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The Role of the Emergency Department in Acute Heart Failure Clinical Trials – Enriching Patient Identification and Enrollment

Sean P. Collins, MD, MSc,

Department of Emergency Medicine Vanderbilt University Nashville, TN

Phillip D. Levy, MD, MPH,

Department of Emergency Medicine and Cardiovascular Research Institute Wayne State University Detroit, MI

Peter S. Pang, MD, and

Department of Emergency Medicine Northwestern University Feinberg School of Medicine Center for Cardiovascular Innovation Institute for Public Health and Medicine Chicago, IL

Mihai Gheorghiade, MD

Center for Cardiovascular Innovation Northwestern University Feinberg School of Medicine Chicago, IL

Abstract

Nearly 800,000 of the one million patients hospitalized with acute heart failure (AHF) every year are initially treated by emergency physicians. Signs and symptoms are typically most severe at initial presentation but, with timely diagnostic and therapeutic management, rapid improvement can be achieved. As a direct result, emergency physicians set the tone for initial AHF management. They dictate early treatment decisions, determine whether patients are admitted or discharged, and if admitted, what the appropriate initial level of care should be (i.e. observation, telemetry, ICU status). Despite this key role, the ED phase of management is often overlooked in AHF research and clinical trials. Consequently, present understanding of AHF patients early in their course is poor and phenotypic characterization has been limited. As a result, the proportion of AHF patients eligible for a given therapeutic intervention is not well known. Moreover, because the traditional approach to AHF clinical trials has relied on cardiology-based research teams to identify patients up to 24 hours after ED presentation, patients admitted to non-cardiology services are often missed and those that are captured tend to be enrolled long after initial therapy has improved acute symptoms. This has resulted in low enrollment HF clinical trials, which has been approximated at 0.41 patients/site/month. We describe the landscape of initial ED management, explain how this may confound clinical trial results, and provide a multi-dimensional template for successful ED/cardiology collaboration aimed at improving patient enrollment and the conduct of AHF clinical trials in the United States.

Introduction

A 65-year old male presents to the emergency department (ED) with complaints of progressive shortness of breath for the previous 3 days. He has a history of coronary artery

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disease and heart failure. He has missed several days of outpatient therapy including his anti-hypertensive medications and furosemide. His presenting blood pressure is 160/92, pulse 95, respiratory rate 16 and oxygen saturation is 88% on room air. On exam he has jugular venous distension, pulmonary rales and lower extremity edema. Diagnostic testing reveals stable mild renal dysfunction, a non-ischemic electrocardiogram, a troponin below the lower limit of detection, and congestion on chest radiograph. He receives sublingual followed by topical nitroglycerin, which brings his blood pressure down to 130/74. He also receives a dose of furosemide which results in 500 cc of urine output in the subsequent hour. His respiratory rate decreases, oxygen saturation improves and he is admitted to the hospital for further management.

Background

This scenario is commonplace in EDs across the United States. The ED is the predominant entry point for patients hospitalized with acute heart failure (AHF), accounting for nearly 800,000 of the one million patients hospitalized with AHF annually.¹ Signs and symptoms are typically most severe at the time of initial presentation, with expeditious management leading to substantial symptom reduction in most patients. This has also been associated with improved outcomes.^{2,3} As a direct result, emergency physicians set the tone for initial AHF management. They dictate early therapeutic decisions, determine whether patients are to be admitted or discharged, and if admitted, what the appropriate initial level of inpatient care should be (i.e. observation, telemetry, ICU status). Despite this key role, the ED phase of management is often overlooked in research and clinical trials. Thus, an in-depth understanding of patients at the time of ED presentation and the impact of ED management is not well characterized.⁴

