Ultra High Dose Diuretic Strategy for Management of Acute Decompensated Heart Failure - A Randomized, Double-Blind Pilot Trial

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Ultra-High Dose Diuretic Strategy for Management of Acute Decompensated Heart Failure - A Randomized, Double-Blind Pilot Trial

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AF	Atrial Fibrillation
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
VT	Ventricular Tachycardia

1. Study Summary

Title	Ultra-High Dose Diuretic Strategy for Management of Acute Decompensated Heart Failure-A Randomized, Double-Blind Pilot Trial
Running Title	Ultra-High Dose Diuretics for Heart Failure
Protocol Number	23-005262
Phase	Phase: 2
Methodology	Randomized, parallel-group clinical trial in acute decompensated heart failure patients with volume overload (requiring hospitalization) **Group 1:** Ultra high dose intervention with intravenous bumetanide 12.5 mg bid over 24 hours **Group 2:** Standard dose intervention with intravenous furosemide as twice the home dose of oral diuretic in furosemide equivalents bid over 24 hours
Overall Study Duration	12 months
Subject Participation Duration	Approximately 24 hours
Single or Multi-Site	Single Site-Mayo Clinic Rochester, MN
Objectives	To determine the safety and efficacy of ultrahigh dose diuretics compared to standard dose diuretics over 24 hours in patients with decompensated heart failure
Number of Subjects	20 patients total
Diagnosis and Main Inclusion Criteria	We will include patients with decompensated heart failure requiring hospitalization for intravenous diuresis regardless of ejection fraction.
Study Product, Dose, Route, Regimen	Patients will be randomized 1:1 to ultra-high dose (IV bumetanide 12.5 mg bid) vs standard dose (IV furosemide as twice the home dose of oral daily diuretic in furosemide equivalents administered bid) for 24 hours. Participants will undergo comprehensive physiological assessment at baseline and 24 hours with short Iohexol clearance for true glomerular filtration rate, apnea hypopnea index, electrocardiography, echocardiography, serum, and urine biomarkers. Patients will be monitored for side effects including muscle cramps, new onset atrial fibrillation (AF), sustained ventricular tachycardia (VT), symptomatic hypotension (MAP<60 or systolic blood pressure <80 mmHg), development of renal insufficiency and dialysis initiation.
Duration of Administration	Patients will be on therapy for 24 hours.

Statistical Methodology	The primary efficacy endpoint is urine output over 24 hours which will be compared by T test between the two groups. Primary safety endpoint will be incident decline in creatinine estimated glomerular filtration rate by 50% over 24 hours. Key secondary endpoints include weight change, NT-proBNP change, urine output, urine sodium excretion, creatinine, and cystatin C estimated GFR changes, apnea-hypopnea index, Iohexol glomerular filtration rate, serum and urine proteomic analyses, peripheral vein pressure and echocardiographic changes over 24 hours, estimated GFR at day 7 or discharge (whichever is sooner) will each be compared by T test between the two groups.

2. STUDY TEAM ROSTER

Role/Name	Contact Information
Principal Investigator	
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3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to demonstrate the superiority of ultrahigh dose diuretics compared to conventional diuretic strategies in terms of urine output at 24 hours.

3.2 Secondary Objectives

The secondary objectives of this study are

a) To demonstrate safety of ultrahigh dose diuretics at 24 hours defined as development of renal insufficiency (creatinine estimated GFR decline of 50%), and hypotension (symptomatic MAP<60 or systolic blood pressure <80 mmHg).
b) To determine mechanistic changes in cardiac function, sleep parameters and biomarker changes in response to ultrahigh dose diuretics compared to standard dose diuretics.
c) To compare 24 hour change creatinine and cystatin C based changes in GFR with gold standard Iohexol clearance testing of GFR among the two diuretic strategies

3.3. Exploratory Objectives

a) To compare length of hospital stay in the ultrahigh versus usual dose groups
b) To compare total diuretic use in hospital between the ultrahigh versus usual dose groups
c) To compare 90-day heart failure rehospitalizations between the ultrahigh versus usual dose groups
d) To compare creatinine based GFR changes from baseline to day 7 or discharge (whichever is sooner) between ultrahigh versus usual dose groups
e) To explore proteomic changes in blood and urine between the ultrahigh versus usual dose groups
f) To examine changes in apnea-hypopnea index between ultrahigh and usual dose groups
g) To determine daytime and nighttime blood pressure patterns between ultrahigh and usual dose groups
h) To compare arterial stiffness alterations between ultrahigh and usual dose groups
i) To explore changes in liver elastography in the ultrahigh versus usual dose groups

4. BACKGROUND AND RATIONALE

4.1 Rationale

Acute decompensated heart failure with volume overload is one of the most common causes of hospitalization and is associated with prolonged lengths of stay and substantial expense. Longer lengths of stay are not only associated with greater expense, but also increase the risk of deconditioning and secondary complications. Furthermore, current diuretic strategies are often associated with little to no weight loss in many patients over their hospital stay likely due to inadequate decongestion.[1] Therefore, there remains an important unmet need to achieve more effective and pragmatic approaches to in hospital diuresis to maximize decongestion in a safe and time-efficient manner.

