Heart Failure Network

Protocol
Diuretic Optimization Strategies Evaluation in Acute Heart Failure

DOSE-AHF

Compiled by:

The Heart Failure Network Research Group

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Amendment 1

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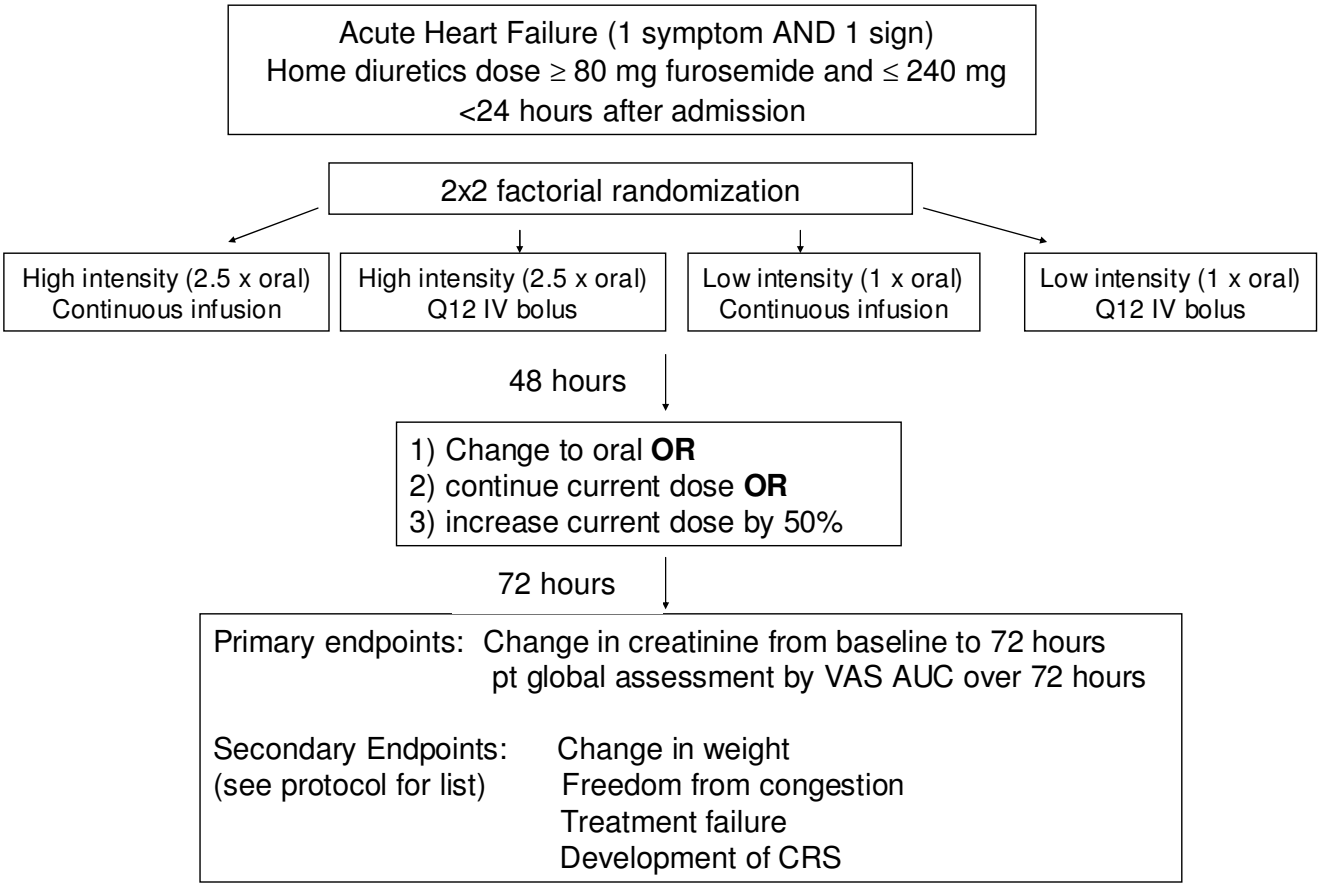
1. EXECUTIVE SUMMARY

Title:	Diuretic Optimal Strategy Evaluation in Acute Heart Failure: the DOSE-AHF study
Indication:	Acute heart failure
Location:	Regional clinical centers and associated hospitals in United States and Canada.
Rationale	Although most patients admitted with AHF receive IV furosemide treatment, little data exist to guide dosing or route of administration. Observational data suggest little relationship between dose and efficacy, and the possibility of dose related adverse effects on renal function and mortality.
Objectives:	To evaluate the safety and efficacy of • High intensification diuretic strategy vs. low intensification diuretic strategy in AHF • IV continuous infusion vs. intermittent IV bolus Q12 hours
Study Design:	300 patient randomized, controlled, multicenter clinical trial using a 2 x 2 factorial design
Treatment Regimens:	• High intensification (2.5 x oral dose) IV furosemide by Q12 hours bolus • High intensification (2.5 x oral dose) IV furosemide by continuous infusion • Low intensification (1 x oral dose) IV furosemide by Q12 hours bolus • Low intensification (1 x oral dose) IV furosemide by continuous infusion
Primary Endpoints:	**Safety:** Change in serum creatinine from randomization to 72 hours **Efficacy:** Patient global well being assessment by Visual Analog Scale (VAS) area under the curve for 72 hours
Secondary Endpoints:	• Change in weight • Freedom from congestion at 72 hours • Change in bivariate vector of creatinine and weight at 72 hours • Differences in Dyspnea VAS AUC over 24, 48 and 72 hours • Differences in PGA VAS AUC over 24 and 48 hours • Change in Creatinine at 24, 48, 96 hours, day 7 (or discharge) and 60 days • Change in Cystatin C at 72 hours, Day 7 (or discharge) and 60 days • Persistent/Worsening Heart Failure • Development of cardio-renal syndrome (CRS) • Treatment Failure • Net fluid loss over 72 hours • Time from randomization to discharge of index hospitalization • Days hospitalized for heart failure or deceased in 60 days from randomization • Changes in circulating biomarkers at 72 hours, day 7 (or discharge) and 60 days

1.1 Study Flow Chart



2. HYPOTHESES AND OBJECTIVES

2.1 Primary Hypotheses: Dose Intensification

The primary hypotheses to be tested in the "high intensification" vs. "low intensification" comparison are:

- That a low intensification strategy causes less renal dysfunction than a "high intensification strategy, as measured by change in serum creatinine from randomization to 72 hours

- That a "low intensification" strategy is more efficacious in relieving acute symptoms compared to "high intensification" strategy, as measured by the area under the curve of serial visual analog assessments for global well being over 72 hours

2.2 Primary Hypotheses: Route of administration

The primary efficacy hypotheses to be tested in the continuous infusion vs. intermittent bolus comparison are:

- That continuous IV infusion of furosemide causes less renal dysfunction than twice daily IV bolus administration, as measured by change in creatinine from baseline to 72 hours

- That continuous IV infusion of furosemide is more efficacious at relieving acute symptoms compared to twice daily bolus administration, as measured by the area under the curve of serial visual analog assessments for global well being over 72 hours

These hypotheses will be evaluated in the context of a randomized controlled clinical trial using a 2 x 2 factorial design. Each factor (main effect) in the design will be tested at the α=0.025 level.

