–21.0)	0.48 (0.28–0.83)
	Interstitial Edema	0.34	0.97	12.0 (5.2–27.0)	0.68 (0.54–0.85)
	Alveolar edema	0.06	0.99	6.0 (2.2–16.0)	0.95 (0.93–0.97)
	Cardiomegaly	0.74	0.78	3.3 (2.4–4.7)	0.33 (0.23–0.48)
	Pleural Effusion	0.26	0.92	3.2 (2.4–4.3)	0.81 (0.77–0.85)
	Any edema	0.70	0.77	3.1 (0.60–16.0)	0.38 (0.11–1.3)
	Pneumonia	0.04	0.92	0.50 (0.29–0.87)	1.0 (1.0–1.1)
	Hyperinflation	0.03	0.92	0.38 (0.20–0.69)	1.1 (1.0–1.1)
Electrocardiogram	Atrial fibrillation	0.26	0.93	3.8 (1.7–8.8)	0.79 (0.65–0.96)
	New T-wave changes	0.24	0.92	3.0 (1.7–5.3)	0.83 (0.74–0.92)
	Any abnormal finding	0.50	0.78	2.2 (1.6–3.1)	0.64 (0.47–0.88)
	ST elevation	0.05	0.97	1.8 (0.80–4.0)	0.96 (0.95–1.0)
	ST depression	0.11	0.94	1.7 (0.97–2.9)	0.95 (0.90–1.0)

LR=Likelihood Ratio CI=Confidence Interval Pulm=Pulmonary

Adapted from: Wang CS, Fitzgerald JM, Schulzer M, Mak E, Ayas NT. Does This Dyspneic Patient in the Emergency Department Have Congestive HF? JAMA. 2005;294:1944–1956.

Table 2

Factors affecting Natriuretic Peptide Levels

	Renal Insufficiency	Age	BMI	Pulmonary Embolism/ Pulmonary Hypertension	Ejection Fraction	Female Gender	Non-white Race
BNP	↑↑[136]	↑[29]	↓[137,138]	↑[139,140]	↓[141]	-Or ↑[29,141]	↓Or - Or ↑[29,142]
NT-proBNP	↑↑[143]	↑↑[144,145]	↓[146,147]	↑[148–151]	↓[152]	- Or ↑[144]	↓[153,154]

Table 3

Synopsis of recommended AHF therapies based on ESC, HFSA and ACCF/AHA, and CCS guidelines.

RECOMMENDATION	ESC	HFSA	ACCF/AHA	CCS
Diuretic Use				
• AHF patients with fluid overload should receive diuretics	I/B	B	I/B	SR/MQ
• Dosing	IV, to symptom improvement, Consider high dose regimen. No specific recommendation (NSR)	IV, Titrate to symptom relief, minimize AE (C)	Initial IV dose should equal or exceed oral daily dose, then adjust based on response (I/B)	We recommend a loop diuretic, such as furosemide, for most patients with HF and congestive symptoms. When acute congestion is cleared, the lowest dose should be used that is compatible with stable signs and symptoms (SR/LQ).
• Inadequate Diuresis	Consider doubling loop diuretic (NSR) Consider add thiazide Consider dopamine @ 2.5 mcg/kg/min (NSR)	Increase dose (C) Continuous infusion (C) Add thiazide (C)	Add thiazide (IIa/B) Increase loop dose (IIa/B) Consider renal dose dopamine (IIb/B)	Increases in loop diuretics, cautious addition of a second diuretic (a thiazide or low dose metolazone) (WR/MQ).
Ultrafiltration	Consider in refractory cases (NSR)	Refractory cases (C) In lieu of diuretics-selected pts (C)	In refractory cases of overload (IIb/B) Pulmonary congestion (IIb/C)	Patients with persistent congestion despite diuretic therapy, with or without impaired renal function, may, under experienced supervision, receive continuous venovenous ultrafiltration. (Practical tip)
Vasodilators, Other Pharmacologic Therapy				Titrated to systolic BP (SBP) > 100 mm Hg, for relief of dyspnea in hemodynamically stable patients (SBP > 100 mm Hg)
• Nitrates	In pulmonary congestion and SBP>110 mmHg (IIa/B) caution in Aortic/Mitral Stenosis	+ diuretic and no hypotension (B)	+ diuretic therapy (IIb/A)	SR/MQ
• Nesiritide	NSR	After first line therapy(C)	+ diuretic therapy (IIb/A)	WR/HQ
• Vasopressin Antagonist	NSR	NSR	Severe volume overload and Na <135 (IIb/B)	symptomatic or severe hyponatremia (< 130 mmol/L) and persistent congestion despite standard therapy, to correct hyponatremia and the related symptoms (WR/MQ).
• Opiates +/− antiemetic	IIa/C	NSR	NSR	NSR
Fluid restriction	NSR	<2L/d if Na<130 mEq/L; stricter if <125	1.5–2 L/d esp in Na<135 and congestion (IIa/C)	NSR

