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Bayesian Adaptive Trial Design in Acute Heart Failure Syndromes: Moving Beyond the Mega Trial:

Collins - Adaptive Trials in Acute Heart Failure

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Abstract

Over the last two decades, early treatment for patients presenting with acute heart failure syndromes (AHFS) has changed very little. Despite strikingly different underlying disease pathophysiology, presenting signs and symptoms, and precipitants of AHFS, the vast majority of patients are treated in a homogeneous manner with intravenous loop diuretics. In-hospital studies of new therapies have produced disappointingly neutral results at best. Patients continue to be enrolled in trials long after initial therapy, at a time when vital signs have improved, symptoms have changed, and initiating pathophysiologic processes, such as myocardial and renal injury, have already begun. The ‘one-size-fits-all’ approach to in-hospital AHFS trials have been recognized as one potential contributor to the disappointing trial results seen to date.

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Studies designed to tailor the therapeutic approach to ascertain which treatment modalities are most effective depending on patient phenotypes have not been previously conducted in AHFS because this objective is not traditional in clinical trial design. Utilizing Bayesian adaptive designs in trials of early AHFS provides an opportunity to personalize therapy within the constraints of clinical research. Bayesian adaptive design is increasingly recognized as an efficient method for obtaining valid clinical trial results. At its core, this approach uses existing information at the time of trial initiation, combined with data accumulating during the trial, to identify treatments most beneficial for specific patient subgroups. Based on accumulating evidence, the study then “adapts” its focus to critical differences between treatments within patient subgroups. Bayesian adaptive design is ideally suited for investigating complex, heterogeneous conditions such as AHFS and affords investigators the ability to study multiple treatment approaches and therapies in multiple patient phenotypes within a single trial, while maintaining a reasonable overall sample size. Identifying specific treatment approaches that safely improve symptoms and facilitate early discharge in patients who traditionally are admitted, often for prolonged periods of time, are necessary if we aim to reverse the disappointing trend in clinical trial results. In this paper, AHFS clinical researchers and biostatisticians with expertise and experience in designing “personalized medicine” trials describe the development of a Bayesian adaptive design for an emergency department-based AHFS trial.

Keywords

Bayesian Adaptive Trials; Heart Failure

Introduction

Over the last twenty years, the early treatment for patients presenting with acute heart failure syndromes (AHFS) remains largely unchanged. Despite substantial patient differences in underlying disease pathophysiology, co-morbid illnesses, presenting signs and symptoms, and precipitants of AHFS, the vast majority of patients are treated in a homogeneous manner with intravenous loop diuretics.¹⁻⁴ Clinical trials of new therapeutic approaches have produced disappointingly neutral results at best (**Table 1**). Early AHFS studies, which aim to study therapies targeted at treatment during the initial presentation, enroll patients up to 24 hours after emergency department (ED) presentation. Allowing a day or more of standard treatment before randomization may dilute the effects of experimental therapy.⁵ As a result of late enrollment, many studies that were designed to be early trials have been conducted as in-patient trials. Not only are patients enrolled long after initial therapy, when the majority of candidates for randomization have experienced significant dyspnea improvement,⁶ treatment approaches tend to be homogeneous. This is despite significant heterogeneity in the underlying substrate and pathophysiology, such as myocardial and renal injury. Theoretically, early intervention with therapy that is targeted to the patient phenotype may interrupt these pathophysiologic processes to a sufficient degree to influence downstream outcomes. Indeed results from two recent therapeutic trials support this, as patients enrolled early appeared to have greater improvements in symptoms than those who were enrolled later.^{7,8}

Similar to the evolution of trials in myocardial infarction and acute stroke, newer AHFS clinical trials have begun to enroll patients earlier in the course of their acute presentation, and both emergency physicians and heart failure cardiologists have recognized the need for collaboration to create the opportunity for early patient enrollment.^{5,9} However, early AHFS studies that attempt to tailor the therapeutic approach by ascertaining which treatment approaches are most effective for specific patient phenotypes remain elusive, primarily due to the limitations of traditional clinical trial design. In a Bayesian adaptive trial with multiple

treatment arms, an arm performing poorly for patients with a certain profile could be down selected or closed relatively early so that future patients with the same profile could be randomized to one of the alternate arms. Combining a Bayesian adaptive trial design methodology with trial enrollment in the ED (during acute symptoms) would provide greater opportunity for an ultimately successful early trial in AHFS patients.