2.3 Secondary Objectives

Other secondary objectives of this protocol will be to examine the effect of the above treatments on:

- Change in weight at 96 hours
- Freedom from signs and symptoms of congestion at 72 hours
- Change in bivariate vector of creatinine and weight at 72 hours
- Differences in Dyspnea VAS AUC over 24, 48 and 72 hours
- Differences in PGA VAS AUC over 24 and 48 hours
- Change in serum creatinine at 24, 48, 96 hrs, day 7 (or discharge), and day 60
- Change in cystatin C at 72 hours, day 7 (or discharge) and day 60
- Persistent or worsening heart failure
- Development of cardio-renal syndrome
- Treatment failure
- Time from randomization to discharge during index hospitalization
- Total days hospitalized for heart failure or dead within 60 days of randomization

- Changes in circulating biomarkers from baseline to 72 hours, day 7 (or discharge), and day 60

3. BACKGROUND AND SIGNIFICANCE

Acute heart failure (AHF) is the most common cause of hospital admission in patients over age 65, accounting for 1,000,000 admissions, over 6 million hospital days, and $12 billion in costs annually (1;2). The prognosis of patients admitted with AHF is dismal, with a 20-30% readmission rate and a 20-30% mortality rate within six months after admission (3;4).

IV furosemide is the most common treatment utilized in patients with AHF during the first days of admission in the United States (US) (5;6). In both previous studies and the recent ADHERE registry, approximately 90% of patients receive IV furosemide during an AHF admission. In the recent VERITAS study (unpublished data), 69% of patients in the US received IV furosemide at baseline (approximately 12 hours from admission) and 87% received IV furosemide during the study period (first 48 hours). This nearly ubiquitous use of loop diuretics in AHF is based on the concept that the majority of AHF symptoms are related to volume overload and congestion, and that loop diuretics are the most effective means to address symptoms and volume overload in AHF. Although these assumptions are based on years of clinical experience, data supporting the safety and efficacy of loop diuretics in AHF are sparse. Importantly, there is little data to guide appropriate dosing of loop diuretics during AHF therapy, and consequently practice varies widely between physicians and centers. Similarly, substantial uncertainty remains about the optimal route of administration (continuous infusion vs. intermittent bolus) for IV diuretics. In a recent publication on unanswered questions in heart failure management, over 50% of the questions related to use of loop diuretics in heart failure (7). In sum, almost all patients with AHF are treated with a therapy (IV loop diuretics) about which there is substantial uncertainty regarding the correct dose and route of administration, both in terms of efficacy and safety. In light of these uncertainties, **the overriding goal of this clinical protocol is to evaluate the safety and efficacy of various strategies of intravenous loop diuretics in patients presenting with AHF and volume overload.**

4. PRELIMINARY STUDIES

4.1 Safety of Loop Diuretics: Relationship to Mortality

As noted above, the use of loop diuretics is nearly universal in patients with AHF (5). A variety of theoretical considerations suggest potential mechanisms of harm from loop diuretics in heart failure, including activation of the renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, and the induction of vasoconstriction or hypotension. A large body of literature supports the concept of higher mortality in patients receiving higher doses of loop diuretics (6;8;9). In an analysis of the recently completed ESCAPE trial (unpublished data), there was a direct relationship identified between dose of loop diuretics and increased mortality (Figure 1).

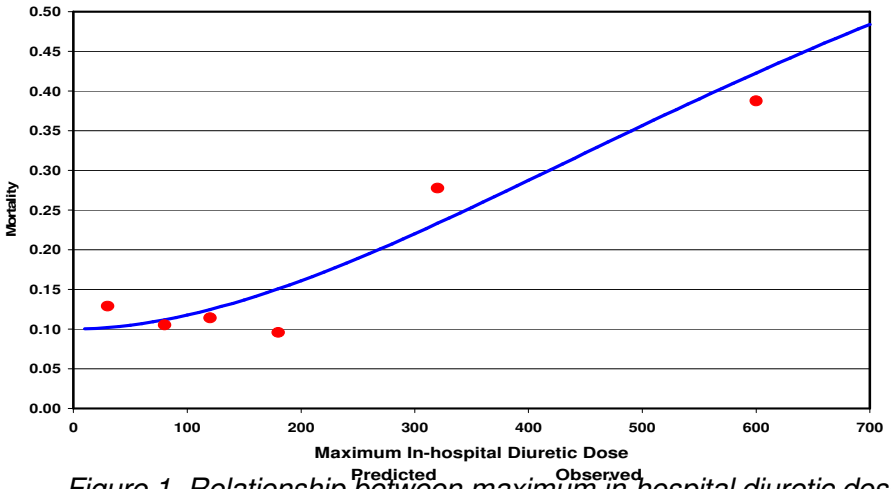


Figure 1. Relationship between maximum in-hospital diuretic dose and mortality in ESCAPE study.

Confounding this and all other such data is the issue of confounding by indication, i.e., the fact that patients who receive higher doses of diuretics may do so because of greater disease severity compared to patients who can be successfully treated with lower doses of diuretics. Although such confounding can never be completely eliminated, a variety of studies have found a persistent adverse effect of loop diuretics even after multi-variable adjustment for other known predictors of mortality (9;10). In further analyses of data from the ESCAPE trial, total diuretic dose was not clearly linked to other measures of disease severity such as levels of B-type natriuretic peptide (BNP) or to measures of volume overload such as pulmonary capillary wedge pressure (Figure 2). Although such data do not eliminate the problem of confounding by indication, they suggest that dosing of diuretics is not closely linked to other measures of disease severity. Taken as a whole, the available data clearly suggest the presence of a dose related mortality signal with increasing doses of loop diuretic therapy in AHF.

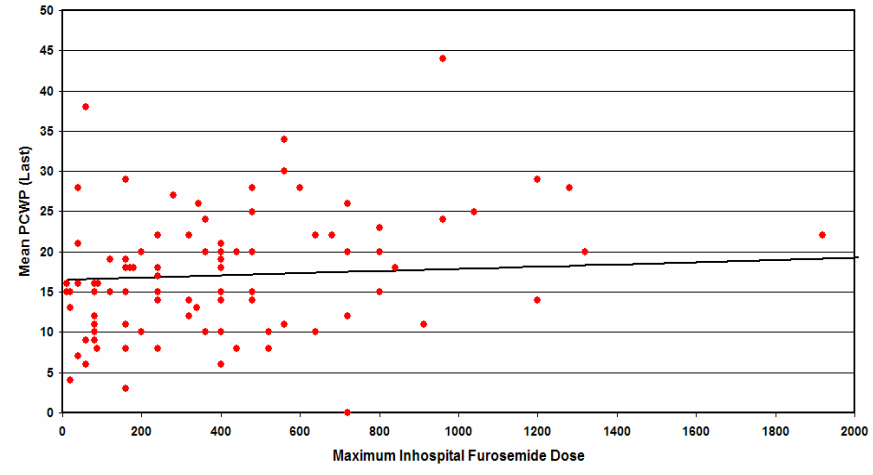


Figure 2. Pulmonary capillary wedge pressure versus maximum in-hospital furosemide dose in ESCAPE.