AHF patients are heterogeneous in terms of etiology, precipitant, co-morbidities, and the extent and severity of presenting signs and symptoms.⁵ While a majority have worsening symptoms that develop over hours to days, have elevated blood pressure and are volume overloaded, less than 20% are admitted to the ICU, and few (~4%) require mechanical ventilation or circulatory support for cardiogenic shock.⁶⁻⁹ The majority of patients are admitted to the hospital for further symptom control, but rarely undergo invasive diagnostic testing or therapy. Because most patients don't require intensive care and respond to "routine" therapy, many are admitted to hospitalists and other non-cardiology services.¹⁰ Those patients who have complicated presentations such as hypotension, cardiorenal syndrome or coronary ischemia, are more likely to be admitted to a cardiologist. The initial presentation, along with complicating comorbidities, high post-discharge event rates, and a lack of easy risk-stratification tools, have resulted in the current practice of most emergency physicians: inpatient admission.

While emergency physicians commonly serve as the primary decision maker regarding admission, who determines inpatient management is less predictable, as patients are likely to be distributed throughout the hospital, under the care of internists, hospitalists and cardiologists. Furthermore, there are differences in admission patterns between tertiary academic centers and community hospitals.¹¹ Compared to inpatient settings, the ED represents a high-yield place to identify eligible, symptomatic patients for enrollment in AHF trials early in their treatment course. The traditional approach to AHF clinical trials, where inpatient-based research teams identify patients 24 or more hours after ED presentation, may not capture patients admitted to non-cardiology services, and increases the likelihood patients will be enrolled long after initial therapy has improved the truly acute symptoms. Bypassing ED screening for clinical trials results in many missed opportunities for enrollment. (**Table 1**) For example, it is possible in the ED to enroll a patient with AHF and no apparent ACS on the basis of a normal initial troponin. With later screening, the

same patient may be excluded when, despite limited clinical suspicion of a coronary event, repeat biomarker assessment reveals a troponin above the reference limit.

Failure to account for the ED phase of management has been proposed as one potential contributor to lack of success seen in AHF trials to date.¹² Regardless of when the patient is randomized, initial standard therapy for AHF patients in both “arms” of the study starts upon ED presentation. Nationwide, ED lengths of stay average approximately 4-6 hours.¹³ During this time, AHF patients undergo a myriad of diagnostic tests and receive urgent therapies to alleviate their symptoms. Thus, the ED phase of management represents a window of opportunity to intervene when evaluable end-points such as dyspnea are maximal, and a potential to demonstrate relative efficacy still exists.² Several retrospective analyses suggest that timing of intervention may be an important determinant of outcomes in AHF^{3,14,15} and early management is consistently associated with a greater clinical improvement.^{2,16-18} Whether or not an ED-based intervention would dramatically change post-discharge outcomes remains a controversial but intriguing hypothesis.

Initial Emergency Department Management

Patients present with chief complaints, signs and symptoms and not a diagnosis. After a diagnosis is made, often contemporaneously with treatment, a disposition decision is made. How each patient travels from ED presentation through to their disposition decision is critically important as it determines their initial diagnostic studies, treatment modalities and ultimately, their disposition and level of care (hospital, observation unit, home). This “ED journey” can introduce many confounders that should be considered when conducting clinical trials in ED patients with AHF. (Table II) These confounders are described in greater detail below.

Diagnosis

Diagnostic, prognostic and ancillary testing may significantly impact a patient's clinical trial eligibility. For instance, patients who receive intravenous contrast dye as part of their initial work-up for a computed tomography scan when pulmonary embolism is considered, may be deemed ineligible. Or a patient with a low natriuretic peptide (NP), but clear clinical AHF may be excluded. A significant subset of patients may ultimately have AHF, but the final diagnosis may have been achieved more circuitously. There is a balance between highly selective enrollment of specific ED patients who fulfill strict inclusion criteria (restrictive trial design) and inclusion of less well-defined ED patients with AHF who are more representative of common presentations (pragmatic ‘real-world’ trial design).

