

Study Protocol

Randomized Evaluation of Heart Failure with Preserved Ejection Fraction (HFpEF) Patients with Acute Heart Failure and Dopamine (ROPA-OP) Trial

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JHM IRB - eForm A – Study Protocol

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1. Abstract

- a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Heart Failure with preserved Ejection Fraction (HFPEF) accounts for 40-50% of all heart failure patients with a frequency of hospital admissions for acute decompensation and short and long term mortality similar to patients with heart failure with reduced ejection fraction (HFREF). Patients with HFPEF are often preload dependent and despite admission to the hospital for acute decompensated heart failure (ADHF), are typically difficult to diurese due to the development of acute kidney injury. In contrast to the many randomized trials showing mortality and morbidity benefit of ACE inhibitors and beta blockers in patients with heart failure with reduced ejection fraction, no drugs have shown a benefit in patients with HFPEF. Furthermore, patients hospitalized for ADHF who develop acute kidney injury during their hospital stay have longer hospitalizations, more frequent re-hospitalizations for heart failure, and worse short term survival compared to those without acute kidney injury. We hypothesize that changing the method of diuresis and/or the addition of low-dose dopamine for the treatment of ADHF in patients with HFPEF will reduce renal injury, resulting in a shorter length of stay, and decrease hospital readmissions over the ensuing year.

2. Objectives (include all primary and secondary objectives)

To evaluate the effects of low dose dopamine and diuretic strategy (intermittent versus continuous) on renal function in patients with HFPEF admitted with acute heart failure.

Primary end point:

1. Percent change in creatinine from randomization to 72 hrs from treatment protocol initiation.

Secondary end points:

1. Change in incidence of acute kidney injury (AKI) as defined by Kidney Disease: Improving Global Outcomes (KDIGO criteria summarized below) from randomization to 72 hrs.¹

2. Incidence of AKI as determined by urine output at 72 hrs (KDIGO criteria, summarized below).¹
3. Change in creatinine at 72 hrs adjusted for volume of fluid removal
4. Change in serum cystatin C randomization to 72 hrs
5. Change in NT pro-BNP from randomization to 72 hrs
6. Volume of diuresis measured in liters
 - a) Cumulative volume of diuresis measured in liters
 - b) Cumulative volume of diuresis measured in liters adjusted for BSA
7. Net weight loss at 72 hrs in kg
8. Need for increase in intravenous diuretic dose
9. Change in distance during 6 minute walk test
 - a) From admission to 72 hrs
 - b) From admission to discharge
10. Global well-being assessment score from admission to 72 hrs, and at discharge. To be assessed by a Visual Analog Scale (VAS).
11. Subjective dyspnea score from admission to 72 hrs, and at discharge. To be assessed by a Visual Analog Scale (VAS).
12. Change in frailty index from admission to 72 hrs, and at discharge. To be assessed by the Johns Hopkins Older Americans Independence Center Online Frailty Assessment Tool
13. Length of stay of hospitalization in days
14. 30 day, 6 month, and 1 year hospital readmission or ER visit for major adverse cardiovascular event, heart failure, renal failure (development of CKD, ESRD, or dialysis need by KDIGO criteria), syncope, or arrhythmia. Readmission events will be adjudicated by a Clinical Event Committee consisting of 2-3 cardiologists not directly in contact with patients enrolled in the study.