4.2 Safety of Loop Diuretics: Relationship to Renal Function

Worsening of renal function during hospitalization for AHF (termed the "cardio-renal syndrome" (CRS)) is a major clinical challenge in AHF management. It is well established that development of CRS during AHF therapy is a major risk factor for increased length of stay, higher morbidity, and greater mortality (10;11). Although a variety of mechanisms have been proposed for CRS, the pathophysiology of this syndrome has not been clearly elucidated (12). Butler et al examined the factors contributing to the development of renal failure in a cohort of patients admitted with AHF, and identified an association between higher doses of loop diuretics and the development of CRS during AHF therapy (9). This relationship persisted even after adjustment for baseline renal function and a variety of other covariates. As with the mortality data, these observational associations regarding loop diuretics and the CRS are highly confounded by indication, and can only be definitively addressed by a well controlled randomized controlled trial. A preliminary small study examining the role of high-dose furosemide, low-dose dopamine and their combination in patients with AHF was terminated early due to increased renal impairment and renal failure in the high dose furosemide arms (13).

4.3 Efficacy of Loop Diuretics in Addressing Symptoms and Volume Overload

Despite the concerns over safety noted above, loop diuretics continue to be given to the vast majority of patients treated for AHF in the US. The clinical rationale for the use of higher doses relates to a desire to relieve congestion and address volume overload as quickly as possible, thereby improving symptoms more rapidly and potentially shortening length of stay. Despite these widespread assumptions about diuretic efficacy, there is little high quality data to support the concept that higher doses of diuretics result in more complete relief of symptoms or greater degrees of weight loss during AHF hospitalization. In the ESCAPE study (unpublished data), higher doses of intravenous loop diuretics were not associated with greater weight loss during the index hospitalization (Figure 3).

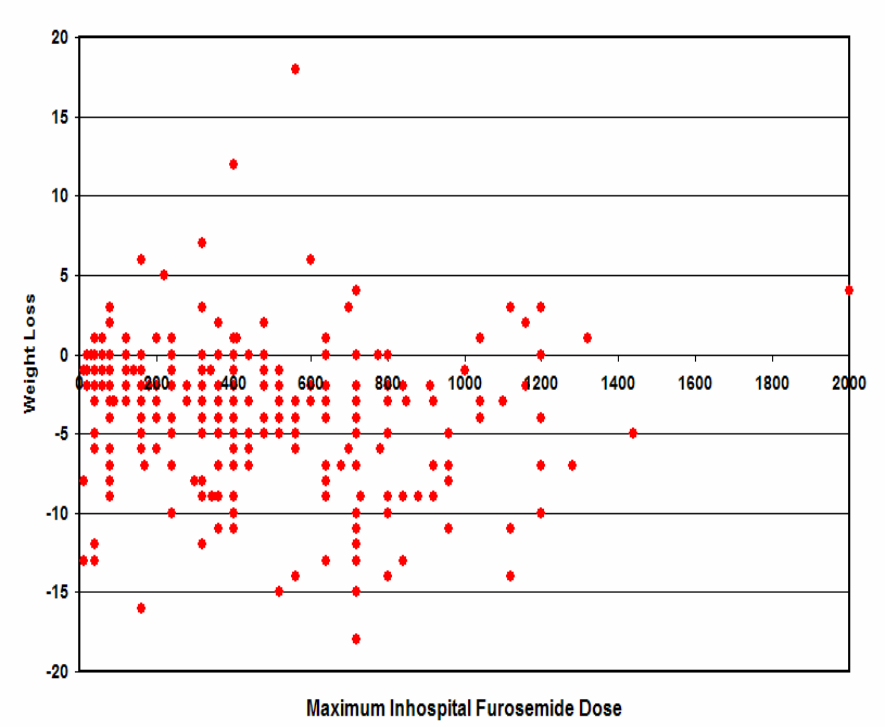


Figure 3. Weight loss versus maximum in-hospital furosemide dose in ESCAPE

Similarly, available data do not support the concept that higher doses of AHF therapy are associated with greater symptom relief. In an analysis of the VERITAS study, in which dyspnea as measured by the visual analog scale (VAS) was the primary endpoint, there was no association between loop diuretic dose in the first 48 hours and relief of dyspnea Figure 4).

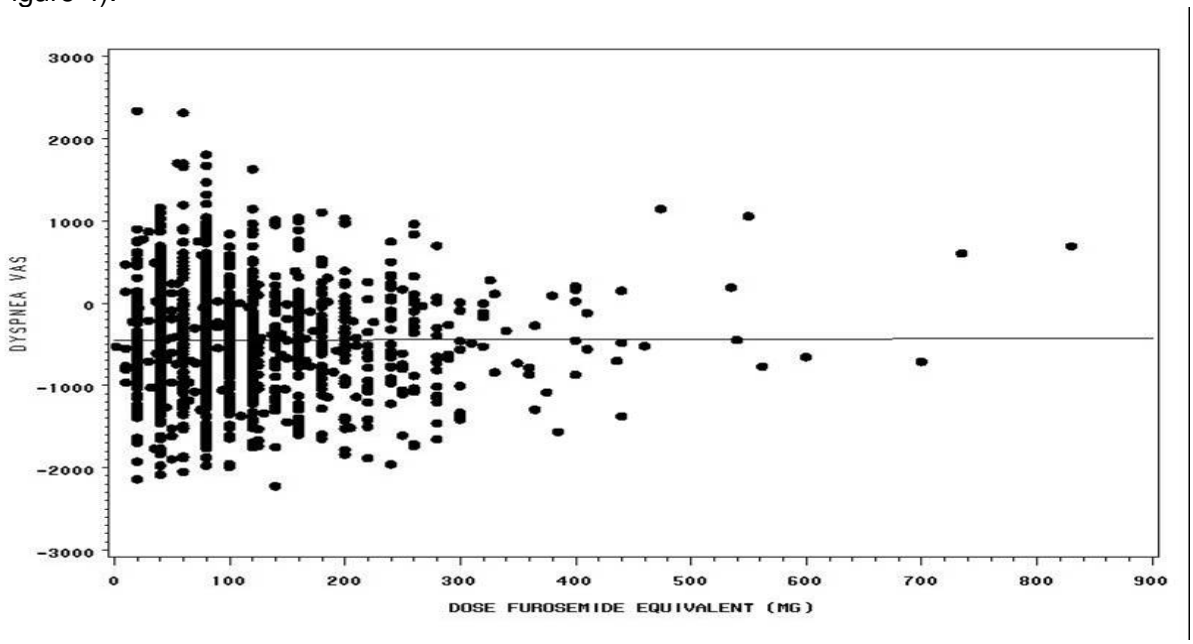


Figure 4. Relationship between diuretic dosage and relief of dyspnea in VERITAS study

Taken as a whole, these sparse available data do not support the concept that higher doses of intravenous loop diuretics are more efficacious at relieving symptoms, achieving weight loss, or shortening length of stay than lower doses of loop diuretics.