Treatment

With the exception of the patient who requires immediate resuscitation, initial ED management focuses on symptom relief. Patients who present in extremis from acute pulmonary edema or hypertensive crises represent a minority of AHF patients, but require intensive initial therapy. The emergency physician may use a combination of non-invasive ventilation (NIV), intravenous nitrate therapy, and intravenous diuretics to prevent intubation, control blood pressure and improve symptoms.⁴ These patients are rarely included in clinical trials both because they are difficult to consent at initial presentation and their symptoms improve significantly with conventional therapy. Exception from informed consent would be a means of enrolling such patients in future clinical trials. Ironically, while these patients look gravely ill upon presentation, their symptoms improve dramatically, and they often spend less time in the hospital and have better post-discharge event rates than those patients with a more indolent initial presentation.¹⁹

Once stabilized, ED treatment focuses on three major management goals: 1) further resolution of congestion; 2) identification of precipitants and 3) avoidance of downstream consequences of therapy. The two main physiologic targets are optimization of hemodynamics, with blood pressure control as a surrogate in the ED setting, and decongestion.⁴ Initial treatment is dominated by IV diuretics, with vasodilator therapy underutilized. The possibility of confounding as a result of multiple medications being administered is minimized by early ED identification and enrollment.

Triage/Risk Assessment

Risk assessment occurs in *two steps* in ED patients with dyspnea, though practitioners may not be explicitly aware. The *first step* occurs upon initial assessment. While the minority of patients present in cardiogenic shock, they are in need of immediate stabilization, and require inpatient admission.^{6,7} Once stabilized, patients are reassessed in a *second step* based on their concomitant work-up which includes an electrocardiogram, chest x-ray and comprehensive laboratory testing.²⁰ Those patients with complicating comorbidities or markers of high-risk such as an elevated troponin, renal dysfunction, or hyponatremia, are admitted to the hospital. Patients without markers of high-risk, an adequate response to initial therapy, and a readily identifiable cause of decompensation (e.g. medication or dietary nonadherence, elevated blood pressure) are at lower risk and considered for observation unit (OU) management, or rarely, discharged home from the ED. Readily available prediction rules to identify the low-risk patient with AHF have not received widespread acceptance; thus most patients are admitted, where further treatment, risk-stratification and education occur. This stepwise approach could influence patient identification and eligibility for clinical trials. Those patients where AHF was not initially considered in the differential diagnosis may have diagnostic and prognostic testing (NP, Troponin) delayed until much later in their ED stay. This results in a delay in or lack of ED enrollment.

An Unmet Need: Screening for AHF Clinical Trials in the ED

Low enrollment in North America (NA), specifically the US, has been encountered in several recent large-scale AHF clinical trials.^{18,21,22} Detailed analysis suggests patients enrolled at low-enrolling centers, such as those in NA, have different profiles and event rates compared to high-enrolling centers.²³ There have been several hypotheses raised as to why this difference is encountered, but missed ED opportunities, resulting in later enrollment of patients with more advanced HF could be one explanation. Those patients enrolled in the US who remain symptomatic 24-36 hours after ED therapy may represent a unique patient population that has a significantly different clinical picture and outcome profile when compared to those enrolled in early in Eastern Europe. ASCEND is an example where patients were enrolled long after ED management.¹⁸ The enrollment window was up to 24 hours after ED treatment, resulting in a median time to enrollment of over 15 hours from hospital admission. This is long after ED management, when multiple therapies have been administered, and may reflect enrollment of patients with refractory symptoms, not those patients who remained symptomatic after initial ED treatment. A table highlighting the timing of enrollment, ED involvement and overall enrollment rates for large AHF clinical trials in the last decade are highlighted in **Table III**. Enrollment in several large-scale clinical trials was approximately 0.41 patients/site/month.²⁴ Capturing ED patients in the US may not only increase overall clinical trial enrollment, it may provide an opportunity to retain a unique cohort of patients who remain symptomatic 6-12 hours after initial therapy, yet are also able to complete the trial protocol.