RECOMMENDATION	ESC	HFSA	ACCF/AHA	CCS
Diuretic Use				
		mEq/L (C)		
Thromboembolism Prophylaxis	I/A	If no contraindication (B)	UFH, LMWH (I/B)	NSR
Respiratory Support				
• Oxygen	If SaO2<90% (I/C)	If hypoxia (C)	NSR	If hypoxia; titrated to an SaO2>90% (SR/MQ)
• NIV	For RR>20, caution in SBP<85 mmHg (IIa/B)	In severe dyspnea (A)	NSR	We recommend CPAP or BIPAP not be used routinely (SR/MQ)
Inotropic Support	SBP<85 mmHg or hypoperfusion (IIa/C)	In selected hypotensive pt (C)	In **short** term support of selected pts (IIb/B)	We recommend hemodynamically stable patients do not routinely receive inotropes like dobutamine, dopamine, or milrinone (SR/HQ).

NSR= no specific recommendation; SR/LQ= Strong Recommendation, Low-Quality Evidence; WR/MQ= Weak Recommendation, Moderate-Quality Evidence; SR/MQ= Strong Recommendation, Moderate- Quality Evidence; SR/HQ= Strong Recommendation, High-Quality Evidence; WR/HQ= Weak Recommendation, High-Quality Evidence

Table 4

Randomized Diagnostic and Phase III Therapeutic AHF Studies over the past 10 years.

Study/Author	Year/ Sample Size	Primary Endpoint	Findings	Limitations
Diagnostic Studies				
BASEL Mueller	2004 (n=452)	Time to discharge and cost of treatment	Time to discharge and costs of treatment were reduced in patients with undifferentiated dyspnea who were randomized to rapid, bedside BNP testing	Conducted in Europe- median LOS and healthcare systems much different than US
IMPROVE-CHF Moe	2007 (n=500)	ED LOS and total direct medical costs of treatment	ED LOS and cost of treatment were reduced with addition of NT-proBNP to clinical gestalt for patients with undifferentiated dyspnea	Conducted in Canada which has different healthcare cost structure than US
REDHOT II Singer	2009 (n=447)	Hospital LOS	No statistical difference in length of stay with serial BNP testing	Convenience sample; potentially underpowered
Therapeutic Studies				
SURVIVE Mebazaa	2007 (n=1327)	All cause mortality at 180 days	No difference in mortality in patients requiring inotrope therapy with randomization to levosidemendan or dobutamine	Conducted in Europe with a drug (levosimendan) that was never FDA approved in the US. Bolus hypotension may have been a significant contributor to adverse events
EVEREST Gheorghiade	2007 (n=4133)	Composite of global clinical status and body weight at day 7	Compared to placebo tolvaptan had significantly greater improvement in the composite	The composite endpoint was largely driven by changes in body weight
VERITAS McMurray	2007 (n=1435)	Change in dyspnea over 24 hours and incidence of death or WHF at day 7	No significant difference in dyspnea or death/WHF between tezosentan and standard therapy	
3CPO Gray	2008 (n=1069)	Death or intubation within 7 days	No difference in mortality with NIPPV versus standard oxygen therapy or either end-point with use of CPAP versus BiPAP	Open label study with extensive crossover to NIPPV in patients randomized to standard oxygen therapy
PROTECT Massie	2010 (n=2033)	Overall treatment success defined as early dyspnea improvement and no death, HF readmission or WRF	No significant difference between Rolofylline and placebo	

Study/Author	Year/ Sample Size	Primary Endpoint	Findings	Limitations
ASCEND O'Connor	2011 (n=7141)	Dyspnea and rehospitalization/death within 30 days	Prespecified dyspnea endpoint not met; no differences in death between nesiritide and standard care	Patients enrolled long after ED stay; significantly greater proportion with hypotension in nesiritide group
DOSE-AHF Felker	2011 (n=308)	Dyspnea and WRF at 72 hours	No significant difference between bolus/drip or high/low dose furosemide	Patients randomized up to 24 hours after ED presentation; population largely white males with low EF, Not powered for longer term outcomes
RELAX-AHF-1 Teerlink	2013 (n=1161)	Improvement in dyspnea measured by both Likert and VAS at day 5	Significant improvement in VAS by serelaxin compared to placebo	No difference in Likert between serelaxin and placebo; clinical meaning of VAS difference unclear
ROSE-AHF Chen	2013 (n=360)	72-hour urine volume and change in Cystatin-C	No difference between low-dose dopamine or low-dose nesiritide compared to placebo in either endpoint	Not powered for longer term outcomes
REVIVE II Packer	2013 (n=600)	Clinical composite of ‘improved’, ‘unchanged’ or ‘worse’ at 6hrs, 24 hrs, and 5 days	More improvement in levosimendan treated patients with less worsening. However, more hypotension and arrhythmias were observed with a numerically higher number of deaths	Bolus hypotension may have been a significant contributor to adverse events
PRONTO Peacock	2014 (n=104)	Targeted BP control in first 30 minutes of intravenous vasodilator	Clevidipine provided more rapid BP control compared to standard therapy	Open label study, more BP overshoot in clevidipine arm, efficacy was monitored only to 12 hours, not powered for longer term outcomes

WRF=worsening renal function; WHF= worsening heart failure; LOS= length of stay; BP = blood pressure; EF=ejection fraction; ED = emergency department

Table 5

Associated clinical characteristics and treatment approaches based on ED presentation phenotype.