4.4 Current Standard of Care for Loop Diuretic Dosing in Acute HF

Response to diuretics in both acute and chronic heart failure is highly variable, and may be influenced by a variety of factors, including renal function, disease severity, and dietary compliance. Standard clinical practice with regard to initial strategies for dosing IV loop diuretics in acute heart failure typically involves some attempt to "benchmark" initial dosing of IV loop diuretics to patient specific characteristics. Given that the majority of acute heart failure admissions represent the development of congestion despite a background of chronic diuretic therapy, AHF hospitalizations can be viewed as a "failure" of current diuretic dosing, and as such require intensification of diuretic therapy. Available data suggest that the degree of intensification varies widely, and that both "low intensification" strategies (such as giving total daily oral dose via IV route) and "high intensification" strategies (such as doubling or tripling total daily oral dose via the IV route) are common. No prospective, randomized data exist to guide the choice between these 2 initial strategies.

4.5 Route of Administration of Loop Diuretics

In addition to the uncertainty about safety and efficacy described above, persistent uncertainty exists about the optimal route of administration for intravenous loop diuretics (bolus dosing or continuous infusion). A recent meta-analysis from the Cochrane Collaboration evaluated the available literature to address this question (14). This analysis identified 8 studies including a total of 254 patients who met rigorous analytical standards. Eight other studies were excluded. In 221 patients urine output was reported over 24 hours. Despite equal total amounts of furosemide administered, it was noted that urine output is higher in patients receiving continuous versus repeated bolus treatment (+271cc/ 24 hours, 95%CI 93-449, $p<0.01$). Other endpoints were reported in only a few of the studies. Duration of hospitalization was reported in one study including 107 patients, and was found to be decreased (8.57±2.3 versus 11.7±2.6 days, $p<0.001$) when continuous infusion was utilized. All cause mortality was reported in 2 studies, including 140 patients. Both studies reported a decrease in mortality, with a relative risk for death in the continuous strategy of 0.53 (0.38-0.71, $p< 0.001$). Cardiac mortality was reported in only one study of 107 patients and was found to be 20/53 in the continuous strategy arm versus 43/54 in the bolus strategy arm, $p<0.001$. Hypokalemia and hypomagnesemia were reported in 3 studies including 71 patients. These events were more prominent in the bolus strategy in one study, in the continuous strategy in a second and equal in the third. Tinnitus and hearing loss were reported in 2 studies including a total of 147 patients. In both studies these events occurred less in the continuous strategy arm, HR 0.06 (0.01-0.44, $p=0.005$). Finally, and most relevant to the present protocol, creatinine changes were reported in 3 studies including 180 patients. One study showed no difference between the strategies while 2 showed less increase in creatinine in the continuous arm (-0.54 mg%,-0.57 to - 0.51, $P<0.001$). Improvement in clinical measures such as dyspnea and recurrent heart failure were not reported in any of those studies.

The data reviewed above suggest the need for an adequately powered, well controlled clinical study to address:

- **The balance between safety and efficacy of a "low intensification" vs. a "high intensification" initial strategy for IV loop diuretic use in AHF**
- **The balance between safety and efficacy of continuous infusion vs. intermittent bolus administration of loop diuretics in AHF**

5. BASIC STUDY DESIGN

This study will be a randomized, controlled, multi-center clinical trial of patients with signs and symptoms consistent with AHF within 24 hours of hospital admission. A total of 300 patients will be enrolled in the trial.

Patients will be randomized to one of 4 treatment regimens (75 patients / treatment regime) defined by a 2x2 factorial treatment design:

1) "High intensification" strategy for IV furosemide (defined as 2.5 x stable PO home dose) vs. "low intensification" dose IV furosemide (defined as 1 x stable PO home dose). This treatment will be double-blinded.

2) Continuous furosemide IV infusion vs. IV furosemide given as IV bolus Q12 hours. This treatment will be double-blinded.

The study treatment regimen will be administered from randomization through 48 hours, at which point the investigator may modify the IV loop diuretic strategy based on clinical assessment of the patient and their response to therapy. Permitted modifications will be:

1. Continue current strategy without change
2. Increase dose by 50% (while remaining blinded to both dose and route of administration assignment)
3. Switch to oral furosemide (dose at the investigator's discretion) in preparation for discharge.

Blinding of initial treatment assignment will be maintained regardless of which of the options are selected.

After 72 hours, all diuretic treatment will be open label at the treating physician's discretion.

The primary assessment for both efficacy and safety will occur at 72 hours after randomization.

The primary endpoint for efficacy will be patient reported global well being by visual analog scale (VAS) quantified as the area under the curve (AUC) over 72 hours.

The primary safety endpoint will be change in serum creatinine from baseline to 72 hours.

Anticipated need for at least 48 hours of IV diuretic therapy will be an inclusion criterion for the study. However, if patients are deemed to have achieved adequate diuresis before 48 hours, they may be switched to oral dosing of diuretics (open label) at the investigators discretion. If patients are discharged prior to 72 hour assessment, the last VAS

assessment and last serum creatinine will be carried forward to 72 hours for the purposes of assessing the primary endpoints.

If patients die prior to 72 hour assessment, the last serum creatinine will be carried forward and the last VAS will be imputed as 0.

Patients will be followed daily during hospitalization for adverse events and for assessing length of stay.

All patients will undergo day 60 follow up visit including physical examination, assessment of interval hospitalizations or ED visits, and assessment of renal function.

6. STUDY POPULATION AND ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

- Male or female patient ≥18 years old
- Prior clinical diagnosis of heart failure with daily home use of oral loop diuretic for at least one month
- Daily oral dose of furosemide ≥ 80 mg and ≤240 mg (or equivalent)
- Must be identified within 24 hours of hospital admission
- A diagnosis of heart failure as defined by the presence of at least 1 symptom (dyspnea, orthopnea, or edema) AND 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography)
- Anticipated need for IV loop diuretics for at least 48 hours
- Willingness to provide informed consent

6.2 Exclusion Criteria

- BNP < 250 ng/ml or NT-proBNP <1000 mg/ml
- Received IV vasoactive treatment or ultra-filtration therapy for heart failure since initial presentation
- Anticipated need for IV vasoactive treatment or ultra-filtration for heart failure during this hospitalization
- Substantial diuretic response to pre-randomization diuretic dosing such that higher doses of diuretics would be contra-indicated (based on investigator judgment)
- Systolic BP <90 mmHg
- Serum creatinine >3.0 mg/dl at baseline or renal replacement therapy
- Hemodynamically significant arrhythmias
- Acute coronary syndrome within 4 weeks
- Active myocarditis
- Hypertrophic obstructive cardiomyopathy
- Severe stenotic valvular disease
- Restrictive or constrictive cardiomyopathy
- Complex congenital heart disease
- Constrictive pericarditis

- Non-cardiac pulmonary edema;
- Clinical evidence of digoxin toxicity;
- Need for mechanical hemodynamic support
- Sepsis
- Terminal illness (other than HF) with expected survival of less than 1 year
- Previous adverse reaction to the study drugs
- Use of IV iodinated radiocontrast material in last 72 hours or planned during hospitalization
- Enrollment or planned enrollment in another randomized clinical trial during this hospitalization
- Inability to comply with planned study procedures

7. TREATMENT INTERVENTIONS

This study will be an active control study, i.e., there will be no placebo group. Treatment interventions will be as follows:

7.1 Randomization to 48 hours

Patients will be randomized in a 1:1:1:1 ratio to one of the 4 treatment combinations (2x2 factorial design).