In the ED, one can establish the diagnosis, identify precipitating and amplifying factors, as well as underlying cardiac abnormalities. The main issue in clinical trials in this patient population is not related to lack of patients but rather the fact that patients may not have

been characterized in detail, including their early diagnostic work-up and treatment. The ED largely serves as the denominator for clinical trials, as the majority of patients receive their initial management in the ED prior to inpatient admission. The ability to screen for and enroll subjects in the ED has long been considered an impediment to early therapeutic trials. *Albeit in a limited fashion*, only recently have ED patients been enrolled in AHF clinical trials. A small number of patients in the RELAX-AHF trial were enrolled in EDs in the US, and a recently completed small trial by EM investigators enrolled all patients within 3 hours of ED presentation.^{21,25} The ED is often viewed as a place that is simply too busy and too ill equipped with high-quality research personnel to sift through patients with varying presenting complaints and identify the ideal individual who meets the specific inclusion and exclusion criteria for a given study. Without guidance from ED investigators to assist with navigation of the ED landscape and clinical trial enrollment, prior studies have experienced a limited ability to capture patients early in their presentation.

However, as we have now seen with the completion of a number of successful randomized trials focused on early treatment for critically ill patients, including those with time sensitive conditions such as severe sepsis, cardiac arrest, myocardial infarction and acute stroke, inability to enroll patients early is a misperception, with a wealth of evidence refuting this position. Adopting a collaborative approach to recruitment that takes into account specific, systems-based needs for infrastructure development is crucial. As demonstrated by federally funded entities like the Neurologic Emergency Treatment Trials (NETT) Network, the Research Outcomes Consortium (ROC) and the Pediatric Emergency Care Applied Research Network (PECARN), attention to the latter can yield an unequivocal return on investment and help ensure that eligible subjects are effectively (and accurately) recruited early in their course.²⁶⁻³⁰

Unlike stroke or cardiac arrest, the presence of AHF may be difficult to delineate within minutes of patient arrival and deciphering the precise cause of dyspnea, its primary symptom, can require diagnostic testing that may delay the diagnosis in some patients. Moreover, little is known about the acute phase of heart failure where ill-defined precipitating factors are layered upon underlying cardiac dysfunction resulting in a state of decompensation. While these considerations make it challenging to align therapy with a specific, intervenable target in the early phase of management, with dedicated resources they are not insurmountable. In fact, the ability to achieve this on a multicenter level in the US has been shown in trials such as Pre-RELAX-AHF, and STAT-PRONTO where subjects were randomized at a median of 6.6 [IQR 4.0-13.4] and 2.5 hours from ED presentation, respectively, and RELAX-AHF where mean time to randomization was 7.9 hours.^{21,25,31} Moreover, ED enrollment, when symptoms such as dyspnea are maximal, may be important when attempting to safely improve this endpoint. An unmet need in ED trials in AHF is the safe, consistent and complete improvement in patient-reported dyspnea.

Enhancing Early Identification

Though early intervention in stroke or myocardial infarction has been unequivocally shown to improve outcomes, the same cannot be said for AHF. A linkage between upstream therapy and downstream consequences in AHF is highly plausible, and registry data suggest the importance of rapid diagnosis and treatment.^{3,15} However, more extensive investigation is needed. The evolution of AHF clinical trials is similar to that of ED trials of patients with acute coronary syndromes (ACS). Early trials of ST-segment elevation myocardial infarction (STEMI) were conducted in the coronary care unit. However, as the “time is muscle” paradigm became better understood, the research infrastructure necessary to rapidly identify, consent and randomize patients in the ED was developed. Similarly, in the door-to-balloon era, in many systems, the catheterization lab is mobilized based on prehospital

identification of STEMI. Of primary importance, early patient recruitment must be inclusive (rather than superimposed) with a collaborative partnership between ED and other HF investigators. This ensures engagement of essential stakeholders. Further, dedicated research personnel who work directly in the ED are required.

