Comparison of oral thiazides vs intravenous thiazides vs tolvaptan in combination with loop diuretics for diuretic resistant decompensated heart failure

NCT 02606253

Document Date 8/31/2019

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1.0 Background

Loop diuretic therapy is the cornerstone of heart failure (HF) symptom management. Symptoms of fluid retention and congestion are responsible for 90% of HF hospitalizations, and almost all (86%- 97%) patients hospitalized for HF receive intravenous (IV) loop diuretics.[1,2-4] The incidence of diuretic resistance is unknown, given the lack of a consensus definition, but resistance is reported to occur in 25-35% of heart failure patients. [5-7] Despite the prevalence of loop diuretic use in HF and frequency of diuretic resistance, guidelines by the Heart Failure Society of America (HFSA) and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) provide nonspecific guidance on diuretic regimen design in response to diuretic resistance. Both guidelines recommend (LOE IIA, Class B) the addition of a second type of diuretic (options listed include oral metolazone and intravenous chlorothiazide). [8,9] As expected, 57% of physician questions about advanced HF management in a recent survey concerned diuretic titration.[10]

Addition of a second diuretic is a common practice to overcome diuretic resistance, despite the scarcity of literature to support this practice. A 2010 literature review of combining thiazide and loop diuretics found, "The aggregate body of literature is limited by the small size of studies, study design with lack of control groups, heterogeneous patient populations, wide variation in diuretic regimens, and focus on physiologic rather than clinical outcomes."[11] In addition to lack of evidence guiding its use, combination diuretic therapy is further complicated by adverse events and costs associated with this practice. Electrolyte derangements are a common adverse effect of combination diuretic regimens, predisposing patients to cardiac arrhythmias. [11] Furthermore, each agent has it limitations: metolazone is subjected to erratic absorption due to its oral dosage form; whereas, intravenous chlorothiazide over comes the absorption issue but is more costly.[12-14] Clearly, a need to better understand the benefits and risk of these therapies exist.

A non-thiazide option, also mentioned in heart failure guidelines for fluid removal, is the oral vasopressin 2-receptor antagonist tolvaptan. This agent could be an equally effective alternative to thiazide diuretics with potentially less electrolyte derangement. In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trials the addition of 30 mg tolvaptan daily was evaluated compared to IV loop diuretics in > 4,000 patients hospitalized for ADHF.[15] Weight reduction was again seen as early as the 1st day, and weights at discharge or day 7 were 0.6 kg lower in trial A and 0.9 kg lower in trial B ($p < .001$). Most notably, no study reported hypokalemia with the combination of loop diuretics and tolvaptan.[15-17] Another study demonstrated that 80mg furosemide plus 30mg of tolvaptan provided a reducing of 1.48kg (± 1.14kg) at 48 hours in a small subset of an acute HF population.[18] However this study was not conducted in patients who had developed diuretic resistance.

Given the importance of adequate decongestion in acute hear failure and the common occurrence of loop diuretic resistance, there is a critical need for evidence regarding the optimal selection of additional agents to restore diuretic efficacy.

2.0 Rationale and Specific Aims

Given the sparse amount of data regarding adjunctive diuretic strategies in acute heart failure, this study aims to address this gap by providing one of the first prospective trials comparing three different medications in addition to loop diuretics. By utilizing a prescriptive algorithm for loop diuretic dosing and other medical therapies that alter diuretic response, the study will address many of the limitations of previous studies such as the lack of a control group, retrospective design, and wide variations of both loop and thiazide diuretic regimens.[13, 14] Metolazone will be

employed as the standard-of-care thiazide to mirror current clinical perceptions and to replicate a recent landmark diuretic study's thiazide use.[11, 19-20] Our selected sample size will provide adequate power to detect clinically meaningful differences in outcomes, a further limitation of previous studies. The results of this study have the potential impact practice immediately as it will provide the first evidence to guide practitioners on the most appropriate next step to over come diuretic resistance. The evidence from the results of this trial would have the potential to be included in future guidelines for heart failure management. Finally, this data could generate other hypotheses which would serve has the foundation of other studies.

Specific Aims

1. *Compare the 48-hour weight change of either intravenous chlorothiazide or oral tolvaptan compared to standard-of-care oral metolazone when combined with standardized loop diuretic dosing for diuretic resistance in acute heart failure*

Current heart failure guidelines recommend addition of a thiazide diuretic, listing either oral metolazone or intravenous chlorothiazide, to loop diuretic therapy as strategy to overcome loop diuretic resistance. At equipotent doses, these two therapies differ 250 fold in cost. To date, no prospective trial has compared the efficacy of these two commonly utilized therapies. We expect intravenous chlorothiazide will not provide an increase in clinically meaningful weight loss at 48 hours compared to oral metolazone.

Tolvaptan, an oral vasopressin 2 receptor antagonist, could restore diuretic efficacy when used in combination with loop diuretics. While the safety of this combination has been established in the EVEREST trials, tolvaptan has been formally studied in a limited capacity as combination therapy to restore loop diuretic resistance. From this sparse data, we expect oral tolvaptan will provide equal weight loss at 48 hours compared to metolazone.

2. *Compare the adverse effects of electrolyte depletion and renal function changes between intravenous chlorothiazide or oral tolvaptan compared to standard-of-care oral metolazone when combined with standardized loop diuretic dosing for diuretic resistance in acute heart failure*

Hypokalemia is a common adverse effect of combining a thiazide and loop diuretic, increasing the risk of atrial and ventricular arrhythmias in a population who is already at high risk. We expect intravenous chlorothiazide will require equivalent cumulative potassium repletion at 48 hours compared to oral metolazone. Hypokalemia as not been reported with the combination of tolvaptan and loop diuretics, likely due to tolvaptan's distinctive mechanism of action. We expect tolvaptan will require less cumulative potassium repletion at 48 hours compared to oral metolazone. This potential benefit could provide tolvaptan a unique advantage for combination diuretic therapy in environments when electrolyte monitoring cannot be routinely performed or in patients with frequent arrhythmic events.