- Low intensification strategy for IV furosemide (1 x outpatient oral dose) by continuous infusion
- Low intensification strategy for IV furosemide (1 x outpatient oral dose) by intermittent bolus Q12 hours
- High intensification strategy IV furosemide (2.5 x outpatient oral dose) by continuous infusion
- High intensification strategy (2.5 x outpatient oral dose) by intermittent bolus Q12 hours

If the outpatient dose has changed over the week prior to admission, the outpatient dose will be defined as that received 7 days prior to randomization for the sake of this study.

For patients receiving outpatient loop diuretics other than furosemide, conversion to furosemide equivalents will be as follows:

1 mg torsemide = 2 mg furosemide
1 mg bumetanide = 40 mg furosemide

If patients are deemed to have had an adequate response to diuretics prior to 48 hours, they will be permitted to change to oral diuretic therapy (open label dosing at investigators' discretion.)

7.1.1 Randomization and Blinding

This study will be double blinded with regard to the dose intensification strategy and with regard to route of administration. All patients will receive both intermittent Q12 bolus and

continuous IV infusion, one of which will contain furosemide and one of which will contain normal saline ("double-dummy" design).

7.2 48 to 72 hours

At 48 hours, the treating physician will choose one of the following options based on the clinical assessment of the patient and their response to therapy:

1. Maintain current strategy without change
2. Increase dose by 50% (while remaining blinded)
3. Change to oral diuretics (dose at MD discretion) in preparation for discharge

7.3 72 hours and afterwards

After 72 hours, all patient care decisions including diuretic dose and administration will be unblinded and at the discretion of the investigator.

7.4 Study Drug Supplies

Investigational pharmacy will prepare both intermittent bolus (furosemide or placebo) and continuous infusion (furosemide or placebo) for each patient in keeping with the "double dummy" study design. Hospital stock should be used. Clinical personnel, investigators, and the patients will be blinded to both dose intensification strategy and route of administration.

7.5 Patient Safety, Concomitant Therapies, and Rescue Therapy

This study will evaluate and compare initial diuretic strategies in patients with acute heart failure and volume overload. Although investigators are encouraged to follow the assigned treatment strategy for the duration of the treatment period (72 hours), **in all cases the patient's safety based on the clinical judgment of the treating physician will take priority over the specific treatment assignment.**

Patients requiring other intravenous vasoactive medications for heart failure (inotropes, vasodilators, etc) will be excluded from the present study. Patients requiring such drugs for clinical reasons during the randomization period will meet the secondary endpoints of "worsening or persistent heart failure" and "treatment failure" (see endpoint section). Patients who are deemed to have a clinical need for additional diuretics during the blinded study period will be permitted to receive unblinded open label diuretics. This will be captured as "rescue therapy" and will meet criteria for secondary endpoints of "worsening or persistent heart failure" and "treatment failure" endpoints. Conversely, patients may develop signs or symptoms of over-diuresis (such as hypotension) that necessitate holding or discontinuing diuretics before completion of the randomization period. This will be captured as a "treatment failure" if it requires specific intervention beyond simply holding diuretics.

As this is a randomized trial comparing initial diuretic strategies, in either case the interpretation of the primary endpoints with regard to both efficacy and renal function will be on an "intention to treat" basis.

8. RECRUITMENT AND SCREENING PROCEDURES

8.1 Common Recruitment/Screening Procedures

All patients admitted to the participating Heart Failure Clinical Research Network centers with signs and symptoms suggestive of AHF will be screened by a study coordinator. Given the short time period after admission (24 hours) for inclusion in the study, it is anticipated that screening in the Emergency Department and screening more than once daily will be effective recruitment strategies. Patients meeting eligibility criteria will be approached regarding participation in this study.

8.2 Estimated Enrollment Period

This study will enroll 300 patients at 9 Regional Clinical Centers (RCCs) and associated satellite centers in the United States and Canada. It is projected that 18 patients per month will be enrolled (2 pts/RCC/month), for a total anticipated enrollment period of approximately 18 months.

8.3 Informed Consent Procedures

8.3.1 Informed Consent

All patients will have the purpose of the study, the study interventions and evaluations, and the potential risks and benefits of participation explained to them and their questions answered. If they consent to participation in this study, they will review and sign the informed consent form (ICF). A template for the ICF appears in Appendix D.

8.3.2 Confidentiality and HIPAA Requirements

All information collected on study participants will be stored in a confidential manner using procedures in place at each participating RCC. Only approved study personnel will have access to data collected as part of the DOSE Study. Study participants will be identified by a Subject ID # on all study documents. Data will be transmitted to the DCC in a secure manner, and stored securely at the DCC using standard DCRI operating procedures.

8.3.3 Protections of Human Subjects

Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 45 CFR 46. Subpart A of the HHS regulations constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects, which has been adopted by an additional 16 Executive Branch Departments and Agencies.

Each institution engaged in (non-exempt) HHS-supported human subjects research must provide a written Assurance of Compliance, satisfactory to the Office for Protection from Research Risks (OPRR), that it will comply with the HHS human subjects regulations. -- 45 CFR 46.103(a)

8.3.4 Summary of the Risks and Benefits

This study will evaluate dosing strategies and route of administration for a commonly used, FDA approved medication for AHF (furosemide). Both the dosing range being evaluated (1 vs. 2.5 x oral dose) and the route of administration (IV intermittent bolus vs. continuous infusion) are both well within current standard of care. As such, it is not anticipated that participation in this study will be associated with increased risks beyond that of standard AHF therapy. The risk of loss of confidentiality will be managed using polices and procedures designed to protect confidentiality described above. There will be no specific benefits anticipated beyond contributing to better understanding of optimal care of AHF that may benefit the study subject during future AHF episodes.

9. BASELINE EVALUATIONS AND RANDOMIZATION

A complete schedule of assessments throughout the study is given in Appendix A.

9.1 Randomization

After providing informed consent and signing the ICF, all study subjects will be randomized using procedures determined by the DCC to one of 4 treatment groups, based on the 2 x 2 factorial design defined above. Randomization will be 1:1:1:1. Blocking will be used to ensure relatively equal distribution of patients to each arm. Randomization will be stratified by clinical site.

9.2 Baseline Assessments

At the time of randomization, all study subjects will undergo

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including O_2 saturation and weight)
- Concomitant cardiovascular medications
- Creatinine, BUN, and electrolytes (local laboratory)
- Patient Global Well being assessment (PGA) by VAS (see Appendix C)
- Dyspnea assessment by VAS (see Appendix C)
- Blood sample for biomarkers core laboratory

10. FOLLOW UP EVALUATIONS

Follow-up evaluations are expected to occur within +/- 2 hours of the nominal time points.