Not surprisingly, the ED is a rich environment for accrual of patients across the spectrum of human illness and, to create economies of scale, research personnel are often shared by a group of primary investigators (PIs). However, to be successful in AHF trial enrollment, the study team needs to have a good understanding of the ED approach and management of AHF. While education regarding successful clinical trial strategies is crucial, this comes with a cost of funding to provide the expertise, infrastructure and oversight necessary to facilitate early, ED enrollment. Partial or complete support of an AHF research coordinator, especially one whose job is not contingent on per patient enrollment fees, may be the optimal solution to ensure maximum quality and quantity of patient enrollment. Ideally, the coordinator would be employed by the ED research team, but this person could be a shared entity between both the ED and inpatient research teams. **Table IV** highlights this and other models of AHF research in the ED, along with a brief outline of potential approaches to funding. These approaches increase the opportunities for extramural support (perhaps as part of a formal research network).

While infrastructure is necessary for the development of a research foundation, it alone is insufficient to ensure success. Traditionally, federal funding pays for fixed resources to fund trials that target a set number of patients. Conversely, industry has reimbursed investigators on a per-patient basis to enroll subjects in clinical trials. Avoiding considerable up-front payment for very few patients is a primary concern in federal funding models. However, industry-funding models may not provide enough infrastructure to maintain a steady stream of patients for identification and enrollment. Both models have advantages and disadvantages and we propose a hybrid model which supports a fixed amount of infrastructure, while simultaneously providing limited reimbursement on a per-patient basis.

The *process* of subject identification is thus equally (if not more) important and, in many ways, represents the practical underpinnings that contribute to trial performance. A number of methods can be used to screen for patients. An open-ended approach involving one or more of the following may be best:

1. Use of dedicated personnel physically present in the ED seeking eligible patients. This affords the opportunity to identify patients very early in their treatment and witness firsthand baseline symptom severity. Downsides include personnel costs, which can be diminished using volunteers or distributing the screening personnel over several studies, and convenience sampling, which can be overcome by providing around the clock coverage. However, because of the decreased number of patients who present during off-hours, it may not be economical to staff the ED 24 hours per day with study assistants. While not ideal, patients who present in the middle of the night may still be within the enrollment window when study personnel begin screening patients early the following morning.
2. Direct referral from clinical staff. While highly specific, this method is dependent on caregivers contacting the research team. Given the current case load experienced by most EDs, this “goodwill” will miss many cases.
3. Admission log review. While comprehensive and accurate, this approach does not allow for real-time patient identification and precludes the ability to capture patients prior to administration of potentially confounding therapies.

4. Remote electronic medical record screening, where the research team culls through patients based on documented chief complaint or admitting diagnosis visible on a patient tracking board. This method reduces the need for personnel to be situated in the ED but adds a time delay to patient evaluation. Further, to truly catch the early phase of management, it requires decision making based on limited information available on the ED tracking board.
5. Automated alerts, where the research team receives a page, text or email message based on a symptom, diagnosis or other trigger. While such an approach (especially automated paging and text messaging) works well for trauma, stroke, sepsis or STEMI care where treatment is often initiated by an on-call team activation for very specific clinical presentations, AHF is not managed this way. On the other hand, virtually every patient with AHF receives intravenous diuretics and most have NP levels measured. When entered through an electronic medical record, such orders could serve as a prompt for automated email message alerts to be sent directly to the research coordinator. Downsides include the potential for false positive alerts and, to avoid convenience sampling, the need for extensive on-call coverage.

Collection of simple registry data prior to trial initiation can facilitate a true understanding of the baseline population. This avoids the situation where a center signs up to do a trial of novel inotropes despite the majority of patients having preserved EF. By doing so, research groups can avoid futile resource outlays and direct screening efforts to those projects where success is more likely.

