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STUDY DESIGN

Mechanisms of Diuretic Resistance Study: design and rationale

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Abstract

Introduction Diuretic resistance is a common complication impairing decongestion during hospitalization for acute decompensated heart failure (ADHF). The current understanding of diuretic resistance mechanisms in ADHF is based upon extrapolations from other disease states and healthy volunteers. However, accumulating evidence suggests that the dominant mechanisms in other populations have limited influence on diuretic response in ADHF. Additionally, the ability to rapidly and reliably diagnose diuretic resistance is inadequate using currently available tools.

Aims The Mechanisms of Diuretic Resistance (MDR) Study is designed to rigorously investigate the mechanisms of diuretic resistance and develop tools to rapidly predict diuretic response in a prospective cohort hospitalized with ADHF.

Methods Study assessments occur serially during the ADHF hospitalization and after discharge. Each assessment includes a supervised 6-hour urine collection with baseline blood and timed spot urine collections following loop diuretic administration. Patient characteristics, medications, physical exam findings, and both in-hospital and post-discharge HF outcomes are collected. Patients with diuretic resistance are eligible for a randomized sub-study comparing an increased loop diuretic dose with combination diuretic therapy of loop diuretic plus chlorothiazide.

Conclusions The Mechanisms of Diuretic Resistance Study will establish a prospective patient cohort and biorepository to investigate the mechanisms of diuretic resistance and urine biomarkers to rapidly predict loop diuretic resistance.

Keywords Heart failure; Diuretic; Diuretic resistance; Acute heart failure

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Introduction

Acute decompensated heart failure (ADHF) is the most common hospital discharge diagnosis among Medicare beneficiaries, directly resulting in approximately 1 million hospitalizations annually and contributing to an additional 2 million hospitalizations as a secondary diagnosis.[1,2] Readmission rates remain remarkably high with nearly 50% of patients rehospitalized within 6 months.[2] Hypervolaemia is the chief problem in the majority of patients admitted with ADHF, and intravenous (IV) loop diuretic therapy is utilized in 80–90% of ADHF hospitalizations.[3–6] Contrary to significant advances in medical therapies for the treatment of chronic heart failure (HF), recent clinical trials of new ADHF therapeutics and treatment strategies have been negative.[7–13] Thus, loop diuretics remain the predominant therapy to treat fluid and sodium retention in ADHF and will remain so for the foreseeable future.

However, diuretic resistance (DR), defined qualitatively as a significantly reduced rate of diuresis/natriuresis to a diuretic, is common and makes the treatment of hypervolaemia in ADHF challenging.[14,15] Notably, an IV furosemide dose of 40 mg increases fractional excretion of sodium (FENa) to 20–25% and produces 3–4 L of urine in healthy volunteers.[16,17] The average patient with ADHF has a log reduction in response, producing only 300–400 mL of

urine output per 40 mg of IV furosemide equivalents.[18,19] Even with high-dose IV loop diuretics, the average peak FENa achieved is only ~5% in ADHF.[20]

The majority of our current understanding of DR mechanisms in ADHF is extrapolated from studies of healthy volunteers and patients with hypertension and/or chronic kidney disease.[16,21–24] Mechanisms of DR that are dominant in other populations, such as reduced glomerular filtration rate, hypoalbuminaemia, and albuminuria, appear to have a minor influence on diuretic response in patients with HF compared with aberrations in tubular sodium handling.[18,25–27] In normal subjects, the negative sodium balance from a loop diuretic can be completely eliminated by a high-sodium intake.[16,28,29] In contrast, several lines of evidence have suggested an equivalent or even superior diuretic response in patients with HF receiving higher sodium chloride intake.[30–33] Similarly, a loop diuretic infusion should unequivocally provide a profound advantage over bolus dosing based on traditional DR paradigms.[34,35] However, multiple clinical trials have failed to demonstrate a meaningful difference between bolus and continuous infusion in ADHF.[36,37]

In addition to our limited understanding of the mechanisms of DR in human HF, our ability to diagnose DR is limited. In clinical practice and ADHF trials, changes in weight and fluid balance are the primary strategies to assess diuretic response.[13,36,38–40] Weight and net fluid loss should correlate perfectly. Yet even in clinical trials, weight and net fluid loss display poor correlation with each other and are notoriously difficult to accurately obtain even in these settings of rigorous monitoring.[41] It is reasonable to assume that the measurement of weight and fluid loss is worse in routine clinical practice, demonstrating the need for better tools to assess diuretic response.