10.1 6 and 12 hours

- PGA assessment by VAS
- Dyspnea assessment by VAS

10.2 24, 48, 72, and 96 hours

On study days 1-4, all study subjects will undergo the following assessments daily:

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including O_2 saturation and weight)
- Creatinine, BUN, and electrolytes (local laboratory)
- PGA assessment by VAS at 24, 48, 72, and 96 hours
- Dyspnea assessment by VAS at 24, 48, 72 , and 96 hours
- Fluid balance over preceding 24 hours (net intake – net output)
- Blood sample for biomarkers core laboratory (72 hours only)
- Changes in cardiovascular medications
- Assessment for adverse events

10.3 Day 7 or Day of Discharge (if earlier than 7 days)

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including O_2 saturation and weight)
- Creatinine, BUN, and electrolytes (local laboratory)
- Blood sample for biomarkers core laboratory
- Changes in cardiovascular medications
- Assessment for adverse events

10.4 Day 60

Patients will return to clinic for Day 60 study-follow up (+/- 7 days). During this clinic visit, they will undergo the following assessments:

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including O_2 saturation and weight)
- Changes in cardiovascular medications
- Assessment for adverse events
- Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits
- Creatinine, BUN, and electrolytes (local laboratory)
- Blood sample for biomarkers core laboratory

11. OUTCOME DETERMINATIONS

11.1 Primary Endpoints

This study will use co-primary endpoints

- **Change in serum creatinine from randomization to 72 hours**

- **Area under the Curve (AUC) for Patient Global Assessment by VAS over 72 hours**

Rationale for Primary Endpoints:
Change in creatinine from randomization to 72 hours was chosen as the primary safety endpoint due to the observed association between diuretic dosage and worsening renal function and the known association of worsening renal function with other adverse outcomes.

For the assessment of short term efficacy, a variety of endpoints have been utilized in prior AHF studies. These include patient self assessments of symptoms, typically either dyspnea or global well being (termed patient global assessment (PGA)). These self assessments are usually performed using a visual analog scale (VAS) or Likert scale. The DOSE-AHF study will use the PGA by VAS over 72 hours as the primary endpoint for efficacy. The rationale for this choice is that although dyspnea is the primary symptom for most patients with AHF, other symptoms (fatigue, edema, etc) may also be important and should be captured in the primary efficacy endpoint. We have chosen a patient symptom assessment r ather than other measures of diuretic efficacy such as weight change or urine output, because while these measures capture the pharmacodynamic effects of diuretic therapy, they may not be tightly correlated with other clinical events (such as rehospitalization or death), and are therefore not ideal surrogates in the assessment of efficacy in AHF. Change in weight and urine output will be secondary measures of diuretic efficacy.

Patients will be asked to self assess both their general well being and their level of dyspnea using a visual analog scale (VAS) method. For PGA, patients will mark their global well being on a 10 cm vertical line, with the top labeled “best you have ever felt” and the bottom labeled “worst you have ever felt”. For dyspnea, the labels will be “I am not breathless at all” and “I am as breathless I have ever been”. The VAS is scored from 0 to 100 but the patient is unaware of the numerical value of their response. Patients will self assess both PGA and dyspnea at randomization, 6, 12, 24, 48, 72, and 96 hours. The area under the curve for PGA assessment over the first 72 hours will be the primary efficacy endpoint (AUC for PGA VAS).

11.2 Secondary Endpoints

- ***Weight Loss:*** Weight loss will be measured over the 96 - hour study period (at 24, 48, 72, and 96 hours from randomization).

- ***Proportion of Patients Free of Congestion at 72 hours:*** Freedom from congestion will be defined as JVP < 8 cm, no orthopnea, trace peripheral edema or less

- ***Change in the bivariate relationship of creatinine at 72 hours vs. weight loss at 72 hours:*** For each of the four treatment groups, weight loss at 72 hours and change in creatinine at 72 hours will be plotted on a two dimensional coordinate grid along with estimates of the mean effect and a 95% confidence ellipse. This will allow visual and statistical assessment of the “trade off” between change in weight and change in renal function. Comparisons among the 6

possible pairwise treatment differences will be constructed to detect differences between treatment strategies.

- ***Differences in Dyspnea VAS AUC over 24, 48, and 72 hours***

- ***Differences in PGA VAS AUC over 24 and 48 hours***

- ***Change in Serum Creatinine from baseline to 24, 48, 96 hours, day 7/discharge, and 60 days***

- ***Change in Cystatin C from baseline to 72 hours, Day 7/discharge, and 60 days***

- ***Worsening or persistent heart failure****:* defined as need for rescue therapy (additional open label loop diuretic, addition of thiazide, IV vasoactive agent for heart failure treatment, ultrafiltration, mechanical circulatory or respiratory support) over 72 hours after randomization

- ***Development of Cardio-renal syndrome:*** defined as increase in serum creatinine > 0.3 mg/dl from randomization at any time point during 72 hours after randomization

- ***Treatment Failures*****,** a composite comprised of ANY ONE of the following during the 72 hours after randomization:
    - development of cardio-renal syndrome as defined above
    - worsening/persistent heart failure as defined above
    - clinical evidence of over-diuresis requiring intervention (such as administration of IV fluids)
    - death

- ***Net fluid loss over study period:*** Assessed at 24, 48, and 72 hours

- ***Time from randomization to discharge during index hospitalization***

- ***Total days hospitalized for heart failure or deceased during the 60 days after randomization***

- ***Changes in circulating biomarkers at 72 hours, day 7 (or discharge) and 60 days***

- ***Death or rehospitalization (to include unscheduled clinic visits or ED visits) at 60 days***

12. METHODS TO PROMOTE ADHERENCE AND MINIMIZE BIAS

12.1 Adherence

Since this study will be an inpatient study of relatively brief duration, it is not anticipated that any specific interventions will be required to promote adherence.

12.2 Blinding

This will be a double-blind, active control study. Randomization as to “high intensification” and “low intensification”, as well as randomization as to continuous infusion or intermittent bolus will be double blinded.

13. PARTICIPANT SAFETY AND ADVERSE EVENTS

13.1 Institutional Review Boards

All Heart Failure Clinical Research Network sites will submit the study protocol, informed consent form, and other relevant study documents to their Institutional Review Board (IRB) for approval.

13.2 Adverse Events

13.2.1 Definitions

An **adverse event** (AE) is any sign, symptom, syndrome, or illness that occurs or worsens during the use of the test article (drug, biologic, or device) regardless of causality. A medical condition that is already present prior to treatment administration is not defined as an adverse event unless this medical condition worsens after the patient has been administered the test article. The details of these signs and symptoms will however be captured in the patient’s CRF for inclusion in the database as baseline conditions. Clinically significant laboratory abnormalities (for example, abnormal ECHOs, ECGs, out of range blood parameters etc.) that occur or worsen during the use of a test article are also adverse events.

A “**Serious Adverse Event**” (SAE) is any adverse event that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of hospitalization which is not specifically required by the protocol nor is it elective.
- Results in permanent impairment of a body function or permanent damage to a body structure
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
- Results in congenital anomaly or birth defect

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when they jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed above. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. Medical and scientific judgment must be exercised when classifying events as serious.

The relation between an adverse event and the test article will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

Not a Reasonable Possibility- It is unlikely that the event was caused by the study drug. The temporal relationship of the adverse event to the study drug administration makes causal relationship unlikely and other drugs, therapeutic interventions or underlying conditions provide a more likely explanation for the event.

Reasonable Possibility - There is a reasonable possibility that the adverse event may have been caused by the study drug. The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event.

The intensity of the adverse event will be defined by the following criteria:

Mild:	The adverse event is noticeable to the patient but does not interfere with routine activity
Moderate:	The adverse event is discomforting and interferes with routine activity.
Severe:	The adverse event significantly limits the patient's ability to perform routine activities despite symptomatic therapy

An **Unexpected Adverse Event** is when the nature or severity of the event is not consistent with the applicable product information (i.e., Investigator's Drug Brochure or package insert).