KDIGO AKI Definition¹:

AKI is defined by any of the following 3 criteria:

1. Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$) within 48 hours; OR
2. Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within prior 7 days; OR
3. Urine volume < 0.5 ml/kg/h for 6 hours

Stages of AKI as defined by KDIGO Criteria are as follows:

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$) increase	< 0.5 ml/kg/h for 6-12 hours

2	2.0-2.9 times baseline	<0.5 ml/kg/h for \geq 12 hours
3	3.0 times baseline OR increase in serum creatinine to \geq 4.0 mg/dl (\geq 353.6 μ mol/l) OR initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m ²	<0.3 ml/kg/h for \geq 24 hours OR Anuria for \geq 12 hours

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

It is estimated that there are 6.6 million patients with heart failure in the United States, a prevalence of nearly 3% of US adults over the age of 18 years.² In 2008, an estimated 280,000 deaths were attributed to heart failure any-mention.² In 2009, there were an estimated over 1 million hospital discharges for heart failure, making acute decompensated heart failure (ADHF) the most common cause of hospital admission in patients over the age of 65.² Of this population, up to 38 to 60% have preserved left ventricular systolic function, or heart failure with preserved ejection fraction (HFPEF).^{3,4} The reported morbidity and mortality of this patient population is equal to or slightly better than that observed in heart failure with reduced ejection fraction (HFREF).^{3,5} Large, randomized controlled trials studying pharmacologic treatments have failed to show consistent benefit in the HFPEF population. With a burgeoning population with the HFPEF diagnosis, there is much need to better understand the associated risk factors, predictors of morbidity and mortality, and potential treatments that may offer improved quality of life and mortality benefit in this population.

Patients with HFPEF and HFREF are treated with intravenous diuretics when admitted to the hospital with acute decompensated heart failure as part of standard therapy. In contrast to patients with HFREF, the best mechanisms to achieve safe and adequate diuresis in patients with HFPEF are unknown.⁶⁻⁷ Our retrospective experience (NA_0082035) shows that with intermittent intravenous diuretic therapy, approximately 50% of patients with HFPEF experience acute kidney injury defined as a creatinine rise $>$ 0.3 mg/dL and /or relative increase in creatinine of \geq 25% over the course of their inpatient hospitalization. Acute kidney injury in a hospitalized heart failure population is associated with prolonged length of stay, more frequent readmissions, and increased short term mortality.⁸ Studies have demonstrated in HFREF patients that a mild reduction in glomerular filtration rate (increase in plasma creatinine of 0.2-0.3 mg/dL) has an impact on patient survival, even in those who were asymptomatic.⁹⁻¹⁰ Efforts to achieve an

effective and safe diuresis without acute kidney injury are important goals in the HFPEF population.

Intravenous diuretic therapy is an essential component of the inpatient management of patients admitted with ADHF. Due to limited prospective data on the optimal method of administration and dosage of intravenous diuretic therapy, clinical practice has varied widely with regards to this component of heart failure management. From a pharmacokinetic and pharmacodynamic standpoint, some data have suggested a possible benefit with continuous infusion diuretic therapy compared to intermittent bolus dosing. However, the Diuretic Optimization Strategies Evaluation (DOSE) trial demonstrated that patients with HFREF admitted with ADHF had no significant difference in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered as intermittent bolus dosing versus continuous infusion, or at high compared to low dosing protocols.⁶ While there is no benefit with continuous intravenous diuretic treatment in HFREF patients, there are very limited data evaluating diuretic treatment strategy in the HFPEF population.⁶ Given the pre-load dependency and likely altered intravascular and extravascular fluid distribution in HFPEF patients, it is important to better understand the effect of diuretic strategy in this population, particularly given the high incidence of AKI that has been observed in these patients.