3. *Pharmacoeconomic analysis of the direct costs of intravenous chlorothiazide or oral tolvaptan compared to standard-of-care oral metolazone when combined with standardized loop diuretic dosing for diuretic resistance in acute heart failure*

The average wholesale price for one dose of each agent according to Redbook online is $1.50, $357, and $375 for metolazone 5mg tablet, chlorothiazide 500mg vial, and tolvaptan 30mg tablet respectively. We will perform a direct cost analysis including drug cost and other therapy-related costs. We expect both intravenous chlorothiazide and oral tolvaptan to have higher direct costs compared to metolazone. We expect the reduction in electrolyte repletion and accompanying adverse event treatment will reduce the cost difference of tolvaptan tablets compared to metolazone tablets.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria
Criteria for inclusion will be:

- Age of 18 years or older
- Hospital admission for hypervolemic decompensated heart failure complicated by loop diuretic resistance.
    - Hypervolemia will be diagnosed by the admitting provider as either (i) pulmonary artery catheterization with a pulmonary capillary wedge pressure greater than 19mmHg plus a systemic physical exam finding of hypervolemia (peripheral edema, ascites, or pulmonary edema on auscultation) or (ii) in the absence of pulmonary artery catheterization data 2 of the following signs or symptoms: peripheral edema ascites, jugular venous pressure > 10mmHg, or pulmonary edema on chest x-ray.
    - Loop diuretic resistance is defined as a provider decision to pursue combination diuretic therapy because of failure to reach provider defined adequate diuresis (can not exceed urine output of 2 L in past 12 hours) despite receipt of an intravenous loop diuretic dose of a furosemide equivalent of at least 240mg/day over at least the past 12 hours (40mg furosemide = 20mg torsemide = 1mg bumetanide).
- Standard-of-care monitoring, including 24 hour telemetry monitoring on an inpatient ward and a basic metabolic panel laboratory assessment twice daily during the study period.

Exclusion Criteria
Candidates will be excluded if they meet any of the following criteria at the time of enrollment:

- Decision to pursue hemodialysis by a nephrologist
- estimated glomerular filtration rate by the MDRD equation < 15ml/min/m^2
- systolic blood pressure < 85mmHg
- pregnancy* or breastfeeding
- serum potassium < 3.0mEq/L
- serum sodium > 145mEq/L or < 130mEq/L
- severe malnutrition
- advanced liver disease
- inability to perform standing weights
- inability to collect and measure urine with either a foley catheter or urine collection containers
- concomitant therapy with strong CYP3A4 inhibitors/inducers (systemic ketoconazole, clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir, nefozodone, rifampin, rifabutin, rifapentin, phenytoin, phenobarbital, carbamazepine, St. John's Wort), p-glycoprotein inhibitors (cyclosporine, erythromycin, tacrolimus, dronedarone, quinidine, or verapamil)
- non-study diuretics (spironolactone doses >75mg/day, eplerenone > 75mg/day, non-study thiazides or loop diuretics, or systemic acetazolamide, triamterene, or amiloride therapy)
- Thiazide mediation administered in the previous 24 hours prior to randomization

*Pregnancy: In women of childbearing age who are not in menopause per patient report during screening, a serum pregnancy test will be ordered and negative prior to enrollment.

4.0 Enrollment/Randomization

We will conduct a single center, randomized, double-blind, double-dummy, parallel design trial comparing oral metolazone, intravenous chlorothiazide, and oral tolvaptan in combination with loop diuretics in patients hospitalized for hypervolemic acute heart failure. The duration of the study will be 48 hours from the first dose of the study thiazide or tolvaptan medication. Vanderbilt University Medical center will be the study site. IRB approval will be obtained from the Vanderbilt Univeristy Medical Center IRB.

All patients will provide informed consent prior to enrollment. After enrollment, all patients will be randomized in a 1:1:1 fashion at VUMC using a random number table in the investigational drug services pharmacy. The investigational pharmacists will perform randomization, and investigators will be blinded to the treatment arm.

5.0 Study Procedures

5.1 Background and Standard of Care Therapies

All patients will be started on a 2L/day fluid restriction and a 2g/day sodium restriction. Decisions regarding the initiation, titration, or discontinuation of standard heart failure medications (ACEI, ARB, Aldosterone Antagonists, Beta Blockers, digoxin, hydralazine, nitrates) are left to the discretion of the treating physicians. All electrolyte repletion, loop diuretic dose titration, and concomitant therapies to enhance diuresis if needed will be utilized at the provider's discretion.

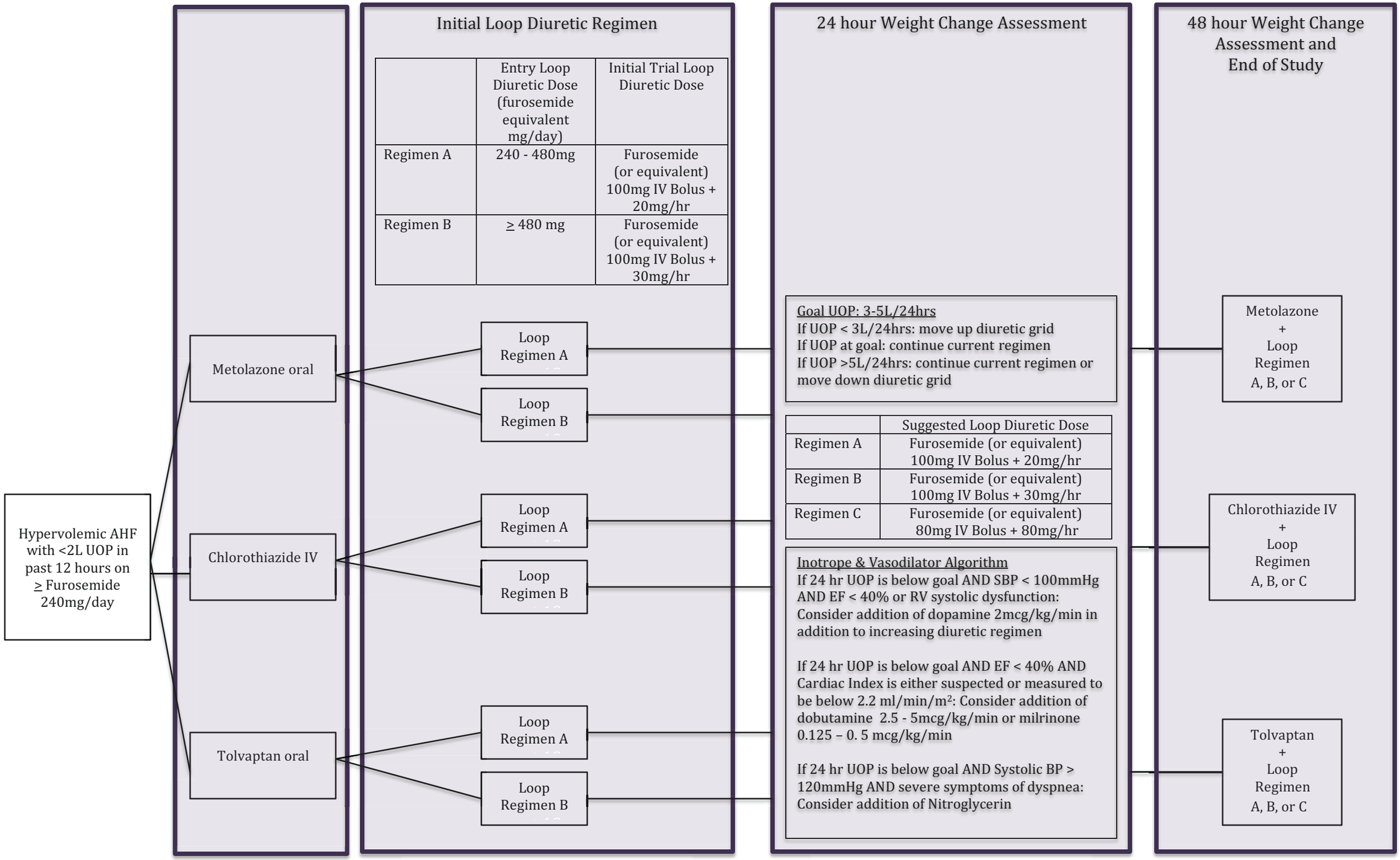
To prevent confounding heterogeneity in the diuretic treatment approach, a stepped care algorithm similar to the CARRESS-HF[19] trial will be utilized for loop diuretics, both initial doses and subsequent dose changes, and for concomitant inotropes and vasodilators. The stepped care algorithm and the initial diuretic treatment regimen are delineated in Study Flow Diagram below. A minimum furosemide equivalent dose of 580mg/24hrs (100mg IV bolus + 20mg/hr infusion rate) must be ordered at enrollment.