Randomized trials of in hospital diuretic strategies are limited but the DOSE trial randomized patients to a high versus low dose diuretic strategy and demonstrated a trend to improved decongestion (that did not reach statistical significance) with small transient rises in creatinine without long term risk of complications or renal failure.[2] More recent data suggested that rises in creatinine during diuresis are actually paradoxically associated with the best outcomes (likely due to it being a marker of effective decongestion), and there was no long term

sequelae of these transient creatinine changes or even more sophisticated markers of tubular injury during diuresis.[3] Therefore, small changes in creatinine during more aggressive diuresis are likely not clinically important. Additionally, patients with heart failure generally improve renal function, cardiac output and blood pressure once effectively decongested due to alleviation of renal congestion, relative pericardial restraint, improvement in right heart afterload from reduction in pulmonary artery pressure, and improvement in mitral/tricuspid regurgitation. Moreover, our observational data suggest that very high dose diuretic strategies in decompensated heart failure appears safe. The central hypothesis for this study is that a *more aggressive diuretic strategy will result in larger volume and more rapid diuresis without harm*. This will have advantages for patient care by simplifying diuretic strategies for decompensated heart failure to potentially a high dose strategy as default diuretic approach, enhance probability of effectively decongesting patients and potentially result in shorter lengths of stay with benefits for patients and healthcare systems. The PI has utilized >50 mg of bumetanide IV equivalents daily as standard of care for practice for management of heart failure patients in the cardiac ICU for the last 2 years (bumetanide bolus followed by 24 hour infusion at 2 mg/hour =>50 mg bumetanide daily) with what appears to be efficacy and safety in observational analyses. The current dose of bumetanide is administered as bolus dosing x2 at less than half of the usual dose utilized in the Mayo CCU by the PI to enhance feasibility and blinding with bolus dosing and will allow formal study of the risks and benefits of this approach in this pilot RCT.

In this pilot study we will therefore compare an ultra-high diuretic strategy with a conventional diuretic strategy in patients with decompensated heart failure with a primary efficacy end point of urine output at 24 hours. The primary safety endpoint will be a decline in serum creatinine estimated GFR by 50% of baseline value at 24 hours. This will be a double-blinded randomized pilot trial of ultra-high dose diuretics (IV bumetanide 12.5 mg bid for 24 hours vs IV furosemide at usual doses (twice the home dose of oral daily diuretic in furosemide equivalents administered bid). New initiation of adjunct diuretics (thiazide, SGLT2 inhibitors, acetazolamide, and spironolactone) will be discouraged during the 24-hour study period. Key secondary endpoints include weight change, NT-proBNP change, urine output, urine sodium excretion, creatinine, and cystatin C estimated GFR changes, apnea-hypopnea index, Iohexol glomerular filtration rate, serum and urine proteomic analyses, peripheral vein pressure and echocardiographic changes over 24 hours, estimated GFR at day 7 or discharge (whichever is sooner) will each be compared by T test between the two groups.

4.2 Hypothesis:
Ultrahigh dose diuretic infusion will be associated with greater diuretic response and will not be associated with clinically significant decline in eGFR over 24 hours (defined as decline in creatinine estimated GFR of 50% from baseline at 24 hours).

4.3 Innovation:
1. Ultra-high dose diuretic strategies have not been compared to conventional diuretic strategies in a randomized trial
2. The use of a double-blind strategy will minimize bias in terms of diuretic adjustment and alternative therapies.
3. The measurement of serum and urine biomarkers of renal injury, peripheral vein pressure and echocardiography changes at baseline and at 24 hours will provide novel insight into the hemodynamic, renal, and cardiac response to decongestion.

4. The relationship between creatinine based GFR during non-steady state conditions such as active diuresis and extracellular volume reduction during diuresis, and true GFR measured by Iohexol clearance testing has never been studied.
5. The effect of rapid diuresis on cardiac structure and function has not been well studied
6. The short-term effect of rapid volume removal on measures of sleep is unknown
7. Proteomic changes associated with high versus usual dose diuretics will be assessed to evaluate for differential expression of key pathways between the two strategies

4.4 .Significance:

1. The demonstration of safety and efficacy with ultra-high dose diuretic strategy compared to conventional diuretic infusion will be an important safety and preliminary efficacy finding to support a multicenter randomized phase III trial for superiority in relation to clinical outcomes.
2. Delineating mechanisms of hemodynamic benefit to more aggressive decongestion and relationship to renal indices will advance our understanding of human cardiorenal syndrome

4.5 Brief Synopsis of Methods:

- Accrual of 20 patients with decompensated heart failure requiring hospitalization randomized to ultra-high vs conventional dose diuretic arms in a double-blind design over 24 hours. Anticipate 25 patients will be enrolled to accrue 20 patients.
- Baseline assessment of renal Iohexol clearance, echocardiography, blood sampling and urine sampling and nocturnal Watch Pat one assessment (apnea-hypopnea index), with all above assessments repeated after 24 hours.
- Follow up phone assessment at 90 days to assess heart failure readmission rates.