Future AHF Studies: Individualizing Therapy in Clinical Trial Patients in the ED

As we continue to better align AHF treatment with presenting precipitants (medication non-adherence, arrhythmia, uncontrolled hypertension) and comorbidities (chronic kidney disease, coronary artery disease) we may further categorize and parse patients for AHF studies based on this. Given the heterogeneity of AHF presentations, and the relative lack of success of Phase III trials using traditional enrollment criteria, future studies may opt to target subgroup populations with specific therapies, or require even larger trials.

Acute precipitants and contributing comorbidities, when readily identified, present an ideal opportunity for early randomization and enrollment in the ED. For example, patients with uncontrolled hypertension would be targeted with intravenous vasodilators, aimed at minimizing diuretic use. Those who have both acute and chronic renal disease could be targeted with novel venodilators or ultrafiltration. The key to these approaches is reaching the patient early in their course, when the precipitant or comorbidity acutely contributes to AHF symptoms. Within 12-24 hours, differences between patients may decrease secondary to treatment, and patients may resemble their chronic HF state with mildly increased acute symptoms. We hypothesize that trials seeking to target acute precipitants and significant comorbidities at the time of ED presentation will have greater impact compared with later enrollment.

Similarly, objective data may lead to targeting of specific pathophysiology. Lung water can be quantified using bedside ultrasound and could be used as an objective target for novel pharmacologic and mechanical means of removing fluid.³² Laboratory results (estimated glomerular filtration rate, serum sodium) and biomarkers (natriuretic peptides) could be used to target patients more (or less) likely to respond to specific interventions such as vasodilation and aquaresis.

Conclusion

The ED is the portal of entry for the majority of patients admitted with AHF, and emergency physicians screen many patients who may be eligible for clinical trials. As a direct result, the emergency physician sets the tone for initial management strategies and determines a patient's disposition. Enrollment in several large-scale clinical trials averaged 0.41 patients/site/month. Screening for AHF clinical trial patients in the ED is an opportunity to improve on this disappointing trend. Several factors must be considered when determining the optimal method for ED screening and enrollment, and prior experience with ED clinical trials is crucial for success. Finally, different clinical profiles of ED patients (i.e. hypertensive, normotensive, hypotensive) may require tailored management strategies, and should be considered in future trial design.³³ Going forward, patient response to initial therapy should be included as an important consideration when designing studies.³⁴ The role of the ED in the early management of AHF remains an important area for further inquiry.³⁵

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References

1. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med.* 2003; 4(Suppl 7):S21–30. [PubMed: 14668697]
2. Mebazaa A, Pang PS, Tavares M, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. *European heart journal.* 2010; 31:832–41. [PubMed: 19906690]
3. Maisel AS, Peacock WF, McMullin N, et al. Timing of immunoreactive B-type natriuretic peptide levels and treatment delay in acute decompensated heart failure: an ADHERE (Acute Decompensated Heart Failure National Registry) analysis. *Journal of the American College of Cardiology.* 2008; 52:534–40. [PubMed: 18687247]
4. Weintraub NL, Collins SP, Pang PS, et al. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. *Circulation.* 2010; 122:1975–96. [PubMed: 20937981]
5. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA.* 2005; 294:1944–56. [PubMed: 16234501]
6. Fonarow GC, Abraham WT, Albert NM, et al. Day of admission and clinical outcomes for patients hospitalized for heart failure: findings from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). *Circ Heart Fail.* 2008; 1:50–7. [PubMed: 19808270]
7. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *Journal of the American College of Cardiology.* 2007; 50:768–77. [PubMed: 17707182]
8. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *Journal of the American College of Cardiology.* 2006; 47:76–84. [PubMed: 16386668]
9. Committee, ASA. Scios, I., editor. Acute Decompensated Heart Failure National Registry(ADHERE®) Core Module Q1 2006 Final Cumulative National Benchmark Report.. 2006.