Therapies targeting renal protection in ADHF have also not consistently shown clinical or renal protective benefit, including nesiritide, nitroprusside, nitroglycerine, and dobutamine.¹¹⁻¹⁴ Dopamine is a catecholamine that exhibits dose-dependent effects on the systemic and renal vasculature. At low doses ($\leq 3 \mu\text{g}/\text{kg}/\text{min}$), it has been found to act on the A1 receptors, resulting in vasodilatation of the renal arteries in addition to the mesenteric, coronary, and cerebral vascular beds. The use of low-dose or "renal-dose" dopamine in ADHF has been proposed as a renal protective therapy. A large meta-analysis of 61 trials evaluating the effects of low-dose dopamine on a broad range of clinical and renal outcomes showed improvement in urine output and transient improvement in renal physiology, without significant effect on mortality, need for renal replacement therapy, or adverse outcomes.¹⁵ More recent studies have suggested that low-dose dopamine may increase renal blood flow and GFR in stable patients with HFREF.¹⁶⁻¹⁷ The Dopamine in Acute Decompensated Heart Failure (DAD-HF) trial randomized 60 patients to either high-dose furosemide, or low-dose furosemide in combination with low-dose dopamine with a primary endpoint of worsening renal function. The trial demonstrated significantly higher incidence of renal impairment in the high-dose furosemide treatment group compared with the low-dose furosemide with dopamine group.⁷ It is important to note that the data available to date on the effects of low-dose dopamine in heart failure is predominantly from patients with reduced ejection fraction (HFREF) patients; exceedingly limited data is available on the use of this therapy in the HFPEF population.

Given the increasing incidence and prevalence of HFPEF, with associated morbidity and mortality nearing that of systolic heart failure, it is imperative to better understand and assess treatment strategies in this patient population. To date, our management of ADHF in HFPEF patients has been largely extrapolated from treatment strategies used in

HFREF patients. It clearly cannot be assumed that HFPEF patients respond in the same way to many of these treatments, including diuretic strategy and the use of renal protective agents, such as low-dose dopamine. Thus, further investigation of the efficacy and safety of these treatments in the HFPEF population is warranted.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This is a prospective, randomized, non-blinded study. The outcome variable collection will be blinded. Subjects will be randomized (1:1:1:1) within 24 hours of admission for acute decompensated heart failure to one of four treatment groups:

Treatment Protocol:

1. Intermittent bolus (every 12 hrs) furosemide diuretic therapy
2. Continuous infusion furosemide diuretic therapy
3. Intermittent bolus (every 12 hrs) furosemide diuretic therapy plus infusion of low dose intravenous dopamine (3 µg/kg/min)
4. Continuous infusion furosemide diuretic therapy plus infusion of low dose intravenous dopamine (3 µg/kg/min)

Each treatment arm protocol is detailed as follows:

1. Intermittent bolus furosemide diuretic therapy:
 - a. If the patient is not on a prior diuretic dose, a standard dose of furosemide 40mg IV every 12 hrs, with total dose of 80 mg IV over 24 hrs will be initiated.
 - b. If the patient is already on a prescribed diuretic dose, their outpatient dose will be doubled and administered as the equivalent IV dose every 12 hrs. Note: standard furosemide dosing has a 2:1 oral to IV ratio when dosing.
 - i. Example: If the prescribed home dose is furosemide 80mg by mouth twice daily, the inpatient treatment dose will be the IV equivalent of furosemide 160 by mouth twice daily (double the home dose). Therefore, the inpatient treatment dose would be furosemide 80mg IV twice daily).
2. Continuous infusion furosemide diuretic therapy
 - a. If the patient is not on a prior diuretic dose, a standard dose of furosemide 80mg IV over 24 hrs, will be initiated.
 - b. If the patient is already on a prescribed diuretic dose, their outpatient dose will be doubled and administered as the equivalent IV dose, continuously over 24 hrs. Note: standard furosemide dosing has a 2:1 oral to IV ratio when dosing.
 - i. Example: If the prescribed home dose is furosemide 80mg by mouth twice daily (160mg total per day), the inpatient treatment dose will be the IV equivalent of furosemide 320mg total per day. Therefore, the inpatient treatment dose would be furosemide 160mg IV administered continuously over 24 hrs.