5. STUDY DESIGN

This study is a double-blind randomized phase II pilot trial testing the safety and efficacy of ultra-high dose diuretics compared to standard dose diuretics over 24 hours in acute decompensated heart failure. Subjects will be screened after admission to the hospital with decompensated heart failure following stabilization and will be consented and offered participation in the trial. Once consent has been obtained, baseline serum and urine measures will be obtained along with administration of randomized treatment assignment for a total of 2 intravenous doses bid. An ambulatory blood pressure monitor (ABPM) will be worn for a 48 hour period starting from randomization. Additional mechanistic measures including short renal Iohexol clearance (2 hour), echocardiography, arterial tonometry, liver elastography, and nocturnal apnea-hypopnea index (Watch Pat) will be performed. Final endpoint assessment with repeat of all baseline measures including Iohexol clearance, echocardiography, arterial tonometry, liver elastography, and nocturnal apnea-hypopnea index (Watch Pat) will be performed on Day 2 after the 24-hour intervention. A final phone call visit at 90 days will assess for adverse events and heart failure hospitalization over the post discharge period.

6. SELECTION AND ENROLLMENT OF PARTICIPANTS

6.1 Inclusion Criteria

1. Age ≥ 18 years
2. Diagnosis of decompensated heart failure receiving intravenous diuretics
3. Ability to provide informed consent

6.2 Exclusion Criteria

1. Patients on home inotrope medications
2. Patients with Chronic Kidney disease stage V and end stage renal failure on dialysis
3. Patients lacking the capacity to consent for themselves
4. Known pregnancy or breastfeeding mothers
5. Complex congenital heart disease
6. Allergy to furosemide or bumetanide
7. Respiratory failure requiring non-invasive ventilation (CPAP/BiPAP) or invasive mechanical ventilatory support at the time of randomization
8. Hypotension with systolic blood pressure <80 mm Hg at the time of randomization
9. Acute coronary syndrome
10. Sustained Ventricular tachycardia requiring treatment in the last 48 hours
11. Patients weighing ≤ 40 kg

6.3 Study Enrollment Procedures

Eligible patients will be identified from screening of the hospitalized heart failure patients and approached in person for potential consent.

7. STUDY INTERVENTIONS

7.1 Interventions, Administration, and Duration

The ultrahigh dose diuretic arm will receive IV bumetanide 12.5 mg bid for 2 doses total within 24 hours. The standard dose diuretic arm will receive IV furosemide at usual doses (twice the home dose of oral daily diuretic in furosemide equivalents) administered as 2 doses total within 24 hours. Furosemide equivalents will be considered as follows (**40 mg of intravenous furosemide = 1 mg oral bumetanide or 40 mg of torsemide or 80 mg of oral furosemide** consistent with prior literature). There is variability in the reported literature on the conversion from torsemide to furosemide ranging from 1 mg: 1-2 mg conversion for torsemide to intravenous furosemide (JAMA 2023 Jan 17;329(3):214-223). We selected a 1:1 conversion from torsemide to IV furosemide for the standard of care arm to avoid excessively high furosemide doses for those on high doses of home oral torsemide such as 100 mg bid. The determination of diuretic dose for each of the two study drug administrations in the usual care group will be determined as twice the total home daily diuretic dose as IV furosemide split over 2 doses for bid administration. (See table for conversion of commonly used doses) If patients are diuretic naïve, they will be administered 40 mg IV bid if randomized to usual care. This will be the lowest administered diuretic dose in the standard of care arm. Therefore, if patients are on very low oral diuretic doses at home, they will be administered no lower a dose than 40 mg IV bid of furosemide for standard of care arm. The maximum allowable dose of IV furosemide in the standard of care arm will be 100 mg IV bid. Patients will be monitored for side effects including muscle cramps, new onset Atrial fibrillation (AF), sustained Ventricular tachycardia (VT), symptomatic hypotension (systolic BP<80), and dialysis initiation. Following the 2 study drug doses, patients will be subsequently treated by their physicians as per standard of care.

Home dose of diuretic	Study diuretic in standard of care arm
<80 mg of oral furosemide equivalent daily	40 mg furosemide IV bid
80 mg of oral furosemide equivalent daily	40 mg furosemide IV bid

(40 mg of oral furosemide bid or 20 mg torsemide oral bid or 80 mg or furosemide daily or 40 mg of torsemide daily or 1 mg of bumetanide daily)	
120 mg of oral furosemide equivalent daily (60 mg of oral furosemide bid or 30 mg torsemide oral bid or 120 mg of oral furosemide daily or 60 mg torsemide oral daily or 1.5 mg of bumetanide daily	60 mg furosemide IV bid
160 mg of oral furosemide equivalent daily (80 mg of oral furosemide bid or 40 mg torsemide oral bid or 160 mg of furosemide daily or 80 mg of torsemide daily or 2 mg of bumetanide daily)	80 mg furosemide IV bid
200 mg of oral furosemide equivalent daily (100 mg of oral furosemide bid or 60 mg torsemide oral bid or 200 mg of furosemide daily or 120 mg of torsemide daily or 2.5 mg of bumetanide daily)	100 mg furosemide IV bid
>200 mg of oral furosemide equivalent daily	100 mg furosemide IV bid

Furosemide oral equivalent conversion

80 mg of oral furosemide = 40 mg of oral torsemide = 1 mg or oral bumetanide = 40 mg of IV furosemide

7.2 Handling of Study Interventions

The study drug will be prepared and provided by the St Marys research pharmacy after randomization.

7.3 Concomitant Interventions

7.3.1 Allowed Interventions

All interventions necessary for the optimal medical therapy of the patients are allowed.