5.2 Randomization

All patients will be randomized in a 1:1:1 fashion at VUMC using an electronic randomization tool embedded in REDCAP. Patients will be randomized to either:

1) intravenous chlorothiazide 500mg IV Q12H + an oral placebo capsule Q12H
2) intravenous placebo infusion Q12H + a capsule containing oral metolazone 5mg PO Q12H
3) intravenous placebo infusion Q12H + a capsule containing oral tolvaptan 30mg once daily and placebo capsule in the evening dose.

(Relative potency[21, 22]: Metolazone 100 fold more potent than chlorothiazide)


Hypervolemic AHF with <2L UOP in past 12 hours on ≥ Furosemide 240mg/day
Metolazone oral
Chlorothiazide IV
Tolvaptan oral
Initial Loop Diuretic Regimen
Entry Loop Diuretic Dose (furosemide equivalent mg/day)
Initial Trial Loop Diuretic Dose
Regimen A
240 - 480mg
Furosemide (or equivalent) 100mg IV Bolus + 20mg/hr
Regimen B
≥ 480 mg
Furosemide (or equivalent) 100mg IV Bolus + 30mg/hr
Loop Regimen A
Loop Regimen B
Loop Regimen A
Loop Regimen B
Loop Regimen A
Loop Regimen B
24 hour Weight Change Assessment
Goal UOP: 3-5L/24hrs
If UOP < 3L/24hrs: move up diuretic grid
If UOP at goal: continue current regimen
If UOP >5L/24hrs: continue current regimen or move down diuretic grid
Suggested Loop Diuretic Dose
Regimen A
Furosemide (or equivalent) 100mg IV Bolus + 20mg/hr
Regimen B
Furosemide (or equivalent) 100mg IV Bolus + 30mg/hr
Regimen C
Furosemide (or equivalent) 80mg IV Bolus + 80mg/hr
Inotrope & Vasodilator Algorithm
If 24 hr UOP is below goal AND SBP < 100mmHg AND EF < 40% or RV systolic dysfunction: Consider addition of dopamine 2mcg/kg/min in addition to increasing diuretic regimen
If 24 hr UOP is below goal AND EF < 40% AND Cardiac Index is either suspected or measured to be below 2.2 ml/min/m²: Consider addition of dobutamine 2.5 - 5mcg/kg/min or milrinone 0.125 – 0. 5 mcg/kg/min
If 24 hr UOP is below goal AND Systolic BP > 120mmHg AND severe symptoms of dyspnea: Consider addition of Nitroglycerin
48 hour Weight Change Assessment and End of Study
Metolazone + Loop Regimen A, B, or C
Chlorothiazide IV + Loop Regimen A, B, or C
Tolvaptan + Loop Regimen A, B, or C

5.3 Blinding

This study will be double blinded. Blinding will be performed by the enrolling site's investigational drug service pharmacy. A double-dummy strategy will prevent investigators from knowing the treatment arm during observation.

5.4 Study Outcomes

The primary outcome will be 48-hour standing scale weight change (kg) from enrollment among the metolazone, intravenous chlorothiazide, and tolvaptan arms, using metolazone group as the comparator group for all other groups.

Secondary outcomes, using metolazone as the comparator group for each, will be:

- 48 hour net urine output (mls)
- mean change in serum creatinine, blood urea nitrogen, and eGFR at 24 hours, 48hours, and at hospital discharge
- mean change in diuretic efficiency at 24 and 48 hours from baseline value at enrollment
- mean change in serum potassium at 24 and 48 hours from baseline value at enrollment
- mean change in serum sodium at 24 hours, 48hrs, and at discharge from baseline value at enrollment
- cumulative dose of potassium (mEq) and magnesium (g) supplementation administered at 24 and 48 hours
- incidence of severe hypokalemia
- need for escalation in study-directed loop diuretic therapy at 24 and 48 hours
- addition of vasoactive or inotropic medication at 24 and 48 hours
- Treatment failure (definition below)
- Patient-scored congestion visual analog scale score at baseline, 24 and 48 hours (Appendix B)
- new cardiac arrhythmias (atrial and ventricular) during the study period
- receipt of inotropic therapy, dopamine, or nitroglycerin; requirement of ultrafiltration or hemodialysis during index hospitalization
- in-hospital mortality
- pharmacoeconomic analysis of the direct costs in each arm including the cost of:
    - study medication
    - additional non-trial protocol laboratory analysis cost related to monitoring of electrolytes
    - treatment of study medication related adverse effects (arrhythmias, hypotension, electrolyte repletion)
    - escalation of loop diuretic therapy doses
    - addition of additional therapies for suboptimal diuresis (inotropic therapy, vasodilators)
    - new initiation of renal replacement therapies (hemodialysis or ultrafiltration)
- Spot urinary electrolytes and diuretic urine concentration
- Pharmacokinetics and pharmacodynamics of the diuretics in the urine and blood
- Fractional excretion of sodium