3. Intermittent bolus (every 12 hrs) furosemide diuretic therapy plus infusion of low dose intravenous dopamine (3 µg/kg/min)
 - a. Intermittent furosemide diuretic therapy from above (1.) with the addition of dopamine at 3 µg/kg/min
4. Continuous infusion furosemide diuretic therapy plus infusion of low dose intravenous dopamine (3 µg/kg/min)
 - a. Continuous furosemide diuretic therapy from above (2.) with the addition of dopamine at 3 µg/kg/min

Conversion guidelines:

2 mg oral furosemide = 1 mg intravenous furosemide

1 mg torsemide = 2 mg furosemide

1 mg bumetanide = 40 mg furosemide

Diuretic titration guidelines:

Should the patient fail to demonstrate adequate diuresis (net negative urine output of at least 500ml in 12 hrs) in response to the first treatment dose, the subsequent diuretic dose to be administered 12 hrs later (dose #2) will be doubled, or the continuous infusion will be doubled, with the goal of net negative urine output of 1 liter over 24 hrs. This titration plan can continue until adequate diuresis is achieved (at least net negative 1L urine output over 24 hr period).

Maximum Diuretic Dose:

The maximum dose permitted within study protocol will be furosemide 200 IV twice daily, or a total dose of furosemide 400 IV over 24 hrs. Should the primary team feel the patient needs higher dosing or the addition of a thiazide diuretic (or alternative agent), the patient will be considered treatment failure and will be removed from the study.

Electrolyte Repletion Guidelines:

The primary team will obtain basic metabolic panels on all study participants every 12 hours for the duration of the study. It will be the responsibility of the primary team to replete electrolytes with the goals of potassium > 4.0, and magnesium >2.0 as needed for study participants.

Fluid and Salt Restrictions:

Each study participant will be maintained on a daily 2 liter fluid and 2 gm sodium restricted diet, to be ordered by the primary team.

Treatment beyond trial end-point guidelines:

Intravenous diuretic therapy with or without dopamine according to the protocol will be continued until the treating physician decides the patient no longer requires intravenous diuretic therapy or 72 hours, whichever comes first.

All other heart failure or non-heart failure treatments will be left to the discretion of the primary team from the time of the patient's admission to the hospital and/or enrollment in the study. This includes anti-hypertensives, anti-arrhythmic drugs, and any other therapies deemed necessary for the treatment of the study subject.

After 72 hrs, the study drug will be discontinued, a primary assessment will be made of primary and secondary endpoints, and all further treatment is at the treating physician's discretion.

Note: Study participants will be permitted to cross over into non-assigned arms of the study, however the study analysis will be completed as an intention-to-treat study. It will be left to the discretion of the primary team, with supervision from the study investigators as to whether a cross over is necessary within the 72 hr study time frame.

Baseline Assessments and Data to be Recorded (all are standard of care unless indicated by *)

1. Directed history and physical exam, focused on signs and symptoms of congestion/volume overload
2. Vital signs (HR, BP, O2 saturation, weight, height)
3. Home medications
4. Basic metabolic panel including serum creatinine, BUN, electrolytes and magnesium
5. Serum Pro-BNP level
6. Serum Cystatin C*
7. High-sensitivity troponin
8. Baseline electrocardiogram
9. Transthoracic echocardiogram if one has not been obtained within 1 year prior to admission
 - i. Including left ventricular (LV) ejection fraction, LV dimensions, left atrium size (LA), LV mass, right ventricular function parameters (RVSP), valvular assessment
10. 6 min walk test*
11. Patient Global Well being assessment by VAS*
12. Dyspnea assessment by VAS*
13. Frailty Index*
14. Blood sample for biomarkers and genetic testing for heart failure*
15. Urine sample for biomarkers*

24 hr Assessment:

1. Routine vitals assessment with weight recording
2. I/O assessment – to be recorded and totaled for each 12 period
3. Twice daily basic metabolic panel and serum magnesium

72 hr Assessment and Data to be Recorded:

1. Routine vitals assessment with weight recording
2. I/O assessment – to be recorded and totaled for each 24 period
3. Twice daily basic metabolic panel and serum magnesium
4. Serum Pro-BNP level*
5. Serum Cystatin C*
6. High-sensitivity troponin
7. 6 min walk test*
8. Patient Global Well being assessment by VAS*
9. Dyspnea assessment by VAS*
10. Frailty Index*
11. Changes in cardiovascular medications
12. Assessment for serious cardiovascular events