7.3.2 Required Interventions

None

7.3.3 Prohibited Interventions

Patients should not be on drugs that can significantly increase the risk side effects with bumetanide and furosemide, i.e., inotropic medications. New initiation of additional diuretic agents for synergistic diuresis (thiazide, acetazolamide, SGLT2 inhibitors and spironolactone) will be discouraged during the 24 hour study period to avoid electrolyte imbalance with potential randomization to very high dose diuretic arm. Following the 24 hour study period, addition of other diuretics and medications is as per the treating team per standard of care.

7.3.4 Adherence Assessment

The number of study drug administered and use of adjunct diuretics outside study protocol will be monitored and collected.

8. STUDY PROCEDURES

An overview of the scheduled evaluations is provided in the following table.

Schedule of Events

	Day of Consent (Day 1)	Day 2	Day 7[4] (-4 days)	Day 90 (Phone visit) (+/- 30 days)
Informed Consent	X			
Physical Exam	X	X		
Randomization to Medical Therapy	X			
Administration of Medical Therapy	X[1]	X[1]		
Iohexol GFR testing	X[2]	X[2]		
Blood testing (NT proBNP, cystatin C, creatinine, hematocrit,)	X	X	X[7]	
Research blood	X[3]	X[3]		
Urine testing (urine sodium, urine creatinine, NGAL, KIM-1)	X[3]	X[3]		
Electrocardiogram	X[5]		X[6]	
Echocardiogram	X	X		
Peripheral vein pressure	X	X		
Nocturnal Watchpat /Nox device screen	X	X		
Arterial Tonometry	X	X		
Ambulatory Blood Pressure	X	X		
Liver Elastography	X	X		
Adverse event assessment		X	X	X
Assessment for re-hospitalization				X
Concurrent medication assessment	X	X		X

[1]Administration of Medical Therapy to be a total of 2 intravenous doses bid, administered by inpatient staff nurses

[2]Iohexol GFR testing (Renal Clearance) to be performed at bedside by CRTU staff

[3]Blood and urine samples to be collected by CRTU staff. Samples will either be collected by CRTU or transported by study staff to CRTU in tubes on ice when necessary.
[4]Day 7 or day of discharge, whichever is earlier
[5]Baseline ECG clinically indicated. If > 48 hours prior to randomization, must be repeated.
[6]ECG for research for comparison
[7]Estimated GFR at day 7 or discharge (whichever is sooner)

8.1 Description of Evaluations

8.1.1 Screening Evaluation

Patients will be evaluated during their hospitalization for eligibility at St Marys hospital, Rochester, MN

8.1.2 Enrollment, Baseline, and/or Randomization

After confirming eligibility, informed consent will be obtained. Following consent, patients will be randomized 1:1 to ultrahigh vs standard dose diuretic strategies.

Day 1 (0-24 hours)
After randomization, patients will undergo comprehensive baseline assessment including weight, echocardiogram, history, and physical examination. Initial randomized therapy will be administered at least 6 hours after last clinically administered dose of IV diuretic (or immediately if no IV diuretic has been administered in the last 6 hours). Participants will be urged to void their bladders and discard urine at baseline immediately prior to receiving study drug. All baseline testing will be performed when feasible once consent is obtained. Baseline testing will include blood sample testing for NT proBNP, creatinine, cystatin C and hematocrit. Urine collection for urine creatinine and sodium will be specifically collected timed 1-2 hours after the administration of study diuretic dose to allow estimation of urine sodium excretion. 32 ml of blood and 30 ml of urine will be stored for future analyses. Peripheral venous pressure will be recorded from existing IV lines through pressure transducer monitoring from study team.
In addition to blood testing as above, Iohexol based GFR calculation using subcutaneously injected Iohexol and timed samples of blood and urine to calculate GFR will be used for research with a procedure following typical inpatient practice Iohexol based GFR measurement. We will use the short Iohexol protocol with subcutaneous iothalmate injection (Time 0:T0), urine sampling at 1 hour after subcutaneous injection, with total urine volume collected over the 1-hour period (T0 to 1 hour). Urine and serum samples will be collected again approximately 45 minutes later from T60. Serum and urine samples for Iohexol will be collected at two time points after T0: i) T60 and ii) 45 minutes after T60. We will also continuously collect urine from subcutaneous injection until the end of the test, for quality control as per standard clinical practice. If Foley catheter is not present at baseline, participants will be asked to void voluntarily prior to renal study initiation with bladder scanning to confirm residual urine following bladder emptying. Ambulatory blood pressure monitoring (ABPM) will be recorded via an upper arm cuff on the non-dominant arm. Over a 48-hour period (Days 1 & 2), a blood pressure reading will be taken every 30 minutes during the day and every hour at night. Arterial stiffness will be assessed via carotid tonometry and placing a femoral and brachial blood pressure cuff on the upper thigh and upper arm. A liver ultrasound scan (Fibroscan) of the abdominal region will quantify liver elastography and potential liver disease.
Nocturnal screening for apnea-hypopnea index as a measure of sleep apnea will be performed using Watch Pat or Nox device. The Watch Pat is a non-invasive wrist monitor and will be worn overnight to test for sleep apnea The Nox device is a portable polysomnography device to

measure sleep quality and determine sleep apnea presence. If patients have known sleep apnea, they will continue their home CPAP/BiPAP during the overnight test.