5.5 Study Definitions

- Urine output: Total urine volume (ml) from time of study enrollment to 48 hours
- Hypokalemia: Serum potassium value < 3.5mEq/L
- Severe Hypokalemia: Serum potassium value < 3.0mEq/L
- Hyponatremia: Serum sodium value < 135mEq/L

- Severe Hyponatremia: Serum sodium value < 130mEq/L and a decrease of 5mEq/L or more from enrollment serum sodium
- Overcorrection of serum sodium: increase in serum sodium from baseline by ≥12mEq/L in 24 hours, increase in >8mEq/L in 12 hours, or receipt of intravenous fluids because of symptoms of overcorrection of serum sodium regardless of the numerical rise
- Hypomagnesiemia: Serum magnesium value < 2mEq/L
- Diuretic efficiency = 24hr urine output/ 24hr Lasix equivalents in milligrams
- Weight: Standing weight on the same scale as used for baseline weight measurement
- New Atrial Arrhythmia: A "new" diagnosis of atrial arrhythmia (includes atrial fibrillation, atrial flutter, ectopic atrial tachycardia) lasting > 30 seconds OR any atrial arrhythmia which causes hemodynamic instability (MAP < 60 and requiring intervention)
- New Ventricular Arrhythmia: Ventricular tachycardia lasting longer than 30 seconds, or frequent non-sustained VT causing hemodynamic instability with MAP < 60 mmHg requiring intervention or > 1 intra-cardiac defibrillation or external cardiac defibrillation shock or ventricular fibrillation requiring defibrillation
- Hypotension: SBP < 85 for 2 repeated measurements within 30 minutes or lasting at least 30 minutes or symptomatic hypotension necessitating clinical intervention (defined as vasopressor support, intravenous fluid boluses, or initiation of inotropes)
- Treatment failure: Patients requiring additional non-study diuretic (spironolactone doses >75mg/day, eplerenone > 75mg/day, non-study thiazides (at a dose of metolazone 2.5mg or greater equivalence) or loop diuretics, or systemic acetazolamide (for diuretic indication), triamterene, or amiloride therapy) at any time during the 48-hour randomization period. These patients will be considered treatment failures for the purpose of analysis of the primary endpoint and all secondary endpoints.
- Patients whose cardiologist adds inotropic or vasodilator medications will not be considered treatment failures. Patients who require an increase in the loop diuretic regimen will also not be considered treatment failures.
- Medication costs will be defined as the Redbook average wholesale price at the time of the trial to reduce inter-institutional price differences and improve external validity of the analysis.

5.6 Study Outcome Timeline

Day 1: Baseline standing weight, BMP every 12 hours, urine collection, 20ml blood collection dyspnea score.
Day 2: 24 hour urine collection/quantification, BMP every 12 hours, 24 hour standing weight, 20ml blood collection, 24 hour dyspnea score, receipt of non-study diuretics, need of new inotropes or vasodilators
Day 3: 48 urine collection/quantification, 48 hour standing weight, 20ml blood collection, 48 hour dyspnea score, receipt of non-study diuretics, need of new inotropes or vasodilators.
End of study.
Day 30 (+/- 2 days): Telephone contact for the following events in past 30 days:

- ER visits and reason for visits
- Hospitalizations and reason for hospitalizations
- Serious adverse events

5.7 Research Blood, Plasma, and Urine Collection

We will collect 20 ml of blood (10ml of serum and 10ml of plasma) at baseline (after consent), at 24 hours, and at 48 hours/study conclusion. We will serially collect urine produced during the study period for analysis. Analyses will include fractional excretion of sodium, diuretic pharmacokinetics/dynamics, and measures of hemoconcentration.

6.0 Risks

This study will evaluate the addition of an oral thiazide, intravenous thiazide, or tolvaptan to augment intravenous loop diuretic therapy in patients with hypervolemic decompensated heart failure and diuretic resistance to adequately dosed loop diuretic monotherapy. Augmentation of loop diuretic therapy with a second diuretic (commonly a thiazide) is considered the standard-of-care in diuretic resistance and is endorsed by the AHA/ACCF and HFSA guidelines.[8,9]

Tolvaptan

Several large scale clinical trials have demonstrated the safety of tolvaptan in patients with hypervolemic decompensated heart failure, including in those without hyponatremia. The EVEREST study evaluated 4,133 patients with decompensated heart failure randomized to placebo or tolvaptan for 60 days. The in-hospital serious adverse event rate was similar between tolvaptan (6.5%) and placebo (5.5%). The most common adverse effects of tolvaptan in these trials have been thirst (16%), dry mouth (8.4%), and polyuria. Hypernatermia occurred in 1.7% of tolvaptan patients vs 0.5% of placebo patients. Acute kidney injury, hypotension, and potassium derangements are not associated with tolvaptan therapy. As our duration of study is only 48 hours, it is not anticipated that study participation will be associated with increased risks beyond standard diuresis augmentation with a thiazide.

<u>Hypernatremia/Over-correction of Serum Sodium</u>

While hyponatremia is not the target population of this study, patients with a serum sodium range of 130-145mEq/L are eligible to participate. Relative to the thiazide arm, patients with hyponatremia randomized to tolvaptan are at the unique, albeit rare, risk of over-correction of serum sodium. Overcorrection of sodium is commonly defined as an increase in serum sodium by more than 12mEq/L in 24 hours. Overcorrection of serum sodium is most likely to occur when the serum sodium is < 125mEq/L at baseline, which is an exclusion criterion of our study. The SALT studies included patients with hyponatremia (serum sodium < 135mEq/L) from various disease states, including heart failure. Only 5 patients (2.2%) of patients experienced a rise if serum sodium > 12mEq/L during any 24 hour time period, on a dose of 15mg to 60mg a day of tolvaptan. No patients experiencing this rapid correction and no patients in EVEREST developed osmotic demyelination syndrome (ODS). The FDA package insert for tolvaptan records that cases of ODS have occurred in post-marketing surveillance. In our study, we will only randomize 20 patients to tolvaptan, calculating to 1-2 patients with hyponatremia being randomized to tolvaptan. The low rate of overcorrection in literature, small sample size, exclusion criteria (sodium < 130mEq/L, advanced liver disease, severe malnutrition), short duration of therapy in our trial, and twice daily serum sodium monitoring makes the risk of a patient experiencing overcorrection of serum sodium low in our study. All patients will be hospitalized for the duration of the study and will be monitored for neurologic symptoms.

To minimize this risk, patients who are at highest risk of ODS at enrollment (serum sodium < 130mEq/L) will receive a serum sodium assessment 12 hours after the first dose of study diuretic. If the serum sodium increases > 8mEq/L from baseline at 12 hours, the will receive protocolized management to prevent ODS.