At Discharge Assessment and Data to be recorded:

1. Routine vitals assessment with discharge weight recording
2. I/O assessment – to be recorded and totaled for each 24 period
3. Basic metabolic panel including creatinine, BUN
4. Serum Pro-BNP level
5. Serum Cystatin C*
6. High-sensitivity troponin
7. 6 min walk test*
8. Patient Global Well being assessment by VAS*
9. Dyspnea assessment by VAS*
10. Frailty Index*
11. Changes in cardiovascular medications
12. Assessment for serious cardiovascular events
13. Urine and serum samples for biomarkers*

*Investigational data to be collected as part of trial protocol.

Day 30, 6 month, and 1 year Assessment and Data to be Recorded:

Patient charts will be reviewed and patients will receive a phone call to assess for potential re-hospitalizations and major adverse cardiovascular events at each respective endpoint since discharge. The first readmission event following index hospitalization will be adjudicated by a Clinical Event Committee consisting of 2-3 cardiologists not directly in contact with patients enrolled in the study.

Vascular Access:

All patients in the intermittent bolus diuretic strategy arm will require the placement of two functioning peripheral IV catheter. Patients assigned to the continuous diuretic strategy and either treatment arm that requires low-dose dopamine will need at least 2 peripheral IVs suitable for continuous infusions. Central venous catheter placement may be required should it be difficult to obtain or maintain peripheral IV

access. This would be determined by the primary team, with consent obtained separately for this procedure by the primary team.

Foley Catheter Placement:

All patients enrolled in this trial will be encouraged to have a foley urinary catheter placed. This will allow for improved patient tolerance of diuresis and improved accuracy of I/O assessment by nursing staff. This will not be required, however, for enrollment in the trial.

b. Study duration and number of study visits required of research participants.

The study duration is the hospital admission. The study drugs will be mandated for 72 hours following enrollment. There are no outpatient visits but patients will receive follow up phone calls, at 30 days and at 6 months following discharge.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

The treatment is not blinded. The primary endpoint of change in renal function will be objectively obtained and should not be affected by lack of blinding. All other variables will be obtained by an investigator blinded to the study drug assignment.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will receive routine care for their acute decompensated heart failure. Currently, many practitioners utilize both intermittent and continuous furosemide infusions in this patient group. Low dose, or renal-dose dopamine is also a frequent adjunct to diuretics to aid in diuresis.

e. Justification for inclusion of a placebo or non-treatment group.

There is no placebo group.

f. Definition of treatment failure or participant removal criteria.

Subjects will be removed from the protocol for:

1. The development of hemodynamic instability including hypotension (SBP < 90), hypertensive emergency, or unstable arrhythmias (SVT or VT).
2. The development of pulmonary edema requiring inotropes or vasopressor or more than 50% inspired oxygen.
3. The development of acute coronary syndrome.
4. The development of acute kidney injury by KDIGO criteria as follows¹:
 - a. If the patient develops Stage II AKI (by KDIGO criteria), the study treatment will be held and a clinical decision will be made whether to resume or discontinue treatment drug
 - b. If the patient develops Stage III AKI (by KDIGO criteria), the study treatment will be discontinued and the patient will be classified as treatment failure and followed only for outcome recording.
5. The need for renal replacement therapy
6. New atrial fibrillation or other supraventricular tachyarrhythmia
7. Sustained ventricular arrhythmias

8. Requirement of furosemide dose increase beyond the study maximum of 200 IV twice daily (or 400 IV over 24 hrs), or the need for addition of thiazide diuretic.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Once the study period ends, or if the study ends prematurely, the patient will receive standard heart failure management at the discretion of the primary team. The patient will resume standard outpatient follow up as advised by the primary team at the time of discharge.