Therefore, a rigorous investigation of DR in a real-world ADHF population is required to better inform diagnostic strategies and understand which mechanisms predominate in ADHF, thus informing treatment strategy. The Mechanisms of Diuretic Resistance (MDR) Study was designed to rigorously investigate the mechanisms of DR and develop tools to rapidly predict diuretic response in a real-world cohort of patients hospitalized with ADHF assessed serially across the hospital episode and after discharge.

Study design

The MDR Study seeks to establish a prospective patient cohort and biorepository, creating a premier data source for the study of DR in ADHF. The primary objective is to study DR mechanisms by combining the methodological rigour of a General Clinical Research Center (GCRC) in multiple study assessments with the generalizability of a heterogeneous, real-world hospitalized ADHF population. The MDR Study is composed of serial assessments following loop diuretic administration, occurring at milestones during and after the ADHF hospital episode. Each timed urine collection is intensely supervised by research personnel with protocolized biospecimen collections to replicate the rigour of a research centre observation during a hospital stay for ADHF. However, the inclusion and exclusion criteria are designed to allow generalizability to a real-world ADHF population. Additional objectives include studying the changes in the mechanisms of DR over time in the ADHF treatment episode, identifying urine variables to rapidly identify DR, and investigating the association between DR parameters and outcomes during and post-hospital discharge (*Table 1*).

The MDR Study is a prospective, observational cohort of patients hospitalized with ADHF at the two main hospitals in the Yale New Haven Hospital System (USA). After enrolment, patients are followed longitudinally with study assessments, termed 'visits', occurring at several milestones within the ADHF hospital episode, an outpatient study visit after hospital discharge, and outcomes assessment after hospital discharge. Within this study, patients with DR at the first study visit are randomized in an open-label, parallel sub-study comparing an increased dose of IV loop diuretic therapy with the addition of IV chlorothiazide to the same dose of IV loop diuretic therapy (NCT02546583).

The philosophy of the MDR Study is to investigate DR mechanisms in a heterogeneous ADHF population with real-world generalizability. Via a pharmacy-generated list, all patients prescribed an IV loop diuretic are screened daily. Full inclusion and exclusion criteria are listed in *Table 2*. Key inclusion criteria include a clinical diagnosis of ADHF with at least one objective sign of hypervolaemia and projected need, based on the treating clinician's assessment, of IV loop diuretic therapy for at least 3 days. To maximize external validity, patients were not excluded based upon estimated glomerular filtration rate.

Patients with DR at Study Visit 1, defined as a cumulative 6 h sodium output %3C100 mmol following the Visit 1 IV loop diuretic dose, are eligible for a randomized sub-study occurring as Study Visit 2. While additional inclusion and exclusion criteria exist to qualify for the randomized sub-study (*Table 3*), these criteria are limited to ensure that a diverse, representative cohort is included while ensuring patient safety. A cumulative 6 h sodium output %3C100 mmol was chosen as this would rarely result in a significant net negative daily sodium balance (maximum possible sodium balance of only negative 70 mmol/day assuming twice daily diuretic dosing and a 130 mmol dietary sodium intake per day).[42–44] Similar to prior studies, patients with an IV loop diuretic dose >160 mg IV furosemide equivalents at Visit 1 are not included, even if they met the criteria for DR, because their loop diuretic bolus dose would exceed

Table 1 Example research questions to be investigated with the Mechanisms of Diuretic Resistance cohort

What variables predict loop diuretic response?
Can widely available urine tests (i.e. urine electrolytes) allow rapid diagnosis of diuretic resistance?
Are specific mechanisms of diuretic resistance more responsive to escalating loop diuretic doses or various combinations of diuretic therapies?
Does tailoring diuretic therapy to the specific resistance mechanism improve natriuresis?
Can the mechanism of resistance be predicted using commonly available laboratory tests?
Which nephron location is primarily responsible for diuretic resistance?
Which specific ion transporters contribute significantly to diuretic resistance?
How does the loop diuretic natriuretic response and specific ion transporter activity change over an acute heart failure hospitalization episode?
How often is the initial empiric oral loop diuretic dose chosen an effective one?
What parameters can be used to detect diuretic resistance in outpatients where cumulative metrics, e.g. urine output, are unavailable?
What is the correlation between post-discharge outcomes and variables such as diuretic resistance mechanisms or natriuretic response to combination diuretic therapies?