1) Intravenous D5W at 3ml/kg/hr
2) Repeat serum sodium every 2 hours
3) Neurologic monitoring for symptoms such as speech disturbances, altered mental status, and seizure activity
4) D5W and every 2 hour serum sodium labs will be continued until the serum sodium is < 8mEq/L above baseline sodium

Patients will continue the loop diuretic therapy during this protocol. If the patient does not develop symptoms of ODS and responds to intravenous D5W therapy by hour 18 (6 hours after first serum sodium), they will be eligible for the scheduled second study diuretic dose at 24 hours. Patients experiencing any neurologic symptoms or who do not respond to intravenous D5W

therapy by hour 18 (6 hours after first serum sodium) will not be eligible for repeat study medication administration. All patients will be followed per the study protocol through Day 30.

Hepatic toxicity

Hepatotoxicity occurred in 3 patients in the TEMPO study, which evaluated the effects of Tolvaptan 60-120mg daily in a polycystic kidney disease patient population. In all 3 patients, the hepatic toxicity occurred after 3 months of therapy and resolved with tolvaptan discontinuation. Our study protocol will exclude patients with advanced liver disease, consistent with the updated FDA package labeling recommendations, and will administer a lower dose for only 48 hours.

Thiazides (Metolazone or Chlorothiazide)

In accordance with previous trials evaluating combination thiazide and loop diuretics (DOSE, CARRESS-HF), the metabolic risks include gout, hypokalemia, and hyponatremia. The risks include: hyponatremia, hypokalemia, gout flare/attack, and cardiac arrhythmias. In the CARRESS-HF study, ultrafiltration was compared to a step-wise diuretic protocol in 188 patients with hypervolemic, decompensated heart failure and worsening renal function. Of the 94 patients in the diuretic arm, 46% of participants received metolazone therapy. Only 3 (3%) patients experienced an electrolyte disorder, which included hypokalemia, hyponatremia, and hyperuricemia. Arrhythmic events were not specifically reported. A retrospective comparison of intravenous and oral thiazide diuretics found the rate of hypokalemia, defined as a serum potassium < 4mEq/L, to be 71% in the oral thiazide group and 83% in the intravenous thiazide group.[14] Given the small size of previous combination diuretic studies, incidence rates of gout attacks and cardiac arrhythmias have not been quantified and are not provided in package labeling.[11] Our study will minimize hypokalemia and hyponatremia by monitoring the serum potassium and sodium every 12 hours during the study period. Electrolyte replacement will be performed at the discretion of the attending cardiologist, in accordance with standard of care practice.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

A **Serious Adverse Event (SAE)** is an adverse event that:

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

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

The determination of adverse event severity rests on medical judgment of a medically qualified investigator. The severity of SAEs will be graded using the following definitions:

- **Mild**: awareness of sign, symptom, or event, but easily tolerated;
- **Moderate**: discomfort enough to cause interference with usual activity and may warrant intervention;
- **Severe**: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

7.1 Assessment of Causality

A medically-qualified investigator must assess the relationship of any SAE to the use of study drug, based on available information, using the following guidelines:

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

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

Expectedness - The expectedness of an adverse event or suspected adverse reaction shall be determined according to the package insert for U.S. marketed furosemide and tolvaptan. Any AE that is not identified in nature, severity, or specificity in the current U.S. package insert is considered unexpected. Events described in the U.S. package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

7.2 Reporting of SAE

All serious adverse events occurring from randomization through the 30 day follow-up period will be collected. The Site Investigator is responsible for monitoring the safety of patients enrolled into the study. The following adverse events are anticipated, disease related-events in patients with decompensated heart failure however they should still be reported on the Serious Adverse Event form in the REDCAP Database (some may require reporting as study endpoints):

- New Atrial Arrhythmia: A "new" diagnosis of atrial arrhythmia (includes atrial fibrillation, atrial flutter, ectopic atrial tachycardia) lasting > 30 seconds OR any atrial arrhythmia which causes hemodynamic instability (MAP < 60 and requiring intervention)
- New Ventricular Arrhythmia: Ventricular tachycardia lasting longer than 30 seconds, or frequent non-sustained VT causing hemodynamic instability with MAP < 60 mmHg requiring intervention or > 1 intra-cardiac defibrillation or external cardiac defibrillation shock or ventricular fibrillation requiring defibrillation
- Hypotension: SBP < 85 for 2 repeated measurements within 30 minutes or lasting at least 30 minutes or symptomatic hypotension necessitating clinical intervention (defined as vasopressor support, intravenous fluid boluses, or initiation of inotropes)
- Myocardial infarction: a cardiac event including an elevation in troponin above baseline with our without ECG changes that is judged to be a myocardial infarction by the treating attending cardiologist
- Cardiac arrest: any ventricular arrhythmic or pulseless electrical event that requires immediate life-sustaining medical therapies
- Acute renal failure: A rise is serum creatinine of 1mg/dl or more from the baseline serum creatinine in the 48 hour treatment period
- Acute renal failure requiring dialysis: an acute renal failure event that began during the 48 hour study period and necessitates new hemodialysis during the hospitalization

- Worsening heart failure: the need for rescue therapy (additional open label loop diuretic, spironolactone doses >75mg/day, eplerenone > 75mg/day, non-study thiazides (at a dose of metolazone 2.5mg or greater equivalence), systemic acetazolamide (for diuretic indication), triamterene, amiloride, ultrafiltration, hemodialysis, or mechanical circulatory or respiratory support) in the 48 hour treatment period
- Death
- Metabolic SAE (during 48 hour treatment period):
    - Severe Hypokalemia: Serum potassium value < 3.0mEq/L
    - Severe Hyponatremia: Serum sodium value < 130mEq/L and a decrease of 5mEq/L or more from enrollment serum sodium
    - Overcorrection of serum sodium: increase in serum sodium from baseline by ≥12mEq/L in 24 hours, increase in >8mEq/L in 12 hours, or receipt of intravenous fluids because of symptoms of overcorrection of serum sodium regardless of the numerical rise
    - Hyperkalemia: serum potassium value > 5.5mEq/L
    - Gout: acute gout attack requiring treatment with an anti-inflammatory agent

All serious adverse events must be recorded in the Serious Adverse Event Record of the patient's REDCAP database. All serious adverse events should be monitored until stabilization or resolution.