8.1.3 Follow-up Visits

Day 2 (24-48 hours)
All baseline testing including blood sampling and storage, urine sampling and storage, short Iohexol clearance, history/physical including weight, echocardiogram, arterial stiffness, liver scan, and nocturnal Watch Pat screen will be repeated 24 hours after initial assessment. ABPM will continue and terminate after 48 hours of blood pressure recording. Following this all study-related procedures will be complete. Hospital length of stay and total diuretic use will be documented. Clinical creatinine measurements obtained at Day 7 or discharge will be recorded for exploratory analyses. All AE's will only be collected for Days 1 through Day 7.

Day 90
Phone call to review hospitalizations, AEs, and concomitant medications. Re- Hospitalizations will be collected as AEs, not lab values. Following this all study-related procedures will be complete.

9. SAFETY ASSESSMENTS

9.1 Adverse Drug Reactions and safety aspects with bumetanide

Muscle aches and myalgias is a known side effect of bumetanide and will be assessed by a Likert questionnaire (scale 0-10). New onset atrial fibrillation, ventricular tachycardia will be assessed by review of telemetry monitoring. Blood pressure will be assessed before administration of each diuretic dose and if blood pressure is <80 mm Hg this will be reviewed by the PI and clinical team before administering subsequent diuretic dose.

9.2 Adverse Drug Reactions and safety aspects with furosemide

Adverse reactions will be recorded as above for bumetanide.

9.3 Specification of Safety Parameters

Renal function panel will be checked at least twice as is standard practice during intravenous diuresis and K and Mg replacement will be adjusted as per electrolyte panel checks with oral KCl and Mg repletion utilized as per clinical practice. Intravenous repletion will be used when oral therapy is not tolerated. In the presence of substantial hypokalemia (K<2.9 mEq/dl), the subsequent diuretic dose will be held until K repletion has been administered.

Blood pressure monitoring prior to each dose will ensure hemodynamic stability prior to administration of subsequent diuretic dose. If the systolic BP is <80 mmHg this will be reviewed by the PI and clinical team before administering subsequent diuretic dose.

During arterial stiffness measures, if aortic pulse pressure is greater than 50 mmHg (derived from brachial BP), we will forgo carotid tonometry and femoral blood pressure measures.

9.4 Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

Hemodynamic safety will be recorded by blood pressure monitoring prior to each administered study dose.

9.5 Adverse Events and Serious Adverse Events

All patients will be evaluated for adverse events (AEs) and serious adverse events (SAEs) routinely at the time of follow-up evaluations. In addition, patients will be instructed to call in with concerns and/or present to their primary care providers. Should concerns for AEs and SAEs be raised, these will then be evaluated further. The time frame of evaluation for AEs and SAEs is confined to the duration of their participation in this study. All events are to be recorded within 1 day of the study team being notified regardless of their relationship to the study intervention and will be adjudicated and classified as outlined below.

For this study, and in agreement with general definitions, an AE is defined as

- Any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen.

A SAE is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

Date and Time of Onset

The date and time of onset is the date and time when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken, or the examination was performed.

Classification of AE Severity

The Investigator must grade each adverse event according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0). According to this guidance document all adverse events are rated on a 5-point scale corresponding to mild, moderate, severe, life-threatening, or disabling and death.

Each adverse event must be graded according to the specific criteria for grading as described in the CTCAE. For events not described in the CTCAE the following criteria will be used:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AE Attribution Scale

AEs will be categorized according to the likelihood that they are related to the study intervention as determined by a clinician. The causal relationship can be one of the following:

0 = unrelated
1 = Unlikely
2 = Possibly related
3 = Probably related
4 = Definitely related

9.6. Reporting Procedure

The reporting system that will be used in this study is summarized in the following table. The study statistician, program manager, and PI will be involved in all data reviews. Any adverse event rate more than twice the expected will be reported to the Mayo Clinic IRB and the study sponsor.

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Quarterly	Study statistician, Program Manager, PI
Status of all enrolled subjects, as of date of reporting	Quarterly	Study statistician, Program Manager, PI
Adherence data regarding study visits and intervention	Quarterly	Study statistician, Program Manager, PI
AEs and rates (including out-of-range lab values)	Quarterly	Study statistician, Program Manager, PI,
SAEs	Per occurrence	Study statistician, Program Manager, PI, sponsor

SAE Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported by the PI to the IRB, and sponsor in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the within 7 days. Other serious and unexpected AEs related to the intervention will be reported within 15 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the IRB, and sponsor and other oversight organizations in accordance with their requirements.

9.7 Follow-up for Adverse Events

The safety profiles of the study intervention are very well characterized and defined (see above). The rates and outcomes are not expected to deviate from clinical practice and thus this study will adhere to practice standards with assessment of AEs at 24 hours and 90 days.

9.8 Safety Monitoring

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

All SAEs will be reported to the IRB according to institutional policy. Screening and application of exclusion criteria will minimize potential risks.

As a service to the investigator, this study may be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist investigators in complying with Food and Drug Administration regulations.

10. INTERVENTION DISCONTINUATION

Discontinuation of the study intervention is recommended for any incapacitating and/or life-threatening side effect. Resuming the study medication will depend on an evaluation if the drug can be safely resumed. Patients may have to permanently discontinue study interventions and for this reason participation in this study if intolerable side effects persist.

At any point in time and for any reason, patients may withdraw voluntarily from participation in the study.