Table 2 Mechanisms of Diuretic Resistance study criteria

Inclusion criteria
Age ≥18 years Clinical diagnosis of acute decompensated heart failure with at least one of the following objective signs of hypervolaemia: • Oedema • Rales • Elevated jugular venous pressure • Pre-admission weight gain Current use of bolus IV loop diuretic therapy and projected need by the treating clinician for continued treatment with IV diuretics for at least 3 days with the goal of significant fluid removal (>1 L net fluid loss per day)
Exclusion criteria
Inability to perform informed consent or comply with the serial urine collection procedures Significant known bladder dysfunction or urinary incontinence Haematocrit %3C21% or active bleeding IV, intravenous.

Table 3 Mechanisms of Diuretic Resistance additional criteria for randomized sub-study

Inclusion criteria
Cumulative 6 h sodium output %3C100 mmol following Visit 1 IV loop diuretic dose Visit 1 IV loop diuretic dose ≤160 mg IV furosemide equivalents[a] Serum sodium >125 mEq/L At least 6 h since last dose of diuretic
Inclusion criteria
Current use or projected future requirement by the treating physician for thiazide diuretics Use of high-dose mineralocorticoid receptor antagonist therapy (≥50 mg of spironolactone or ≥100 mg of eplerenone) or amiloride IV, intravenous. [a]40 mg IV furosemide = 1 mg IV bumetanide.

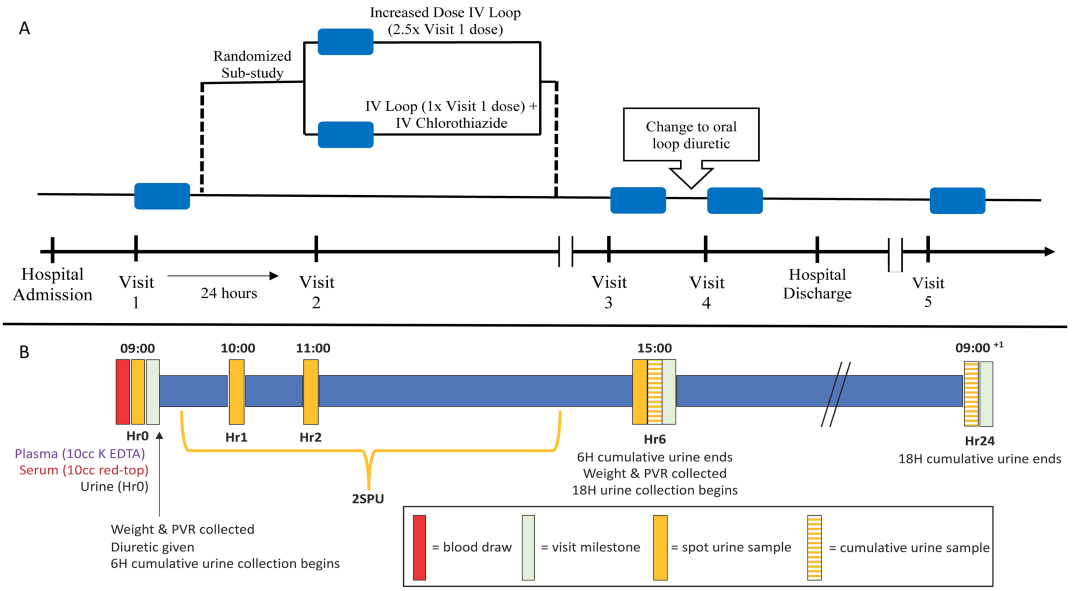
400 mg IV furosemide equivalents if randomized to the 2.5 times the Visit 1 IV diuretic treatment arm.[36] Patients not meeting the full inclusion and exclusion criteria listed in *Table 3* are not included in the randomized sub-study but are eligible for subsequent study visits.

Study assessments

A flow diagram of the study assessment timeline is provided in *Figure 1A*. After consent, patients undergo serial study 'visits' during the ADHF hospital episode. Each visit includes a supervised 6 h urine collection timed to loop diuretic administration with protocolized biospecimen collections. Visit 1 occurs early in the ADHF treatment course during open-label IV loop diuretic therapy. Patients with DR at Visit 1 can be included in the randomized sub-study, termed Visit 2. At Visit 2, patients are randomized to open label increase in loop diuretic therapy (2.5 times the Visit 1 IV loop diuretic dose) or combination of loop dose and thiazide diuretic therapy (1 times the IV loop diuretic at Visit 1 plus 500 mg of IV chlorothiazide, unless the estimated glomerular filtration rate is %3C30 mL/min/1.73 m^2 in which case they receive a 1000 mg dose) the following day. Visit 2 is not conducted in patients who do not meet the sub-study inclusion and exclusion criteria in *Table 3*. Additional reasons for not having Visit 2 include both medical (e.g. haemodynamic instability, diuretic discontinuation, use of non-study diuretic therapies, altered mental status, and new bladder incontinence or retention) and logistical (patient refusal, new loose stools preventing urine collection, transfer to hospital ward where study procedures are not possible, etc.). With the exception of Visit 2, the diuretic therapy is at the discretion of the treating medical provider. Visit 3 occurs during IV diuretic therapy later in the hospital stay, ideally on the last day of IV diuretic therapy when able to be predicted. Visit 4 occurs upon transition to oral diuretic therapy prior to hospital discharge. Visit 5 occurs in a clinical research centre after hospital discharge on oral diuretic therapy. After discharge, patients are prospectively monitored for rehospitalization and death via electronic medical records and the Social Security Death Index.