The following adverse events are anticipated, disease related-events in patients with acute decompensated heart failure and therefore do not require reporting on the Adverse Event form of the CRF (although some may require reporting as study endpoints):

- Atrial fibrillation
- Ventricular tachycardia
- Myocardial infarction
- Acute coronary syndrome
- Electrolyte disturbance
- Acute renal failure
- Worsening heart failure

13.2.2 Recording and Reporting

The Site Investigator is responsible for monitoring the safety of patients enrolled into the study at the study sites. All adverse events (except those listed above) must be recorded in the Adverse Event Record of the patient's CRF and source supportive documentation must be provided to support CRF data. All adverse events should be monitored until stabilization or resolution.

Adverse events which meet the criteria of serious, study drug-related, and unexpected per the U.S. package insert, qualify for expedited reporting to the regulatory authorities. The Site Investigator will assess all SAEs occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The Site Investigator is required to complete and submit a MedWatch Online Voluntary Reporting form (3500) for the

events identified as serious, drug-related and unexpected at https://www.accessdata.fda.gov/scripts/medwatch/ . A copy of this report should be kept at the site and also forwarded to the Data Coordinating Center.

Investigators are also responsible for promptly reporting adverse events to their reviewing IRB/EC in accordance with local requirements.

A Data and Safety Monitoring Board (DSMB) will review safety composite data at regular intervals through-out the study.

14. STATISTICAL CONSIDERATIONS

14.1 Overview

Means, standard deviations, medians, 25th and 75th percentiles will be presented for continuous variables; the number and frequency of patients in each category will be presented for nominal variables. Statistical tests with a p value < 0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).

14.2 Analysis of Primary Endpoints

The primary analysis will be made on an intention-to-treat basis, with patients allocated to the treatment to which randomized. General linear models will be used to examine the effect of each of the main effects on the two co-primary outcomes. The dependent variables in the regression model will be the change in creatinine value from baseline to 72 hours and the AUC for the PGA VAS from baseline through 72 hours. Independent variables in the model will include the main effects of furosemide dose and mode of administration, and the baseline creatinine level. An interaction term will be included if the p-value for that parameter estimate is less than 0.025. For each co-primary outcome, the two main effects will be tested at the two-sided α=0.025 significance level. The null hypothesis for each test will be that the treatment (either dose or mode of administration) has no effect on either of the co-primary outcomes.

We anticipate that some patients may die before all scheduled post-baseline creatinine values can be taken, and that these losses will introduce bias into the main effects comparisons. For the primary analyses, the values imputed will be 0 for the PGA VAS after the time of death and the highest post-baseline creatinine measurement. Sensitivity analyses, including analysis of only complete cases and imputing the worst creatinine value for deaths, will be employed to assess the degree to which these missing values impact the results.

14.3 Sample Size

For purposes of power calculations, we have applied a Bonferroni adjustment to the alpha level (0.05/2 = 0.025) to allow for two co-primary endpoints. We assume that the effect of both dose and administration mode will be additive (i.e. no interaction). In our sample size calculations shown below we assess the sensitivity of the power to subadditivity of the main effects. Due to the short-term nature of the study, missing data due to loss-to-followup are expected to be rare. In addition, because this study design is testing initial treatment strategies, we do not anticipate problems with adherence to the protocol guidelines.

14.3.1 Change in Creatinine at 72 hours

The standard deviation observed for the change in creatinine from baseline to discharge in the ESCAPE trial (unpublished data) was 0.47 mg/dL. Similarly, in the control arm of the UNLOAD study (unpublished data), the standard deviation of the change in creatinine from baseline to discharge was 0.5 mg/dL. With 300 patients, we will have approximately 88% power to detect a difference in mean creatinine of 0.20 mg/dL for each main comparison, assuming a standard deviation of 0.5 mg/dL. Assuming a smaller standard deviation of 0.4 mg/dL, we would have approximately 98% power to detect a difference of 0.2 mg/dL. The effect of various standard deviations on the power to detect given mean differences in peak creatinine (mg/dL) at the 2.5% significance level is given in Figure 5.

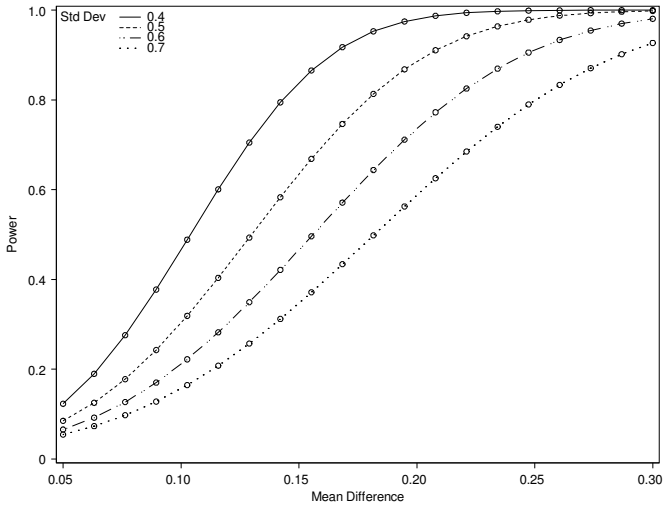


Figure 5. *Power with 150 patients per group to detect various mean differences in creatinine (mg/dL) assuming normal distribution with various standard deviations at the two-sided 2.5% significance level*

14.3.2 Change in PGA VAS at 72 hours

For this measure, the maximum possible score on the VAS AUC is 7200 points (100 points x 72 hours). Based on unpublished data from the MEASURE AHF registry, the standard deviation observed for the PGA VAS AUC measure among patients with acute heart failure was approximately 1500 points (over 72 hours). With this standard deviation and the assumed 2.5% significance level, 300 patients will provide 88% power to detect a difference on the PGA VAS AUC of 600 points for each of the treatment factors.

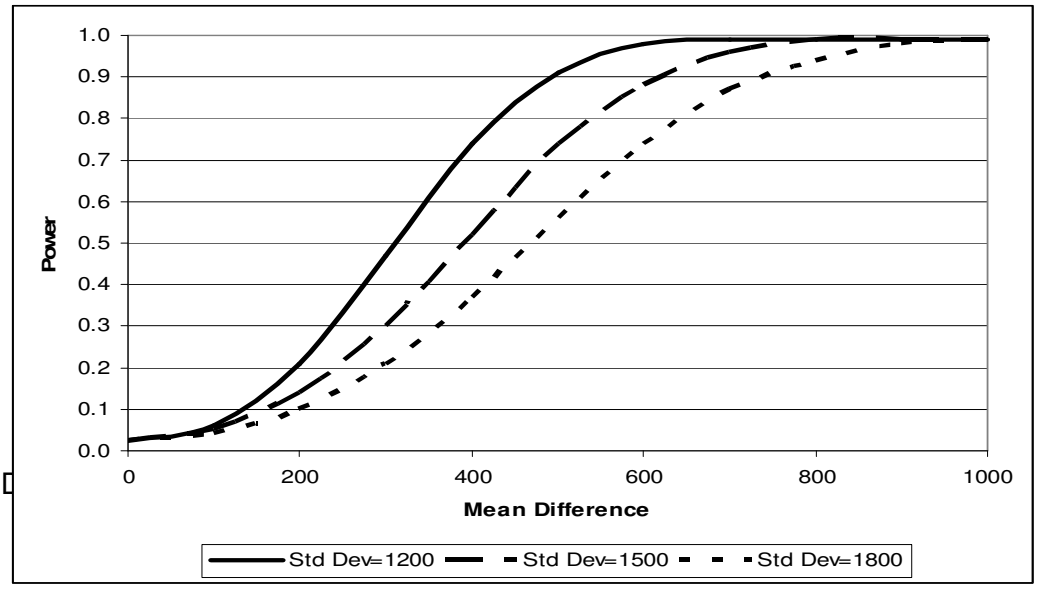


Figure 6. *Power to detect mean differences in general well-being VAS AUC with 300 patients at the two-sided 2.5% significance level at various standard deviations*