Bayesian Adaptive Clinical Trial Design

Suppose you could observe every patient's assigned therapy and its outcome in a clinical trial and that you have the ability to change the way in which patients are assigned to therapy. In the trial you see that a particular therapy is performing poorly for patients in a particular subgroup, perhaps a subgroup of AHFS patients with hypertension. You might worry that the observation was a fluke and so continue to use the therapy, although perhaps lowering its probability of being assigned to such patients. Suppose you continue to see poor performance in this subgroup of hypertensive patients, but the therapy's performance is acceptable in other patients. You might reasonably decide to drop the therapy from being assigned to those in the subgroup of non-responders. Similarly, you might determine another therapy has done very well in hypertensive patients and so stop randomizing those patients altogether.

Such a scenario would not be acceptable to any researchers. The overarching problem is you cannot make legitimate inferences about therapeutic effects. In particular, you could not calculate the trial's type I error rate. Now suppose that you develop a prospective algorithm that will make the decisions you would want to make in the actual trial if you were guiding it. You can evaluate the operating characteristics of the algorithm by applying it to thousands of simulated trials using previously accrued clinical trial data, with patient assignments and stopping rules depending on the accumulating data in the ongoing clinical trial. You might even adjust the algorithm to control type I error, for example. This is a standard approach for building efficient clinical trials and evaluating their operating characteristics.

A traditional 1:1 randomized controlled trial comparing treatment and control usually addresses a single treatment effect question. The traditional frequentist statistical approach is to carry out a single analysis at the end of the trial with the unit of inference being the entire trial. Bayesian measures can be calculated at any time during the trial.¹⁰ These measures include the probabilities that an experimental treatment arm is better than a control for various subtypes of patients and the probability that a follow-on trial of a particular design will show a treatment benefit in a particular patient population. Bayesian measures use all information available at the time of the calculation. The units of inference include subsets of patients and even individual patients. Regardless of what measures are being used to make decisions during the trial, traditional frequentist measures of type I error rate and power can be calculated for any prospective design, with simulations based on previous trial data being necessary for complicated designs.

An adaptive trial design uses accumulating data obtained while the trial is ongoing to modify its course. Traditional two-armed trials have an adaptive component in that they allow for early stopping when efficacy or futility have been clearly established—so called group-sequential designs.¹¹ The most common types of adaptations in Bayesian adaptive clinical trials are (i) stopping early, (ii) stopping late, that is, extending accrual, to enable a stronger conclusion of superiority or futility, (iii) adaptively assigning doses to efficiently assess dose–response, (iv) dropping arms or doses, (v) seamless phases of drug development within a single trial, (vi) modifying the randomization proportions assigned to the various arms, (vii) adaptively identifying a responding subpopulation, (viii) adding arms or doses,

and (ix) changing accrual rate. There is some overlap in these types of adaptations and some trials use more than one of them. Indeed, it is possible for a single trial to include all of them. A principal focus of this article is a version of (vii), identifying which of several therapies is appropriate for which subtypes of patients.

Bayesian adaptive clinical trial design is increasingly recognized as an efficient method for obtaining valid clinical trial results. There is a published guidance available from the FDA's *Center for Devices and Radiological Health*.^{12,13} A draft guidance from FDA's Center for Drug Evaluation and Research and Center for Biologic Evaluation and Research concerning adaptive designs is not specific to Bayesian adaptive design.^{10,14,15} Based on accumulating evidence, the study then “adapts” the assignment of patient subgroups to specific treatment arms. Adaptive trial design thus allows the randomization scheme to vary and evolve, so patients likely to benefit from a particular treatment are more likely to be randomized to that treatment group. Conversely, treatments found to be ineffective can be dropped from a study, either globally or just for a specific patient phenotype, and alternatives can be added as the trial is ongoing. As such, Bayesian adaptive design addresses a longstanding ethical dilemma when traditional trial design is employed: if there is no longer equipoise about whether an experimental treatment arm is beneficial, investigators should no longer continue to expose patients to this therapy. When following an adaptive design, as evidence accumulates about harm or benefit, enrollment into an experimental arm can decrease or increase, respectively. This not only exposes fewer patients to ineffective therapy, it minimizes the number of patients enrolled and it accelerates the dissemination of critical information to the medical community.