10. Amin A. Who is managing acute decompensated heart failure? The need for a multidisciplinary approach. *J Hosp Med*. 2008; 3:S1–6. [PubMed: 19084889]
11. Roytman MM, Thomas SM, Jiang CS. Comparison of practice patterns of hospitalists and community physicians in the care of patients with congestive heart failure. *J Hosp Med*. 2008; 3:35–41. [PubMed: 18257099]
12. Felker GM, Pang PS, Adams KF, et al. Clinical trials of pharmacological therapies in acute heart failure syndromes: lessons learned and directions forward. *Circ Heart Fail*. 2010; 3:314–25. [PubMed: 20233993]
13. Storrow, AB.; Jenkins, C.; Collins, SP., et al. Emergency Department Disposition and Charges for Heart Failure: Regional Variability. Society for Academic Emergency Medicine; Chicago, IL: 2012. 2012
14. Peacock, Wf.; Fonarow, GC.; Emerman, CL.; Mills, RM.; Wynne, J. Impact of early initiation of intravenous therapy for acute decompensated heart failure on outcomes in ADHERE. *Cardiology*. 2007; 107:44–51. [PubMed: 16741357]
15. Peacock WF, Emerman C, Costanzo MR, Diercks DB, Lopatin M, Fonarow GC. Early vasoactive drugs improve heart failure outcomes. *Congest Heart Fail*. 2009; 15:256–64. [PubMed: 19925503]
16. Pang PS, Gheorghiade M, DiHu J, et al. Effects of tolvaptan on physician-assessed symptoms and signs in patients hospitalized with acute heart failure syndromes: analysis from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) trials. *American heart journal*. 2011; 161:1067–72. [PubMed: 21641352]
17. Pang PS, Konstam MA, Krasa HB, et al. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. *European heart journal*. 2009; 30:2233–40. [PubMed: 19561338]
18. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *The New England journal of medicine*. 2011; 365:32–43. [PubMed: 21732835]
19. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006; 296:2217–26. [PubMed: 17090768]
20. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *Journal of cardiac failure*. 2010; 16:e1–194. [PubMed: 20610207]
21. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet*. 2012
22. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA*. 2004; 291:1963–71. [PubMed: 15113814]
23. Butler J, Subacius H, Vaduganathan M, et al. Relationship Between Clinical Trial Site Enrollment With Participant Characteristics, Protocol Completion, and Outcomes: Insights From the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) Trial. *Journal of the American College of Cardiology*. 2012
24. Gheorghiade M, Vaduganathan M, Greene SJ, et al. Site selection in global clinical trials in patients hospitalized for heart failure: perceived problems and potential solutions. *Heart failure reviews*. 2012
25. Peacock, WF.; Chandra, A.; Collins, SP.; Fonarow, G.; Garrison, NA.; Mebazaa, A. Clevidipine Improves Dyspnea in Emergency Department Acute Heart Failure: A Randomized, Open Label Study. American Heart Association; Los Angeles, CA: 2012. 2012
26. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *The New England journal of medicine*. 2012; 366:591–600. [PubMed: 22335736]
27. Aufderheide TP, Nichol G, Rea TD, et al. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *The New England journal of medicine*. 2011; 365:798–806. [PubMed: 21879897]
28. Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet*. 2009; 374:1160–70. [PubMed: 19758692]

29. Idris AH, Guffey D, Aufderheide TP, et al. Relationship between chest compression rates and outcomes from cardiac arrest. *Circulation*. 2012; 125:3004–12. [PubMed: 22623717]
30. Corneli HM, Zorc JJ, Mahajan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *The New England journal of medicine*. 2007; 357:331–9. [PubMed: 17652648]
31. Teerlink JR, Metra M, Felker GM, et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet*. 2009; 373:1429–39. [PubMed: 19329178]
32. Picano E, Frassi F, Agricola E, Gligorova S, Gargani L, Mottola G. Ultrasound lung comets: a clinically useful sign of extravascular lung water. *J Am Soc Echocardiogr*. 2006; 19:356–63. [PubMed: 16500505]
33. Collins S, Storrow AB, Kirk JD, Pang PS, Diercks DB, Gheorghiade M. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. *Annals of emergency medicine*. 2008; 51:45–57. [PubMed: 17868954]
34. Collins SP, Lindsell CJ, Pang PS, et al. Bayesian adaptive trial design in acute heart failure syndromes: Moving beyond the mega trial. *American heart journal*. 2012; 164:138–45. [PubMed: 22877798]
35. Peacock WF, Braunwald E, Abraham W, et al. National Heart, Lung, and Blood Institute working group on emergency department management of acute heart failure: research challenges and opportunities. *Journal of the American College of Cardiology*. 2010; 56:343–51. [PubMed: 20650354]