In the absence of any reason for premature termination as outlined above, participation will end for every patient after 6 months of trial participation.

Blood pressure will be assessed before administration of the second dose of assigned IV diuretic. In the event of symptomatic hypotension (symptomatic MAP<60 or systolic blood pressure <80 mmHg), the participant will be evaluated by the PI and study team and further dose of study medication will be suspended. The patient, PI and clinical team will be unblinded to allow the clinical team to make a determination of optimal subsequent plans of care and diuretic dosing.

Study stopping rules for safety

We will also implement Bayesian monitoring with utilization of an independent study monitor Dr Kent Bailey who will have access to unblinded patient data as they accrue with continuous monitoring of safety. Among the high dose diuretic arm, assuming a probability of serious adverse events of 1/20 (5%) as prior information, we will monitor for 1) symptomatic hypotension (defined above) and 2) a decline in estimated GFR from 0-24 hours of >50%. Based on prior experience with this intervention, we formulated a Bayesian prior distribution for the adverse event rate p associated with this intervention, tantamount to observing 1 adverse event in 20 previous patients, or a 5% prior probability. Based on this prior, the Bayesian prior probability that the true adverse event rate exceeds 20% is only 6%. We have developed a stopping boundary, based on the Bayesian analysis of the accumulating data and the criterion that we would stop the trial if the posterior probability that the true AE rate exceeds 20% gets to 40% or more. This leads to the monitoring boundary at which point, we will pause the study and consider protocol modification and/or cessation of the study as appropriate. This decision will discussed and made by the PIs from cardiology (Dr Pereira, Reddy) and nephrology (Dr Larson) and statistician (Dr Bailey)

Posterior probability (%) that p > 20%

Number of AE	1	2	3	4	5	6	7	8	9	10
0	5	4	3	2.8	2.3					

1	15.5	13.5	12.5	10	8.5	7	6			
2		30	27	24	21	18	16	14		
3			**46**	**42**	39	35	32	29	26	
4				62	**58**	**54**	**50**	**47**	**43**	
5					75					

Based on Mayo observational data, we do not anticipate safety concerns with the high dose diuretic arm. “The recommended use of higher than recommended diuretic dosing for bumetanide is consistent with heterogeneous clinical practice and forms the basis for this prospective study. In our retrospective analysis of 102 patients with severe heart failure admitted to the Cardiac intensive care unit, 28% of patients were receiving very high dose of diuretics (mean dose of 1386 furosemide equivalents administered as bumetanide infusion which would be equivalent to roughly 35 mg of bumetanide administered daily which exceeds the commonly recommended max daily dose of 10 mg of bumetanide which is not based on any data). Very high dose bumetanide compared to conventional therapy (1386 mean furosemide equivalents in 24 hours compared to 257 furosemide equivalents, p<0.0001) was not associated with differences in change in mean arterial pressure over the 72 hours of ultra high dose diuretics (mean BP change 2.2 +/- 12.1 vs 4.1 +-12.6, p=0.48) but there was greater loss in weight (-10.8 +- 8.7 vs -7.2 +-8.6 kg, p=0.05) and urine output (10.0 +-4.7 vs 8.1 +/-3.8, p=0.04) with no concerning worsening of renal function (creatinine change -0.03 +/- 0.91 vs -0.02 +/- 0.89, p=0.81). It is currently the PI’s current practice in the CCU in the last 2 years to use a 12.5 mg bumetanide bolus followed by an infusion at 2 mg/hr (equivalent of 60.5 mg of bumetanide daily) in critically ill cardiac ICU heart failure patients, which has been extremely successful at decongestion with no apparent serious adverse events or untoward hypotension. However, this strategy of upfront high dose diuresis has not been tested with the rigor of a randomized trial forming the basis for this study. The chosen dose of 12.5 mg of bumetanide bid is < half of the currently used diuretic strategy in most CCU patients treated by the PI and many others at Mayo Clinic, Rochester, and a bolus of 12.5 mg of bumetanide has been reported in other studies of heart failure patients [redacted]. There remains no randomized data that high dose diuretics are nephrotoxic and the transient changes in renal function observed in clinical randomized trials are reversible and not associated with need for dialysis and are paradoxically associated with better outcomes.3

11.STATISTICAL CONSIDERATIONS

11.1 General Design Issues and possible approaches to address them

Muscle cramps is a possible side effect of high dose bumetanide infusions and may limit continuation of bumetanide therapy. In the event of severe muscle pain, the dose of subsequent blinded infusion can be decreased to half the infusion to minimize pain with analgesic use as needed. If side effect is severe requiring change in therapy despite electrolyte correction and decrease in diuretic dosing, patients will be unblinded with subsequent therapy provided as per clinical practice. Providers are variable in adjunct strategies with vasodilators, inotropes, and adjunct diuretics during management of acute decompensated heart failure. We will exclude patients with anticipated initiation or use of inotropes at baseline, and adjunct thiazide diuretics will be discouraged for the 24 hours during the study protocol. We will only recruit patients with

stable respiratory status without use of non-invasive or invasive mechanical ventilation to minimize need for rescue therapies.

11.2 Sample Size and Randomization

This is a pilot study and sample size of 20 is selected based on feasibility to determine probably efficacy and safety to guide design of a pivotal trial. The dose separation between ultrahigh and standard dose diuretics is higher than has previously been tested and there is no data on diuretic differences at such high doses.