Utility in Complex Medical Problems with a Variety of Treatment Options

Statistical conclusions are straightforward when using a classical 1:1 randomized controlled trial comparing treatment and control in a patient population assumed to be homogenous. Addressing treatment effects within subgroups of patients is possible retrospectively but subgroup analyses are notoriously dangerous.¹⁶ Confirmations within subsets and developing personalized therapeutic strategies within phenotypic groups require a long sequence of trials and a large number of participants. Bayesian adaptive design mitigates some of these limitations, and is ideally suited for investigating complex, heterogeneous conditions such as AHFS. Bayesian adaptive design affords investigators the ability to study multiple treatment approaches and therapies in multiple patient phenotypes within a single trial, while maintaining a reasonable overall sample size (**Figures 1 and 2**).^{10,17}

Hundreds of clinical trials have been designed or monitored from a Bayesian perspective for cooperative groups in oncology and neurology, and for industry in a variety of diseases.¹⁸ For example, I-SPY 2 uses Bayesian adaptive trial design to compare the efficacy of novel cancer drugs with standard chemotherapy within key biomarker signatures.^{15,17} As is typical of complicated adaptive trials, I-SPY 2 required extensive simulations to find the design's operating characteristics. The data used to generate these simulations were based on I-SPY 1, a precursor trial that was a collaboration of several federal initiatives, clinicians, biostatisticians and bioinformatics investigators.¹⁹ While the pathophysiologies of cancer and AHFS are distinctly different, the ability to target different patient “signatures” or profiles with a variety of therapeutic approaches is a commonality shared by both diseases. Despite the potential benefits of Bayesian adaptive clinical trials, there remain significant barriers to frequent adoption, including incomplete understanding of the steps required to design such a study.

What Steps are Necessary to Implement a Bayesian Adaptive Trial Design?

Designing a Bayesian adaptive trial requires extensive planning and coordination between statisticians and clinicians. As noted above, the statistician conducts comprehensive simulations to derive probabilistic models of expected clinical outcomes. The models are informed by clinical inputs. All possible combinations of outcomes are considered within the model's framework. The richer the adaptations, the more complex and varied are the outcomes that must be considered. Importantly, the process requires the study team consider all possible trial results in advance of the trial, including interim results. Because it is prospective, neither the study team nor anyone else can change the trial design when the actual data become available in the trial. But the study team can make changes at the design stage if they do not approve of the tack the design takes when confronted with simulated data. In effect, the design is an automaton that is programmed to make appropriate decisions when faced with any possible data.

In an adaptive trial, the final sample size may not be fixed in advance but may depend on the evidence accumulating in the trial. Typically, the maximum sample size is specified in advance in the protocol. The distribution of the trial sample size, its mean, for example, becomes an operating characteristic that enables comparing different designs. This distribution can depend on any assumed prior distribution or on any assumed values of the unknown parameters.

The optimum adaptive trial design depends on the underlying goals of the trial. To ensure that the trial's goals are being achieved, not only on average but also within the actual individual trial, investigators should examine a sample of simulations. It may be sufficient to examine 5 to 20 simulations from among the hundreds of thousands being generated to calculate operating characteristics. Moreover, some of these simulated trials should be included as an appendix to the protocol, at least in part to educate reviewers and IRBs as to how the design works.

Robust historical clinical data can help inform the probabilistic models in the design. The previously mentioned ISPY2 study was designed using data from another clinical trial, ISPY1, a study in which chemotherapy was administered prior to surgery and biomarkers were compared to tumor response based on MRI characteristics, pathology at the time of surgery, and clinical follow-up.^{14,17} Setting up and interpreting the simulations require extensive statistical programming and close collaboration between clinicians and statisticians to ensure the trial will achieve its goals as sufficiently as possible. Thus, data from other studies are needed to act as the foundation for the simulations necessary to set up the Bayesian adaptive trial. Further, if Bayesian adaptive trial design is implemented in a dose-finding Phase IIb trial, a transition to a larger Phase III study may be necessary.

Familiarity of Regulators, Pharmacy and Federal Agencies with Adaptive Design

The observations in a clinical trial may be more informative, either positively or negatively, than anticipated, and the interim analyses will reveal such information. This has the potential to minimize risk to participants and maximize the ethicality of the clinical trial.^{20,21} However, because of the unfamiliarity with this process, barriers to widespread adoption remain.