5. Inclusion/Exclusion Criteria

a. Inclusion Criteria :

1. Admission to the hospital for acute decompensated heart failure within 24 hours of enrollment into the study.
 - 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, elevated jugular venous pulse, hepatojugular reflex, peripheral edema, ascites, pulmonary vascular congestion on chest radiography)
2. Patient ≥ 18 years of age
3. Estimated GFR of $> 15 \text{ mL/min/1.73m}^2$ determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD- EPI) equation
4. Willingness to provide informed consent
5. Known ejection fraction by noninvasive testing of $\geq 50\%$ within 12 months of admission to the hospital with no interval myocardial infarction since inclusion TTE, by history, or by ECG.
6. Negative pregnancy test in a female of child bearing potential
7. Willingness of primary attending physician for patient to participate.

b. Exclusion:

1. Systolic BP < 90 mmHg on admission
2. Hemoglobin (Hgb) < 8 g/dl
3. Known allergy or intolerance to furosemide or low dose dopamine.
4. Hemodynamically significant arrhythmias including supraventricular tachycardias not responsive to rate control therapies or resulting in hemodynamic instability, ventricular tachycardia, or defibrillator shock within 4 weeks
5. Acute coronary syndrome within 4 weeks as defined by electrocardiographic (ECG) ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent)
6. Cardiac diagnoses in addition to or other than HFPEF:
 - i. Active myocarditis
 - ii. Hypertrophic obstructive cardiomyopathy
 - iii. Severe valvular disease

- iv. Restrictive or constrictive cardiomyopathy, including known amyloidosis, sarcoidosis, hemochromatosis
 - v. Complex congenital heart disease
 - vi. Constrictive pericarditis
 - vii. Severe pulmonary hypertension (RVSP \geq 60), not secondary to HFPEF
- 7. Non-cardiac pulmonary edema
 - 8. Clinical evidence of digoxin toxicity
 - 9. Received IV vasoactive treatment or ultra-filtration therapy for heart failure since initial presentation
 - 10. Anticipated need for IV vasoactive treatment or ultra-filtration for heart failure during this hospitalization
 - 11. History of temporary or permanent renal replacement therapy or ultrafiltration within 6 months
 - 12. History of renal artery stenosis > 50%
 - 13. Need for mechanical hemodynamic support
 - 14. Sepsis
 - 15. Terminal illness (other than HF) with expected survival of less than 1 year
 - 16. Previous adverse reaction to the study drugs
 - 17. Enrollment or planned enrollment in another randomized clinical trial during this hospitalization
 - 18. Inability to comply with planned study procedures
 - 19. Pregnancy or nursing mothers

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Furosemide is that standard of care diuretic for patients admitted to the hospital for acute decompensated heart failure. Dopamine at low dose is often used to assist diuresis and reduce acute kidney injury in patients at high risk for acute kidney injury with heart failure from systolic dysfunction.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variables.

1. Percent change in creatinine from randomization to 72 hrs from treatment protocol initiation.

b. Secondary outcome variables.

1. Change in incidence of acute kidney injury (AKI) as defined by Kidney Disease: Improving Global Outcomes (KDIGO criteria summarized below) from randomization to 72 hrs.¹
2. Incidence of AKI as determined by urine output at 72 hrs (KDIGO criteria, summarized below).¹
3. Change in creatinine at 72 hrs adjusted for volume of fluid removal
4. Change in serum cystatin C randomization to 72 hrs
5. Change in NT pro-BNP from randomization to 72 hrs
6. Volume of diuresis measured in liters
 - c) Cumulative volume of diuresis measured in liters
 - d) Cumulative volume of diuresis measured in liters adjusted for BSA
7. Net weight loss at 72 hrs in kg
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10. Global well-being assessment score from admission to 72 hrs, and at discharge. To be assessed by a Visual Analog Scale (VAS).
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13. Length of stay of hospitalization in days
14. 30 day, 6 month, and 1 year hospital readmission or ER visit for major adverse cardiovascular event, heart failure, renal failure (development of CKD, ESRD, or dialysis need by KDIGO criteria), syncope, or arrhythmia. Readmission events will be adjudicated by a Clinical Event Committee consisting of 2-3 cardiologists not directly in contact with patients enrolled in the study.