Table I
Missed Opportunities for AHF Enrollment

Opportunities to Enroll ED Patients in AHF Clinical Trials that may be missed using the Traditional Model of Enrollment within 24 hours

Type of Patient	Seen in the ED?	Seen in the Hospital?
Acute Pulmonary Edema	++	-
Hypertensive Urgency/Emergency	+++	+
Enroll prior to 2 nd dose of diuretic	+++	+
Enroll Prior to Troponin elevation	++	+
Enroll Prior to Creatinine Increase	++	+

ED = Emergency Department;

Table II

Impact of ED Evaluation, Treatment, and Disposition Decisions on Clinical Trial Enrollment

Item	Confounding	Strategy to Overcome
ED Diagnostics	1)Testing may delay diagnosis 2)Patients with a clinical diagnosis of AHF may not fulfill trial criteria	1)Liberal enrollment criteria 2)Pragmatic study design
ED Therapeutics	1)Treatment for concurrent illnesses 2)AHF Therapy prior to randomization	1)More selective criteria to select a more homogeneous patient 2)-Exception from informed consent - Early identification and enrollment
ED Disposition Decisions	1) Perceived disease severity dictates disposition decisions, yet may not match actual disease severity	1) Avoid enrollment of low-risk patients by using known markers of risk

Table III**AHF Clinical Trials: Timing of Enrollment**

Trial And Intervention	Year	Number of patients	When was patient enrolled?	Targeted ED Enrollment in NA?
VERITAS Tezosentan v Placebo	2005	1448 (1760) [*]	After admission	No
OPTIME-CHF Milrinone v Placebo	2002	951	After admission	No
VMAC Nesiritide v Nitrates v Placebo	2002	489	After admission	No
EVEREST Tolvaptan v Placebo	2007	Trial A = 2048, Trial B = 2085	After admission	No
SURVIVE Levosimendan v Dobutamine	2007	1327	After admission	No
REVIVE-II Levosimendan v Placebo	2005	600	After admission	No
ASCEND-HF Nesiritide vs Placebo	2011	7141	Enrolled within 24 hours of first IV therapy for AHF	Minimal
PROTECT Rolofylline vs Placebo	2010	2033	Within 24 hours after admission for AHF hospitalization	No
RELAX-AHF Relaxin vs Placebo	2012	1161	Randomized within 16 hours of presentation for AHF	Yes- enrolled 25% of patients in US

The n listed is the planned enrolment.

#NA = North America

^{*} VERITAS was discontinued before full enrolment due to improbability of achieving significant treatment effect.

Table IV

Research models, their targets and advantages and disadvantages.

Research Model	Potential Funding	Pros	Cons
Convenience sampling	Industry derived revenue	1)Simplest time commitment 2) Lower personnel costs	1)Selection bias 2)Spectrum bias
Clinical trials center (shared resources)	1)Industry derived revenue 2)Internal support 3)Extramural funding	1)Economies of scale 2)Broadened coverage 3)Cost sharing	1) Lack of familiarity with study protocol 2) Concurrent trials may pull personnel away from HF studies
Dedicated heart failure team	1)Industry derived revenue 2)Internal support 3)Extramural funding	1)Highly knowledgeable, focused staff 2)Experience with protocol 3)Point person for regulatory aspects	1)Expensive with need for upfront funding 2)May disincentivize productivity