In part because modern adaptive designs of clinical trials are not familiar to researchers and others, they are not as readily accepted as are traditional designs. Another barrier is there is a dearth of methodologists knowledgeable enough to implement new trial designs. A third barrier is that to reap the benefits of adaptation, data flow and data management processes must be rapid. The aspects of the data that are used to guide the trial's conduct, perhaps just the primary end point information, must be kept up to date and connected with the treatment

assignment algorithm. Further, since only the maximum sample size is fixed in advance, with fewer participants than the maximum likely to be required, funding agencies and pharmaceutical companies must learn to deal with budget uncertainty. Similarly, regulatory bodies may not be fully familiar with Bayesian adaptive trial design. Experience with any innovation is necessary before it can be accepted. Preliminary guidance has been disseminated for medical device trials.¹²

The clinical research community should familiarize itself with novel approaches to clinical trials, at least as regards their existence and the range of possibilities. Such approaches attempt to maximize the relevance, information value, and efficiency of trials. However, to achieve benefits we must overcome bottlenecks such as budget uncertainty and regulatory concerns. And we must educate researchers to understand and appropriately interpret findings from such trials. In the example below we describe a process of adopting a Bayesian adaptive clinical trial methodology to address the initial treatment of patients presenting with AHFS

Application of Bayesian Adaptive Trial Design in Early AHFS Clinical Trials

First we categorize patients into subgroups (AHFS phenotypes) using readily available clinical variables. Then we use adaptive methodology to ascertain the most effective early treatment approaches for each of the subgroups. The schema accounts not only for the severity of the AHFS presentation, but also the impact of underlying comorbidities and acute precipitants. A recently proposed 6-axis model takes these variables into consideration.²² The significance of acute clinical evaluation is accounted for by examining blood pressure, heart rate and acute disease severity such as pulmonary edema or cardiogenic shock. The impact of underlying disease is captured by examining precipitants (coronary ischemia, medication nonadherence) comorbidities (renal dysfunction, concomitant pulmonary disease), and heart failure status (worsening chronic heart failure vs de novo).

In the planning phase we performed simulations to build the trial's design. These simulations were informed by data from previous studies and patient registries. The primary source is a set of complementary observational cohort studies that have collected clinical, treatment and outcome data on over 1500 patients being evaluated for AHFS, and of whom over 700 were treated for AHFS.²³ The patients in these studies are highly heterogeneous (**Table 2**). The wealth of data available allowed the generation of multiple phenotype and response profiles (i.e. subgroups or strata), although our focus will be on a parsimonious set of variables, which includes presenting blood pressure (> 160 mmHg or ≤ 160 mmHg), dyspnea severity (respiratory rate > 24 or ≤ 24 , and renal function ($>$ or ≤ 60 ml/min/1.73 m²) (**Table 3 and Figure 1**).

Our treatment will focus on a strategy of determining how to best apply standard ED therapy when considering patient phenotypes. We will use a combination of nitroglycerin (topical/sublingual, bolus or infusion) and furosemide ($0.5 \times$ daily dose [low dose], daily dose, and $2.5 \times$ daily dose [high dose]) and assign therapy to the patient subgroups (**Figure 2**). The design is an adaptive randomized partial factorial within each of the patient subgroups, and will allow us to vary treatment and determine which subgroups of patients benefit most from which therapies. The modeling and simulations conducted have identified a maximum sample size of 1000 patients. This will provide sufficient power to determine the correct therapy for each combination of AHFS patient signatures (blood pressure, dyspnea severity and renal function) as well as the 5 possible therapies. Because our primary outcome will be discharge readiness within 23 hours of ED therapy with no recidivism or mortality at 5 days after discharge, we will exclude patients at increased risk of adverse events, or those likely

to remain in the hospital despite significant improvement in AHFS signs and symptoms (**Table 4**). Our hypothesis is that specific subgroups of patients will preferentially respond to targeted therapy, facilitating early discharge. For example, preliminary data suggests patients with elevated blood pressure at ED presentation may preferentially respond to an approach which employs aggressive parenteral use of nitrates.^{24,25} While we will study how to best optimize standard ED therapy in our proposed trial, subsequent studies could dedicate specific arms of an adaptive trial to promising novel therapies.

Concurrent with development of the Bayesian adaptive design, we also are developing a structured data coordinating center (DCC). Because randomization adapts based on the occurrence of prespecified endpoints, and depends on pre-randomization data about the participants being enrolled, information about the endpoints encountered and clinical covariates must be continuously uploaded via a web-based system and validated in real-time. This is more challenging in the acute, rapid-pace setting of an early AHFS trial, where there are minutes, not days, between enrollment and treatment. Thus the randomization scheme must be tied to the data upload system so that modifications in randomization may ensue over the next several days as the primary endpoints are encountered. Then, because randomization adapts based on observations in the trial, outcomes must be uploaded and validated as soon as they are determined. The DCC serves a critical role, minimizing the lag between availability of new information and clinical action.