11.2.1 Treatment Assignment Procedures

Randomization will be performed 1:1 after consent without block randomization or stratification.

11.3 Interim Analyses and Stopping Rules

Given small sample size, no interim analyses are planned

11.4 Outcome Measures

11.4.1 Primary trial objective

To determine the diuretic effect of ultrahigh compared to standard diuretic measures

11.4.1.1 Primary outcome measures
Urine output at 24 hours

11.4.2 Secondary trial objective
Determine renal, cardiac, and systemic effects of ultra-high dose compared to standard diuretic regiments

11.4.2.1 Outcome measures
Key secondary endpoints include weight change, NT-proBNP change, urine output, urine sodium excretion, apnea-hypopnea index, Iohexol glomerular filtration rate, peripheral vein pressure and echocardiographic changes over 24 hours

11.5 Data Analyses

11.5.1 Statistical Considerations and Methodology

1.1 Overview: This is a single-site, randomized, double-blind, parallel-group clinical trial in acute decompensated heart failure patients with volume overload requiring hospitalization. Patients will be randomized in a 1:1 fashion to either ultra high dose intervention with intravenous bumetanide 12.5 mg bid over 24 hours (Group 1) or standard dose intervention with intravenous furosemide as twice the home dose of oral diuretic in furosemide equivalents administered bid over 24 hours (Group 2).

1.2 Primary and Secondary Objectives

1.2.1 Primary objective: To determine the diuretic effect of ultra high compared to standard diuretic measures.

1.2.2 Secondary objective: To determine renal, cardiac, and systemic effects of ultra high dose compared to standard diuretic regiments.

1.3 Primary and Secondary Outcomes

1.3.1 Primary outcome: urine output at 24 hours after initiation of intravenous diuretic.

1.3.2 Secondary outcomes: changes in the following measures over 24 hours after initiation of intravenous diuretic:

1.3.2.1 Body weight

1.3.2.2 NT-proBNP change

1.3.2.3 Urine sodium excretion

1.3.2.4 Apnea-hypopnea index

1.3.2.5 Iohexol glomerular filtration rate

1.3.2.6 Peripheral vein pressure

1.3.2.7 Echocardiographic measures of cardiac output, estimated RV systolic pressure, RA pressure, LA strain, LV and RV global longitudinal strain, E/e'

1.4 Primary Analysis

1.4.1 The primary analysis will be to compare urine output at 24 hours after initiation of intravenous diuretic. All patients meeting eligibility criteria who provide informed consent, are randomized, and receive any dose of intravenous diuretic will be included in the primary analysis based on intention-to-treat (ITT) principles. The difference in 24-hour urine output between groups will be estimated using a linear regression model; 95% confidence intervals will be constructed using t-based methods. A p-value less than 0.050 will be considered statistically significant.

1.5 Secondary Analysis

1.5.1 Linear regression models will be used to estimate the between group difference in 24-hour change in each of the secondary outcomes; 95% confidence intervals will be constructed using t-based methods.

1.6 Exploratory Analysis

1.6.1 We will quantify any differential treatment response by heart failure subtype (HFPEF, HFrEF) by including heart failure subtype as a covariate and as an interaction with the group effects in the models mentioned above.

1.7 Sample Size Determination

1.7.1 Sample size was determined based on a combination of feasibility and also the variability of 24-h net urine output observed in the ATHENA-HF trial (Butler et al. 2017). Butler et al. observed a median (25^{th} percentile, 75^{th} percentile) net urine output of 1183 ml (510, 1955) in the usual care alone group and 1100 ml (483, 2131) in the high dose spironolactone group**. With a total sample size of 20 patients (10 per group), we will have 80% power at the alpha=0.05 level of significance (two-sided) to detect a 1688 ml difference in 24-h urine output assuming a common standard deviation of 1200 ml and a dropout rate of 10% or less.** With all other assumptions being the same, the following gives estimates of power for a range of differences. Power was estimated using nQuery Advisor version 7.0 (two group t-test of equal means).

Difference (mL)	**Power**
1500	70%
1600	75%
1700	**80%**
1800	84%
1900	88%
2000	**91%**

1.8 Randomization

1.8.1 Participants will be randomized in a 1:1 fashion while maintaining a level of unpredictability to future randomization assignment. The randomization sequences will be prepared by the study statistician (CTB) using random variable block sizes of two or four patients per block. REDCap's randomization module will be used to reveal the randomized assignment on a per-patient basis by pharmacy staff.

1.9 Blinding

1.9.1 Patients and all study staff will be blind to the randomization assignment except for pharmacy staff and the study statistician.

1.10 Multiplicity Considerations

1.10.1 We will report unadjusted p-values and describe the correlation of primary and secondary outcomes in publications to allow for additional researchers to evaluate the robustness of the findings.

12.DATA COLLECTION AND QUALITY ASSURANCE

12.1 Data Collection Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

The data collection tool for this study will be sponsor defined case report forms. The investigator will maintain complete and accurate study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the study coordinator study monitor/sponsor, screening and consent information, severe adverse event reports, laboratory reports, subject diaries, data clarifications requested by the sponsor, and any other documentation deemed relevant and pertinent to the study and the study subjects. Subject data necessary for analysis and reporting will be entered into a validated database or data system in accordance. Clinical data management will be performed in accordance with applicable data management vendor standards and data cleaning procedures. The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. The handling of data, including data quality assurance, will comply with regulatory guidelines.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

12.2 Data Management

All study data will be collected at Mayo Clinic with the Department of Cardiovascular Diseases as the primary coordinating and data management center.