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Stages of AKI as defined by KDIGO Criteria are as follows:

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$) increase	< 0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR increase in serum creatinine to ≥ 4.0 mg/dl (≥ 353.6 $\mu\text{mol/l}$) OR initiation of renal replacement therapy OR, in patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m ²	< 0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

a. Statistical plan including sample size justification and interim data analysis.

1. Overview:

- a. This is a factorial design study evaluating two simultaneous unrelated interventions. Sample size justification and primary endpoint analysis is described below.

2. Analysis of Primary Endpoints:

- a. The primary analysis will be conducted on an intention-to-treat basis. Non-parametric testing for the continuous primary endpoint (creatinine) will be performed using the Wilcoxon-Mann-Whitney U test. Confirmatory test for interaction between dopamine and diuretic strategy will be performed with linear regression analysis with dopamine*diuretic term, $p=0.10$ for significance.

3. Sample Size Justification:

- a. A difference of 30% in creatinine pre and post- treatment is considered to be clinically meaningful. Setting parameters as follows: two-sided, alpha (Type I error rate) of 0.05, power of 0.80, and using mean creatinine calculations based on our own retrospective experience at

Johns Hopkins as well as data from prior studies in patients admitted with ADHF, we estimate a sample size of approximately 63 patients per treatment arm. This translates to 63 patients assigned to the diuretic-only treatment arm (intermittent bolus and continuous) and 63 patients assigned to the low-dose dopamine arm (in addition intermittent bolus diuretic and continuous diuretic treatment). Taking into account drop-out rate, we plan to enroll 140 patients (70 per treatment arm; 34 per specific treatment strategy).

4. Randomization:

- a. Patients will be randomized in a blinded fashion to one of four treatment arms upon enrollment. We plan to perform block randomization into the treatment arms and plan to stratify patients by race, CKD status, and receipt of IV contrast dye (during the same admission), as these factors are felt to be significantly associated with the development of AKI.

5. Analysis of Secondary Endpoints:

- a. Summaries of continuous variables will be displayed using the mean, standard deviation, and median. For nominal variables, the number and frequency of subjects in each category will be presented. Statistical tests with p-values < 0.05 will be considered statistically significant, unless otherwise stated.

b. Early stopping rules.

A study subject will be removed from the trial if the above mentioned scenarios from Section 5 were to occur:

- i. The development of hemodynamic instability including hypotension (SBP < 90), hypertensive emergency, or unstable arrhythmias (SVT or VT)
- ii. The development of pulmonary edema requiring inotropes or vasopressor or more than 50% inspired oxygen.
- iii. The development of acute coronary syndrome.
- iv. The development of acute kidney injury as follows:
 - a. If the patient develops Stage II AKI (by KDIGO criteria)¹, the study treatment will be held and a clinical decision will be made whether to resume or discontinue treatment drug
 - b. If the patient develops Stage III AKI (by KDIGO criteria)¹, the study treatment will be discontinued and the patient will be classified as treatment failure and followed only for outcome recording.
 - i. The need for renal replacement therapy
 - ii. New atrial fibrillation or other supraventricular tachyarrhythmia
 - iii. Sustained ventricular arrhythmias

- v. Requirement of furosemide dose increase beyond the study maximum of 200 IV twice daily (or 400 IV over 24 hrs), or the need for addition of thiazide diuretic.