ED Presentation Phenotype	Clinical Characteristics	Treatment
Low BP (SBP < 100)	▪ Known/suspected low LVEF ▪ Likely CAD and CRI	▪ Diuretics (+ + +) ▪ [notropes/Pressors (+ +) ▪ Mechanical support (+)
Normal BP (SBP 100 – 140)	▪ Sub acute symptoms ▪ Preserved or reduced LVEF ▪ Dietary/medical indiscretion	▪ Diuretics (++) ▪ IV Vasodilators (+) ▪ Topical Nitrates (++)
High BP (SBP > 140)	▪ History of HTN ▪ Abrupt symptom onset ▪ Flash pulmonary edema ▪ Multiple non-CV comorbidities	▪ Topical/SL Nitrates (+ +) ▪ Diuretics (+) ▪ IV Vasodilators (+ + +) ▪ NIV

+ = Relative intensity of use; NIV = non-invasive ventilation; HTN = hypertension; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; CRI = chronic renal insufficiency; SL=sublingual; BP=blood pressure

Table 6

Selected and recent AHF risk-stratification studies determining events within 30-days or less of index ED presentation.

First Author Year	Study Type*	N	Predicted Outcome	Variables In Final Model
Lassus[155] 2013	I,P	441–4,450 (pooled analysis, total n varied by biomarker evaluated)	30-day and 1-year mortality	ST2, MR-proADM, CRP, NT-proBNP, BNP, MR-proANP in addition to clinical model (age, gender, blood pressure on admission, estimated glomerular filtration rate <60 mL/min/1.73 m2, sodium and hemoglobin levels, and heart rate)
Stiell[156] 2013	E, P	559	30-day death and 14-day serious non-fatal events	h/o TIA/CVA, Vital signs, ECG and lab findings
Lee[88] 2012	E, R	12,591	7-day mortality	HR, creatinine, BP, O2 sat, Tn, cancer, home metolazone, EMS transport
Peterson[157] 2010	I, R	39,783	In-hospital mortality	Age, SBP, BUN, HR, Na, COPD, nonblack race
Fonarow[158] 2008	I, R	5,791	In-hospital mortality, 60 –90 day mortality or rehospitalization	Pneumonia, cardiac ischemia, worsening renal function
Hsieh[10] 2008	I, R	8,384	Inpatient mortality or serious medical complications, 30-day mortality	pH, pulse, renal function, WBC, glucose, sodium
Abraham[159] 2008	I, R	48,612	In-hospital mortality	Age, HR, SBP, Na, creatinine, HF as primary cause for admission, LVSD
Rohde[160] 2006	I, P	779	In-hospital mortality	Cancer, SBP, creatinine, BUN, Na, age
Diercks[97] 2006	E, P	499	Stay <24 hours in observation and no 30-day adverse cardiac events	Tn, Systolic BP
Auble[99] 2005	R	33,533	Inpatient mortality or serious medical complications, 30-day mortality and AHF readmission	pH, pulse, renal function, WBC, glucose, sodium
Fonarow[161] 2005	I, R	65,275	In-hospital mortality	BUN, Systolic BP, Creatinine

* I = inpatient, E = emergency department patients, R = retrospective, P = prospective BUN= blood urea nitrogen, WBC= white blood cell count, BP= blood pressure, TIA= transient ischemic attack, HR= heart rate, COPD= chronic obstructive pulmonary disease, LVSD= center ventricular systolic dysfunction, CVA= cerebrovascular accident, Tn= troponin, BNP= b-type natriuretic peptide, CRP= C-reactive protein, ANP= atrial natriuretic peptide

Table 7

Components of the Emergency HF Mortality Risk Grade (calculation available online at www.annals.org).[88]

◆ Age	◆ Creatinine
◆ Transported by EMS	◆ Potassium
◆ Systolic blood pressure	◆ Cardiac troponin
◆ Heart rate	◆ Active cancer
◆ Oxygen saturation (lowest initial/triage)	◆ Metolazone at home

Table 8

Recommendations for appropriate candidates for an OU Stay.[98]

Clinical Features of Patients Considered for Observation Management		
	Recommended	**Suggested**
Blood pressure	SBP > 100 mmHg	SBP > 120 mmHG
Respiratory rate	< 32 breaths/min	NR
Renal function	BUN < 40 mg/dl	NR
	Creatinine < 3.0 mg/dl	NR
ACS	No ischemic changes or elevated troponin	NR
Natriuretic peptides	NR	BNP<1000; NT-proBNP<5000

NR = no recommendation