In Table 1, we illustrate the sensitivity of the power estimates to hypothetical changes in the mean 96-hour creatinine values across the 4 treatment groups. Scenario 1 corresponds to our assumption of additivity (or no interaction) while scenarios 2 and 3 represent subadditivity and superadditivity, respectively. As expected, the power to detect main effect differences is improved if there is superadditivity of the effects and diminished if there is subadditivity of the effects.

Table1. Sensitivity of the power to the assumption of additive treatment effects.

	Low Dose & Infusion	Low Dose & Bolus	High Dose & Infusion	High Dose & Bolus	Power for the main effect tests	Power for the interaction test	Power for the 3 df overall test
Null Scenario	0.1	0.1	0.1	0.1	2.5%	2.5%	2.5%
Scenario 1 – additivity	0.1	0.3	0.3	0.5	88%	2.5%	98%
Scenario 2 – subadditivity	0.1	0.3	0.3	0.3	30%	57%	60%
Scenario 3 – superadditivity	0.1	0.3	0.3	0.7	99%	57%	99%

14.4 Analysis of Secondary Endpoints

General linear models and nonparametric approaches will be used to analyze the continuous outcomes of weight loss; dyspnea AUC at 24, 48, and 72 hours, length of hospital stay, and changes in biomarkers. Analysis of the additional safety and efficacy endpoints will emphasize comparisons among the treatment groups defined by the randomization.

14.5 Subgroup Analyses

Further analyses will be conducted to determine whether the effect of furosemide dose or mode of administration is modified by each of the following covariates:

- Admission blood pressure
- Baseline creatinine ($\leq$ 1.6 v. > 1.6 mg/dL)
- Age ($\leq$ 70 v. > 70)

Estimation of subgroup effects will be conducted within the linear models framework. To provide a conservative framework for the interaction testing, we will consider the interaction terms to be statistically significant if $p<0.001$.

15. DATA MANAGEMENT PROCEDURES

The DOSE-AHF trial is a prospective, randomized, controlled study where data will be collected, analyzed, and interpreted by the Duke Clinical Research Institute which functions as the DCC for the NIH Heart Failure Clinical Research Network. Data other than safety data cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB or Heart Failure Clinical Research Network. This is necessary since dissemination of preliminary information may inappropriately affect the objectivity of this study. For this reason Study Investigators or other parties will not be allowed to perform subset analyses at any point before the conclusion of this study.

All prospective publications or presentations must be reviewed and approved by the HF Network steering committee and DCC representatives.

16. STUDY ADMINISTRATION

16.1 DSMB

A DSMB will be appointed by the NHLBI. This will be a group of individuals with pertinent expertise in heart failure and clinical trials. The DSMB will advise the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

16.1.1 Statistical Monitoring Plan

Interim data analysis for efficacy will not be conducted due to relatively small size and short duration of this phase II clinical trial. Safety data will be periodically assessed by the DSMB based on reporting of adverse events. There will be a planned assessment by the DSMB after 50 patients have been enrolled to evaluate compliance with the assigned treatment strategy (i.e., crossover). This will serve to allow reassessment of the planned sample size if needed.

16.2 Data Coordinating Center (DCC)

The Duke Clinical Research Institute will function as the DCC for this trial as specified by the sponsor (NIH Heart Failure Clinical Research Network grant).

16.3 Core Laboratories

This study will utilize a biomarkers core laboratory designated by the NHLBI and the DCC. Plasma specimens at baseline, 72 hours, day 7 (or discharge if earlier) and 60 days will be processed according to the procedures provided by the core laboratory and sent to the core laboratory on dry ice. Planned analyses include:

- Natriuretic peptides (BNP)
- Neurohormonal activation (Endothelin-1)
- Renal function (Cystatin C)
- Myocardial necrosis (Troponin T)

- Measures of collagen turnover/fibrosis (pro-collagen III NTP)
- Uric acid

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18. APPENDICES

18.1 Appendix A. Schedule of Assessments

	Baseline	6, 12 hours	24 hours	48 hours	72 hours	96 hours	Day 7 or discharge	60 days
Informed Consent	X							
History and physical	X		X	X	X	X	X	X
CV Medication History	X		X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X
Oxygen saturation	X		X	X	X	X	X	X
Body weight	X		X	X	X	X	X	X
VAS for PGA	X	X	X	X	X	X		
VAS for Dyspnea	X	X	X	X	X	X		
Fluid balance/24 hours			X	X	X	X		
Cr, BUN, electrolytes	X		X	X	X	X	X	X
Plasma collection for Biomarkers	X				X		X	X
Adverse events			X	X	X	X	X	X

18.2 Appendix B. List of Abbreviations

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ADHF	acute decompensated heart failure
AHF	acute heart failure
AICDs	automatic implantable cardioverter-defibrillators
AUC	area under the curve
BNP	B-type natriuretic peptide
CO	cardiovascular flow
CRP	C-reactive protein
CRS	Cardio-renal syndrome
DOSE	Diuretic Optimization Strategies Evaluation
ED	Emergency Department
EF	ejection fraction
JVP	Jugular venous pressure
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
IV	Intravenous
IVRS	Interactive voice response system
KIM	Kidney injury marker
NIV	noninvasive positive pressure ventilation
NYHA	New York Heart Association
PGA	Patient global assessment
PAC	pulmonary artery catheter
PCWP	Pulmonary capillary wedge pressure
SVR	systemic vascular resistance
US	United States
VAS	visual analogue scale

Site Number: _ _ _ **Patient Number: _ _ _ - _ _ _**

Assessment Date: _ _ (day)/_ _ (month) _ _ _ _ (year) **Time: _ _: _ _**

18.3 Appendix C. VAS Instruments

VAS – Global Well Being (PGA)

Please draw a line on the scale to show how you feel right now. The number "0" equals the worst your have ever felt and the number "100" equals the best you have ever felt.

100 = Best you have ever felt

0 = Worst you have ever felt

Site Number: _ _ _ **Patient Number: _ _ _ - _ _ _**

Assessment Date: _ _ (day)/_ _ (month) _ _ _ _ (year) **Time: _ _: _ _**

VAS - Dyspnea

Please draw a line on the scale to show how your breathing feels right now. The number "0" equals the worst your breathing has ever felt and the number "100" equals the best your breathing has ever felt.

100 = I am not breathless at all

= I am as breathless as I have ever been

18.4 Appendix D. Informed Consent Form

Separate attachment.