Reporting to Local IRB. Investigators are also responsible for promptly reporting unexpected adverse events (serious and non serious) to their reviewing IRB in accordance with local requirements. The Vanderbilt investigational site will report DSM reports to the Vanderbilt IRB annually at the time of continuing review at a minimum. If 5 unexpected SAES occur, the trial will be temporarily halted and the Vanderbilt IRB will be informed. After review, the study will resume if the IRB approves continuation with or without alterations in the study protocol.

Reporting to the Industry Sponsor
The investigator will notify the Sponsor within 24 hours of being notified of any SAE.
The investigator will also notify the Sponsor of any pregnancy during the study period within 3 days of being notified. For all non-serious adverse events, the investigator will notify the Sponsor of all events as a line item list at the end of the study.

7.3 Study Termination
The study may be terminated based on review of serious adverse events and unexpected events. If 5 unexpected SAEs occur this will trigger a temporary halt to the study until additional review of these events is conducted by the PI and IRB.

8.0 Study Withdrawal/Discontinuation
A patient may withdraw at the study at anytime. The patient will inform the site investigator of their desire to withdraw. All study-based therapy will stop at this point, and the attending cardiologist will perform any further care. All study data collected to that time point will be included in the analysis. The withdrawal reason will be documented.
The site investigator will withdraw patients requiring therapy for overcorrection of serum sodium who experience any neurologic symptoms or who do not respond to intravenous D5W therapy within 6 hours. All patients will be followed per the study protocol through Day 30.

9.0 Statistical Considerations
9.1 Sample Size

The study will have a sample size of 60 patients, equally allocated to the three study treatment groups.

9.2 Power Analysis

We have collaborated with Department of Biostatistics at Vanderbilt University Medical Center to employ the best statistical methods that allow our study to be realistic and achievable. Power calculations are difficult because of the lack of prospective trials comparing combination diuretic therapy and the numerous flaws in the methods of these previous studies. We will utilize change in weight as the primary outcome because weight change has been utilized as a primary efficacy outcome in landmark heart failure diuretic trials (CARRESS-HF[19]) and has less standard deviation than net urine output. In previous studies standard deviation of weight loss changes between groups varied with an approximate value of 1.6kg.[14, 23] If the minimum clinically meaningful difference in the experimental and control means is 1.5kg, we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with 82.3% power. The Type I error probability associated with this test of this null hypothesis is 0.05.

9.3 Statistical Methods

We will utilize an intention-to-treat analysis for the primary outcome. We will also perform a per-protocol analysis for the primary outcome in patients completing the 48-hour treatment period without missing study doses. Metolazone will be the comparator arm, against which both chlorothiazide and tolvaptan treatment arms will be individually compared. Parametric continuous variables will be presented as mean (standard deviation) and non-parametric continuous variables will be presented as median (interquartile range). Nominal data will be presented as the number (percentage). We will employ a student's t test for the independent continuous primary outcome variable and other secondary outcomes using metolazone as the comparison group for both intravenous chlorothiazide and oral tolvaptan. For secondary outcomes, of which metolazone will again be the comparison group, fisher's exact test will be used for secondary outcomes that are nominal data. A two tailed p-value of less than or equal to 0.05 will be considered significant.

10.0 Privacy/Confidentiality Issues

All study protocols and procedures will be submitted to the site's Institutional Review Board for approval. All data collected will be stored in a secure REDCAP database, accessible only by key study personnel. The following identifying information will be collected: age, medical record number, admission date, and discharge date. Patient-reported congestion score surveys will be de-identified, using a study identification number. All patient-reported congestion score surveys and consent forms and will be stored in a locked cabinet in the site investigator's office. For statistical analyses, all identifying information will be removed. Candidates aged > 89 years will be condensed into a category of age greater than or equal to 90 years of age to protect their identity.

11.0 Follow-up and Record Retention

This study is anticipated to last 12 months. All records will be stored in a secure REDCAP database.

References

1. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2007;153:1021-8.
2. AbrahamWT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005;46:57-64.
3. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319-31.
4. CuffeMS, CaliffRM,AdamsKF, Benza R,Bourge R,ColucciWS,et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541-7.
5. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144:31-8.
6. Yilmaz MB1, Gayat E, Salem R, Lassus J, Nikolaou M et al. Impact of diuretic dosing on mortality in acute heart failure using a propensity-matched analysis. European Journal of Heart Failure (2011) 13, 1244–1252.
7. Testani JM1, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. JACC 2011;58:375-382.
8. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16:e1-194.
9. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:1495-539.
10. Shah MR, Stevenson LW. Searching for evidence: Refractory questions in advanced heart failure. J Card Fail 2004;10:210-8.
11. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol 2010;56:1527-34.
12. Metolazone [package insert]. Morgantown: Mylan Pharmaceuticals; 2004.
13. Michael Moranville, Suji Choi, Jennifer Hogg, Jonathan D. Rich Metolazone Versus Chlorothiazide as Add-On Therapy to Loop Diuretics in Patients with Acute Decompensated Heart Failure and Renal Insufficiency; 2013 HFSA abstract. Journal of Cardiac Failure Vol. 19 No. 8S August 2013.
14. Kissling K, Pickworth KK. Comparison of the Effects of Combination Diuretic Therapy with Oral Hydrochlorothiazide or Intravenous Chlorothiazide in Patients Receiving Intravenous Furosemide Therapy for the Treatment of Heart Failure. Pharmacotherapy. 2014;34(8):882–887.
15. Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J,Zampino M, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003;107:2690-6.
16. Udelson JE, Bilsker M, Hauptman PJ, Sequeira R, Thomas I, O'Brien T, et al. A