REDCap will be used for clinical data management and randomization. These tools are institutionally supported and allow for rapid database development. The implementation of the software within a project includes training on the system's use, robust error checking, security considerations, and full audit trail. Balance, which is integrated into *REDCap*, allows for a variety of randomization and minimization algorithms.

Demographic and clinical data will be extracted from medical records including age and gender, vital signs, physical exam findings.

For biospecimens, NT-pro-BNP, creatinine, hematocrit and cystatin C, urine sodium will be measured in real time, and the remainder will be stored for future analysis of cardiac biomarkers.

The echocardiographic parameters that will be captured comprise: systolic, diastolic LV and RV function parameters including LVEF by M-Mode, 2 D, biplane Simpson, lateral and medial E/e', left atrial volume index, right ventricular size and function, tissue velocities of the tricuspid annulus, TAPSE, lung ultrasound for B lines, IVC diameter/collapse, internal jugular dimension/size relative to carotid.

All individually identifiable patient records and data will be stored in a database under coded accession numbers. A password is required to gain access to this protected and privileged information. Only the approved and trained study staff will have access to the database. For individuals providing data, e.g., core laboratory personnel, access will be limited to entering data only. All data are monitored regularly for entry and access, and a formal policy regarding protection of personal privacy is in place throughout Mayo Foundation. The key to identification of subjects will be maintained in a secure office environment under the direction of the investigators. The institutional commitment at Mayo Clinic to protect patients' (and study participants') privacy is a high priority.

12.3 Quality Assurance

12.3.1 Training

The study will be performed only by adequately trained personnel. This applies to the entire study team roster. Only approved and trained study staff, experienced in trials such as these, will interact with the patients and manage the data forms and database. The echocardiography and laboratory teams are likewise experienced in these types of trials as is the section of biostatistics at Mayo.

12.3.2 Quality Control Committee

This study will not assemble a quality control committee.

12.3.3 Metrics

The primary outcome measure is urine volume. We will compare change in urine volume to body weight change as a metric of accurate urine output collection. Source document verification will be performed to ensure data fidelity as well. To ensure compliance with applicable regulatory requirements, the sponsor or designee may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

12.3.4 Protocol Deviations

Protocol deviations in diuretic administration and/or adjunct diuretic use will be recorded

12.3.5 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

13. PARTICIPANT RIGHTS AND CONFIDENTIALITY

The study will employ standard methods for protecting the confidentiality of research materials through the use of coded identification numbers that are specific to the study on all materials except those that are necessary for participant contact, follow-up, and ongoing linkage with data such as those from medical records, using password-protected computer data files and databases, and locked file cabinets for storing hard copies of any other study materials. Only study personnel who need to track participants for follow-up purposes have access to the identifying information for individual study participants. No personally identifiable information (protected health information) except the minimum necessary for study purposes are shared with co-investigators, and any sharing of data is by encrypted, password-protected data files. In addition to the procedures outlined above, confidentiality and privacy are further enhanced as each institution maintains research databases behind institution-specific password-protected firewalls.

Blood specimens will be stored in appropriate freezers coded with study-specific identification numbers and barcodes with no other identifying information on them. Barcodes include information on time of storage and are linked to a password-protected research laboratory information management system (RLIMS) database that was built specifically for these purposes. Study staff members are trained to follow established confidentiality procedures. Samples will be kept in central, secured repository. Should it become necessary to ship samples to collaborating investigators for approved sub-analyses, this will be done without any identifying information except for study-specific identification numbers.

Echocardiographic images will be stored on a secured data platform.

No preliminary or final results will be released or published with identifying information or reported on an individual level, and all epidemiologic data will be presented as statistical summaries. No statistics will be published based on fewer than 5 subjects, a practice consistent with HIPAA and most confidentiality guidelines.

A description of the plan for data and safety monitoring and adverse event reporting to the IRB, the Data and Safety Monitoring Board, the NIH and others, as appropriate, is provided in the Data and Safety Monitoring Plan to ensure the safety of subjects.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why?
- Who will use or disclose that information?
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should

be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

13.1 Institutional Board Review (IRB) Review

13.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and will be documented in the participant's record.

For patients not fluent in English, an interpreter will be present to translate the informed consent and for the discussion of the informed consent with the trained study team member. It is already a standard of care at Mayo Clinic that all patients considered not fluent enough in English will have interpreter services. Thus, this study builds and extends on this practice.

Adults who lack the capacity to consent may not participate in the study. Other vulnerable adults and children will not be included in the study.

13.3 Participant Confidentiality

The confidentiality of all participants will be maintained according to the Health Insurance Portability and Accountability Act (HIPAA), any special data security requirements, and record retention per the sponsor's requirements.

Any data, specimens, forms, reports, or records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

13.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

14. ETHICAL CONSIDERATIONS

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent

15. COMMITTEES

As an all Mayo, phase 2 trial, this study will not convene any committee such as a Steering Committee or an Executive Committee, a Publication Committee, or an Adjudication Committee.

16.PUBLICATIONS OF RESEARCH FINDINGS

17.REFERENCES

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2. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805.

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