The investigators will report all adverse events to the IRB and will follow these patients throughout the duration of the study.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Furosemide is considered a standard of care diuretic for the treatment of acute heart failure. While it is a commonly used medication, the risks commonly associated with furosemide include (but are not limited to) acute kidney injury (pre-renal azotemia, acute interstitial nephritis), and electrolyte disturbances (hypokalemia, hypomagnesemia). Severe but uncommon risks of furosemide include orthostatic hypotension, drug hypersensitivity syndrome, erythema multiforme, erythroderma, Stevens-Johnson syndrome, toxic epidermal necrolysis, pancreatitis, arnucytosis, aplastic anemia, thrombocytopenia, anaphylactoid reaction, and anaphylaxis.

Diminished hearing or deafness, reversible and irreversible, has been reported with the use of furosemide. Usually, the effects on hearing are associated with fast injections, severe renal impairment (loss of kidney function), hypoproteinemia (low protein in the blood), use of higher than recommended doses or in combination with other ototoxic agents. The effects on hearing are rare and would more likely occur from intermittent doses, than continuous infusions.

Dopamine is often used in the treatment of acute heart failure exacerbation to assist with diuresis, particularly when there is a risk of development of acute kidney injury. The common side effects and risks associated with low-dose dopamine include chest pain, increase in blood pressure, fast or irregular heart rates, injection site reaction, and hair follicles may stand erected. Serious but uncommon risks include ectopic beats, ventricular arrhythmia, wide QRS complex, and gangrenous disorder.

b. Steps taken to minimize the risks.

All patients will be admitted to telemetry floor beds for close monitoring of hemodynamic state. All patients will undergo vital sign checks every 4-8 hrs depending on clinical stability. Standard of care for inpatient acute heart failure management includes twice daily basic metabolic profile check to assess renal function and electrolytes. A standardized electrolyte replacement protocol will be enforced for all patients to minimize the risk of cardiac arrhythmias in the setting of diuresis. In patients whose GFR is below and/or creatinine is above the cutoff for the standard electrolyte repletion protocol, this will be managed by the primary team physicians. In addition, the

above stated exclusion criteria are designed to minimize enrollment of patients who are apt to have side effects.

A subject will not be considered for enrollment if they have any signs of hemodynamic instability (please refer to Exclusion criteria). This includes hypotension for any reason (SBP < 90), hypertensive emergency (SBP >200 or signs of end-organ damage), supraventricular tachycardias (atrial fibrillation, atrial flutter) that are not responsive to rate control therapies, or ventricular arrhythmias beyond occasional PVCs or NSVT.

In the dopamine strategy group, if the subject develops tachycardia as defined by heart rate of >120 beats per min the infusion will be stopped. After 3 hours, if heart rate is < 120 beats per min, the IV infusion will be restarted at 1 µg/kg/min (<50% of the previous dose). If the heart rate is >120 beats per min after 3 hours or if tachycardia recurs, then the infusion will be terminated and this will be captured as “treatment failure.”

c. Plan for reporting unanticipated problems or study deviations.

All unanticipated problems such as transfers to the CCU, atrial or ventricular arrhythmias, acute coronary syndrome, or acute renal failure requiring renal replacement therapy will be reported within 48 hrs and reviewed by the study team. All deaths will be reviewed by the study team and reported to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

e. Financial risks to the participants.

There is no financial risk to the patients in this study.

9. Benefits

a. Description of the probable benefits for the participant and for society.

We are studying strategies of diuresis for HFPEF patients presenting with acute heart failure. If one of these strategies is beneficial it will help future patients and the patients on that arm of the study. In addition, patients will derive benefit from this study as they will receive close observation and monitoring during their admission and all assessments made for the purposes of this study will assist in their heart failure management. In addition, all patients will receive heart failure teaching from the HF nursing staff and follow up appointments in the Heart Failure Bridge Clinic will be made for these patients.

10. Payment and Remuneration

- a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There is no compensation to the patients enrolled in this study.

11. Costs

- a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The cost of dopamine for this trial and non-standard laboratory tests (cystatin-C, pro-BNP following admission value) will be compensated for through research funds of the PI and co-Investigators.

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