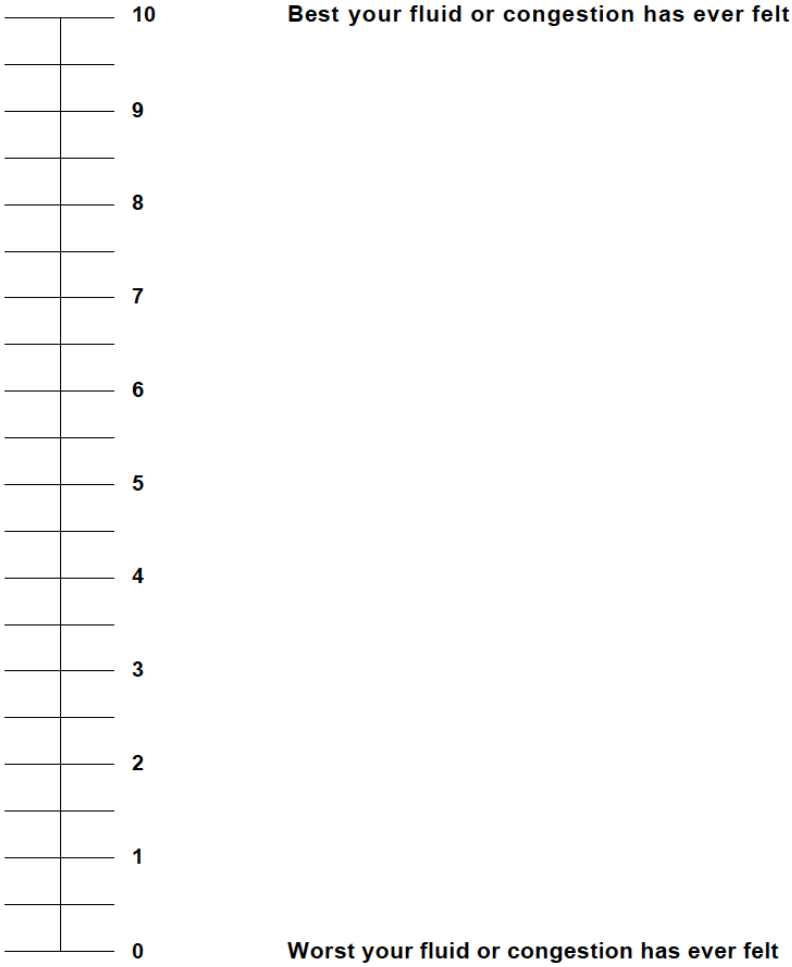
multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. J Card Fail 2011;17:973-81.
17. Gheorghiade M, Konstam MA, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332-43.
18. Udelson JE, Bilsker M, Hauptman PJ, et al. A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Tolvaptan Monotherapy Compared to Furosemide to the Combinations of Tolvaptan and Furosmide in Patients with Heart Failure and Systolic Dysfunction. J Cardiac Failure 2011; 17:973-981.18
19. Bart BA, Goldsmith SR, Lee KL, Redfield MM, Felker GM, O'Connor CM, et al. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. J Card Fail. 2012;18(3):176-82.
20. Sica DA. Metolazone and Its Role in Edema Management. CHF. 2003;9:100-105.
21. Goodman & Gillman's The Pharmacological Basis of Therapeutics 12th edition.
22. Borhani NO. Chlorothiazide and hydrochlorothiazide: a comparative study of their hypotensive, saluretic, and hyperuricemic action. Ann Intern Med 1960;53:342–58.
23. Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomized controlled trial. Br Heart J. 1994;71:146-150.

Appendix A: Schedule of Study Assessments

	Screen	Baseline	12 hrs	24hrs	36 hrs	48 hrs	Day 30 (Phone Call)
Informed Consent	x						
Inclusion/Exclusion Criteria	x						
Screening electrolytes, renal function, liver function, pregnancy status if applicable	x						
Vital Signs	x	x	x	x	x	x	
Standing Weight		x		x		x	
Current Cardiovascular Medications		x		x		x	
Loop diuretic regimen evaluation	x	x		x		x	
BMP	x	x	x	x	x	x	
Biobank blood		x		x		x	
Biobank plasma		x		x		x	
Urine Collection	x	x	x	x	x	x	
Congestion Score Assessment		x		x		x	
Adverse Event Assessment				x		x	
Outcomes Assessment						x	x

Appendix B: Patient-Reported Congestion Score
This score will be done at enrollment and repeated at 24 and 48 hours.

To be completed by patient. "Please draw a horizontal line on the scale to show how you think your fluid or congestion is right now. The number "0" equals the worst your fluid or congestion has ever felt and the number "10" equals the best your fluid or congestion has ever felt."



Appendix C: 30-Day Follow up Telephone Call Script
The site investigator will perform this phone call at 30 ± 2 days after enrollment.

Hello, my name is Dr. (name) from (Medical Center). I am calling to briefly follow up with you about the research study you participated in during your recent hospitalization for heart failure approximately one month ago. The study compared 3 different types of fluid removal medications in combination with furosemide (Lasix) and was called "Comparison of oral thiazides versus intravenous thiazides versus tolvaptan in combination with loop diuretics for diuretic resistant decompensated heart failure".

Do you have time now to complete the brief post-study survey that was mentioned to you at the start of the study? It should take no more than 5 minutes of your time. Thank you for your participation.

<u>If subject has deceased since discharge</u>
I am very sorry for your loss. It is important that we ask 3 simple questions to understand this unfortunate event. Could you please tell me:

- Date of death
- Cause of death
- Location of death
    - Out-of-hospital
    - In-hospital
        - Initial reason for hospitalization

<u>If subject is alive</u>
Since your discharge from (Medical Center) on (Discharge Date), have you experienced any of the following events?

1. Admission to any hospital?
    a. Admission reason:
        i. Heart failure
        ii. Heart rhythm issue
        iii. Low blood pressure
        iv. Heart attack
        v. Cardiac arrest
        vi. Kidney failure
            1. Was dialysis required?
        vii. Other (free text)

2. Gone to any emergency room?
    a. Reason for emergency room visit:
        i. Heart failure
        ii. Heart rhythm issue

iii. Low blood pressure
iv. Heart attack
v. Cardiac arrest
vi. Kidney failure
vii. Other (free text)

3. Any other serious health event?
    a. Document event if so

This ends your participation in this research study. Thank you very much for your participation in this research study and for your time today. Your participation is helping our medical team understand how to treat patients with heart failure better. Do you have any other questions at this time?

Goodbye.

End of Script

Vanderbilt University Institutional Review Board
Informed Consent Document for Research

Principal Investigator: Zachary L. Cox, PharmD **Revision Date:** October 27, 2017
Study Title: Comparison of oral thiazides vs intravenous thiazides vs tolvaptan in combination with loop diuretics for diuretic resistant decompensated heart failure
Institution/Hospital: Vanderbilt University Medical Center

This informed consent applies to adults, aged 18 or greater, with heart failure

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

1. What is the purpose of this study?

You are being asked to take part in this research study because you are an adult patient with too much fluid from heart failure (HF) who requires diuretic therapy beyond the use of oral or intravenous (IV) loop diuretic therapy (Lasix (furosemide), Bumex (Bumetanide), Demadex (torsemide)) alone. The purpose of this study is to determine the next option for medication to add to the loop diuretics in order to increase the amount of urine output and to improve symptoms of acute or progressing HF.

Some patients with extra fluid from HF develop resistance to loop diuretic therapy. In order to overcome this issue, the addition of second diuretic from a different class is often used including oral metolazone, IV chlorothiazide, or oral tolvaptan. Despite the common practice of using these drugs together with loop diuretics when resistance occurs, the best way to remove excess fluid in these situations is unknown.