Conclusion

Prior AHFS trials have been disappointing. Despite significant heterogeneity suggesting that a personalized approach is necessary, clinical trials continue to study one therapy across a broad spectrum of patients. Targeting patients early, at the time of initial therapy, as well as individualizing therapy to maximize dyspnea relief and minimize myocardial and renal injury, will likely result in improved clinical outcomes. Bayesian adaptive clinical trial design is a proven, efficient approach to investigating complex, heterogeneous conditions where treatment options are broad and knowledge on how to best match therapies to individual patients is limited. This methodology requires expertise and time to prepare the randomization scheme and trial architecture. Clinicians and statisticians must work together, combining their strengths to ensure a well-organized planning period prior to patient randomization and enrollment. These collaborations have been highly successful in cancer clinical trials. Given the burden of AHFS, and the disappointing trials to date, novel approaches to improve outcomes are necessary. A Bayesian adaptive AHFS clinical trial represents an innovative and potentially paradigm-shifting method of studying personalized treatment options for AHFS.

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Figure 1.

A schematic comparison of the Bayesian AHF design which is a partial factorial design, as indicated in Figure 2.

Figure 2.

Schematic of treatment combinations of nitroglycerin and furosemide dosing and route. The open circles are potential combinations not considered in this trial. The design is an adaptive, randomized, partial factorial within each of the patient subgroups. B=bolus; I=infusion, T=topical; L=low dose; D=daily dose; H=high-dose

Table 1

Timing and location of enrollment in select recent AHFS trials

Trial	Enrollment Window	Location of Enrollment	Endpoint	Result
DOSE-AHF 2010 (continuous vs bolus diuretic) ²⁶	Within 24 hours of ED treatment	Inpatient	Co-primary: Change in creatinine and dyspnea over 72 hours	No difference in symptom relief or change in renal function
ASCEND-HF 2010 (nesiritide vs placebo) ⁸	Within 24 hours of ED treatment	Inpatient	Co-primary: Dyspnea at 6 and 24 hours & 30-day death/readmission	No significant outcome improvement over SOC
PROTECT	Within 24 hours of ED treatment	Inpatient	Trichotomous Success: improvement in dyspnea at 24 and 48 h or day of discharge, and not treatment failure. Failure: death, HF readmission or worsening HF within 7 days, or persistent renal impairment. Unchanged: neither criteria for success or failure	No significant outcome improvement over SOC
REVIVE	Within 48 hours of admission	Inpatient	Composite of improvement of clinical signs/symptoms of HF at 5 days	Excess hypotension, atrial and ventricular arrhythmias and trends towards early mortality in levosimendan
OPTIME	Within 48 hours of admission	Inpatient	Reduction in number of days hospitalized through day 60	No difference in number of days hospitalized
EVEREST 2007 (tolvaptan vs placebo) ^{27,28}	Within 48 hours of admission	Inpatient	All-cause mortality, CV death, rehospitalization, symptoms	No improvement in clinical outcomes or symptoms
SURVIVE 2007 (levosimendan vs dobutamine) ²⁹	After admission	Inpatient	Long-term survival	No improvement in survival
VERITAS 2007 (tezosentan vs placebo) ³⁰	Within 24 hours of admission	Inpatient	Co-primary: Change in dyspnea, worsening HF, & death	No improvement in symptoms or clinical outcome
VMAC 2002 (nesiritide vs nitrates vs placebo) ³¹	Within 48 hours of admission	Inpatient	Dyspnea and PCWP at 3 hours	Marginal clinical improvement in dyspnea

Table 2

Demographic and Clinical Characteristics of Patients Enrolled in STRATIFY/DECIDE

	STRATIFY*	DECIDE*
N	1503	600 - ongoing
Age	64 (20-99)	64 (22-94)
Female	44% (664)	42% (228)
Caucasian	60% (905)	55% (295)
History of hypertension	80% (1199)	83% (450)
History of coronary artery disease	52% (770)	62% (333)
History of heart failure	69% (1037)	73% (399)
ACE Inhibitor	41% (623)	43% (232)
Beta-blocker	61% (910)	65% (350)
Heart rate	87 (24-173)	88 (24-173)
Systolic blood pressure	140 (53-262)	145 (70-262)

* Values given as median and range or counts and proportions.