2. What will happen and how long will you be in the study?

Patients with extra fluid from heart failure will be screened for possible participation in this study. If you are found to qualify for the study during screening, based on inclusion characteristics, and are interested in hearing about the study, we will review this informed consent with you. If you decide to take part we will have you sign and date this consent form.

If you agree to the study, you will be treated for your heart failure similar to normal care. You will be started on a 2-liter per day fluid and 2 gram per day sodium (salt) limitation. Any starting, stopping, clinical test, labs, dose changes, medication changes or orders, or procedures will be the decision of the treating physician(s). You will continue to receive a loop diuretic. However, to prevent difference in diuretic treatment, your physician(s) will follow a standardized approach to dosing your furosemide (Lasix). In addition to furosemide (Lasix), you will also be assigned to one of three treatment groups:
1) intravenous (IV) chlorothiazide 500mg every 12 hours plus an oral placebo capsule every 12 hours
2) IV placebo infusion every 12 hours plus a capsule containing oral metolazone 5mg every 12 hours
3) IV placebo infusion every 12 hours plus a capsule containing oral tolvaptan 30mg once daily in the morning and placebo capsule in the evening.
You and your doctor will not know which treatment you will be receiving. The use of the placebo drugs in this trial will be used to blind treatment to the physicians and researchers; however, you will be receiving one of the three active treatments in addition to furosemide (Lasix).

The duration of the study will be 48 hours from the first dose of study medication. During this time your vital signs, standing weight, and urine output will be monitored and you will be followed closely. As noted, all procedures, monitoring, medication and treatment decisions, excluding the diuretics therapy, will occur according to the

physician discretion and according to standard of care. You will have three extra blood tests from this study. These will occur at the start of the study, 24 hours later, and 48 hours later at the end of the study. Each of these will take 20 milliliters (about 1 and a half tablespoons) of blood. We will collect some of your urine to study in the lab each day. One extra question you will have each day is to rate your "shortness of breath" on a scale of 1 to 100 once a day. This will take less than half a minute to complete.

3. Costs to you if you take part in this study:

If you agree to take part in this research study, you and/or your insurance will not have to pay for the diuretic treatments and blood/urine lab tests used for research.

However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

4. Side effects and risks that you can expect if you take part in this study:

Tolvaptan is commonly known to cause some, all or none of the side effects listed below.

- Dry mouth (likely)
- Thirst (likely)
- Making large amounts of urine and urinating often (likely)
- Constipation (infrequent)
- Weakness (infrequent)
- Fever (infrequent)
- Increased blood sugar levels (infrequent)
- Depressed appetite (infrequent)
- Increased sodium in the blood (infrequent)

If the sodium concentration is corrected too quickly, the following serious side effects are rare, but could happen:

- Brain injury resulting in motor speech disorder (infrequent)
- Loss of speech (infrequent)
- Difficulty swallowing (infrequent)
- Extreme fatigue (infrequent)
- Extreme weakness of your legs and arms (infrequent)
- Seizures (infrequent)
- Coma (rare)
- Death (rare)

We would not allow you to participate in this study if your sodium was very low. To minimize your risk of sodium overcorrection, the sodium concentration in your blood will be monitored and you will observed for signs of overcorrection during the study. Specifically, your blood sodium amount will be measured every 12 hours.

If your serum sodium is found to be too elevated compared to baseline, you will receive some additional sodium lab monitoring and IV fluids to slow your sodium changes. You will be observed for signs of overcorrection of sodium. When your serum sodium improves enough, the intravenous fluid will be stopped. You will have another check of your serum sodium at 24 hours and you may receive additional intravenous fluid depending upon the value.

Patients who develop overcorrection of their serum sodium will be eligible to continue in the study if they have no symptoms of fast sodium changes and if their sodium responds to the additional IV fluid in 6 hours.

Being a part of this study while pregnant may expose the unborn child to unnecessary risks. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a pregnancy test will be done and it must be negative before you can enter this study.

The following are common side effects with metolazone and chlorothiazide, although the exact likelihood for each has not been defined; however, most are not life-threatening or severe:

- Low potassium (likely)
- Low magnesium (likely)
- High uric acid (likely)
- Low calcium (unlikely)
- High glucose (unlikely)
- Constipation (unlikely)
- Diarrhea (unlikely)
- Nausea (unlikely)
- Increase in serum creatinine (unlikely) – a sign that kidney function may be affected
- Abnormal heart rhythm (unlikely, but potentially serious)
- Low blood pressure (rare)
- Allergic reaction (rare)

5. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator [with Sponsor input] that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury.

There are no plans for Vanderbilt [or the Sponsor] to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt [or the Sponsor] to give you money for the injury.

6. Good effects that might result from this study:

a) The benefits to science and humankind that <u>might</u> result from this study include a better understanding of diuretic treatment in decompensated heart failure in order to optimize care.

b) The benefits you might get from being in this study may be that the symptoms you are experiencing from increased fluids will improve. However, there is a chance you may not benefit personally from being in this research study.

7. Other treatments you could get if you decide not to be in this study:

If you choose not to take part in this study, other commonly prescribed medicines and treatments could be used. Your physician(s) may utilize the same treatments as used in this trial if you end up not being in the study. You do not have to in this study to receive treatment for your condition.

8. Payments for your time spent taking part in this study or expenses:

There will be not direct payment to you for taking part of this study. You will not get billed or your insurance charged for any of the study medications.

9. Reasons why the study doctor may take you out of this study:

The physician(s) may take you out of the study at their discretion if they determine a different treatment course in needed, such as use of ultrafiltration, or if you decided to not be in the study at any point.

10. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

11. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Zachary Cox at [redacted]. If you cannot reach the research staff, please page the study doctor (Zachary Cox) at [redacted].

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at [redacted] or toll free at ([redacted]3.

12. Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

13. Confidentiality:

All data collected will be stored without personal identification in a database, accessible only by key study personnel. Link to patient information will done using a study identification number. All patient reported congestion score surveys and consent forms and will be stored in a locked cabinet in the site investigator's office.

The investigators, sponsors, and Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. The sponsors, Vanderbilt, Dr. Cox and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

14. Authorization to Use/Disclose Protected Health Information
All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If

you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Cox and his study team may share the results of your study and/or non-study linked lab test, congestions assessments, cardiac tests, and vitals as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, and the Vanderbilt University Institutional Review Board. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Zachary Cox, PharmD in writing and let him know that you withdraw your consent. His mailing address is: [redacted]. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____ _____
Printed Name and Title Time

Date of IRB Approval: 11/02/2017
Date of Expiration: 10/23/2018

Institutional Review Board
VANDERBILT