Table 3

Prospectively collected data available for simulations from STRATIFY and DECIDE

Category	Variables
<i>Baseline variables collected</i>	
Demographics	Age, gender, race, marital status, insurance status, time of presentation
Past medical history	Anemia, angina, cerebral vascular accident/stroke, coronary artery bypass graft surgery, cancer, liver disease, renal disease, lung disease, diabetes, heart failure, heart valve prosthesis, aortic stenosis, MR, AI, myocardial infarction, peripheral vascular disease, permanent pacemaker, percutaneous transluminal coronary angioplasty, psychiatric disease, seizure, syncope, transient ischemic attack
Past heart failure history	Number of heart failure hospitalizations in last 6 months, ejection fraction in the last year
Medication-related	Recent medication changes, self-reported medication adherence
Social history	Smoking history, employment status, cocaine use, alcohol use
ED history	Chest pain, dyspnea, fatigue, new-onset CHF, orthopnea, paroxysmal nocturnal dyspnea
ED physical examination	Altered mental status, cyanosis, diastolic blood pressure, hepatjugular reflex, jugular venous distension, murmur, oxygen saturation (and percent FI02), peripheral edema, pulse, respiratory rate S3, S4, systolic blood pressure, rales
Electrocardiography	Rate, rhythm, ST-segment deviation, T-wave inversion, left bundle branch block, right bundle branch block, pathological Q-waves, ECG diagnostic category*
Laboratory	PaO ₂ , PaCO ₂ , arterial pH, AST, ALT, b-type natriuretic peptide (BNP) levels, blood urea nitrogen, creatine kinase, CK-MB, calcium, creatinine, bilirubin (total and direct), hematocrit, hemoglobin, glucose, potassium, sodium, troponin I, white blood cell count
Radiographic	Cardiomegaly, effusion, pulmonary vascular congestion, interstitial edema, pulmonary edema, infiltrate, pneumothorax
<i>Variables collected throughout hospitalization</i>	
Physical examination	Altered mental status, cyanosis, diastolic BP, hepatjugular reflex, JVD, murmur, O ₂ saturation (and percent FI02), peripheral edema, pulse, respiratory rate, S3, S4, systolic BP, rales
Medications	Home use and dose of heart failure medications, ED and hospital AHFS medications and dose
Laboratory	PO ₂ , PCO ₂ , arterial/venous pH, AST, ALT, BNP levels, blood urea nitrogen, creatine kinase, CK-MB, calcium, creatinine, bilirubin (total and direct), hematocrit, hemoglobin, glucose, potassium, sodium, troponin, white blood cell count
Radiographic	Cardiomegaly, effusion, pulmonary vascular congestion, interstitial edema, pulmonary edema, infiltrate, pneumothorax
Other	Electronic heart sounds (S3 or S4), patient self-reported symptom improvement, urine output
<i>Outcomes assessed</i>	
	Panel of cardiologists determined: 5-day and 30-day: Death, cardiac events, intubation, CPR, defibrillation, emergent dialysis

Table 4

Inclusion and exclusion criteria for ED patients with AHFS that will be included in the proposed study.

Inclusion Criteria	Exclusion Criteria
1) ED MD diagnosis of AHFS and plan to treat for AHFS and:	1) Renal disease requiring dialysis
a. Any two of the following:	2) Systolic Blood Pressure < 100 mmHg
i. Chest radiograph consistent with AHFS (vascular / interstitial / pulmonary congestion)	3) BNP < 100 pg/ml
ii. Jugular venous distension	4) Need for immediate intubation
iii. Pulmonary rales on auscultation	5) Acute Coronary Syndrome-
iv. Lower extremity edema	6) Fever >101.5°F
v. S3 gallop	7) Chest radiograph OR clinical picture consistent with pneumonia
b. Prior history of heart failure	8) End stage HF as defined by transplant list, ventricular assist device, current or planned use of inotropic therapy
c. Home dose of diuretic identified	9) Treatment prior to randomization with more than one dose of diuretic or an intravenous vasodilator (including the ambulance)
	10) Known severe aortic stenosis
	11) Use of phosphodiesterase inhibitors
	12) Treating physician feels delay to randomization would impact care
	13) Withdrawal of consent