Each study visit includes a 6 h supervised urine collection with timed spot urine collections (*Figure 1B*). In the 3 h prior to loop diuretic administration, a urine sample is collected any time the patient urinates, and the time and full volume

Figure 1 Study assessment diagram. (A) Patients hospitalized with acute decompensated heart failure enrolled in the Mechanisms of Diuretic Resistance Study undergo serial 'visits', indicated by a blue box. Visits 1, 3, and 4 occur during open-label intravenous (IV) loop diuretic therapy. Patients who are diuretic resistant at Visit 1 and meet sub-study criteria are randomized to increased loop diuretic therapy or combination of loop and thiazide diuretic therapy at Visit 2 the following day. Visit 3 occurs during IV diuretic therapy later in the hospital stay. Visit 4 occurs on the day of oral diuretic therapy prior to hospital discharge. Visit 5 occurs in a clinical research centre after hospital discharge on oral diuretic therapy. (B) Each visit includes a supervised 6 h urine collection with urine and blood sample collection and standing weight measurements timed to a dose of loop diuretic. Spot urine is collected at Hours 0, 1, 2, and 6. A spot sample from the second spontaneous urination (2SPU) is also collected if it occurred outside of these timed spot urine samples. A sample from the 6 and 18 h cumulative urine collections is also collected. H, cumulative hours; Hr, hour of biospecimen collection; PVR, post-void residual.



of the urination are recorded as *contingency urine*. Prior to diuretic administration, patients are instructed to empty their bladder, which is confirmed with post-void bladder ultrasound. A standing weight with serum, plasma, and urine collections is performed at Hour 0 (Hr0). If the patient is unable to urinate at Hr0, the *contingency urine* from the most recent void in the previous 3 h is saved as Hr0. After diuretic administration, spot urine is collected at Hours 1 (Hr1), 2 (Hr2), and 6 (Hr6). A spot sample from the second spontaneously produced urination is also collected if it occurred outside of these timed spot urine samples. The time and volume of each spot urination are recorded. The 6 h cumulative urine collection is measured via graduated cylinder to the nearest 5 mL. To account for urine sampled throughout the visit, sample volumes are added back to calculate the total urine output. After the 6 h supervised urine collection, an additional 18 h urine collection is initiated at Hr6, to quantify 24 h urine output. The 18 h urine collection is measured for volume, and a sample is collected.

A full list of all study assessments is provided in *Table 4*. After consent and enrolment in the MDR Study, admission and prior-to-admission variables are collected from the electronic medical record. Some visits have specific additional assessments unique to the study visit, which are also displayed in *Table 4*. A validated method of loop diuretic dose logarithmic transformation will be utilized when expressing diuretic response in relation to increasing diuretic dose.[26] Sodium and urine output will be the predominant descriptors utilized for diuretic response. Sodium-based diuretic response will be described using cumulative sodium output, representing the absolute sodium excretion rate of the kidney, and FENa, representing natriuresis 'per nephron'. Post-discharge outcomes are prospectively assessed for mortality and rehospitalization back to the Yale New Haven Hospital System.

Urine and blood samples

Each urine sample is divided into two conicals for analysis. A 15 mL urine conical is analysed via urine dipstick for pH and standard urine analyses, centrifuged for 10 min at 4°C and 1500 *g*, and then divided into up to ten 1 mL aliquots for storage in the biorepository. In addition, up to 42.5 mL of urine is treated with protease inhibitor and stored to isolate microvesicles at a later time point.

Serum is allowed to clot at room temperature for no %3C60 min and then put on ice for 10 min prior to centrifugation. Plasma is refrigerated until separation is visible and qualitatively analysed for haemolysis prior to centrifugation.

Table 4 Study assessments

Admission assessments[a]
Demographics and co-morbidities
Concomitant medications
Baseline clinically obtained laboratory values
Physical exam
Vital signs and weight
Assessments repeated at each study visit
Physical exam assessment[a]
All diuretic medications[a]
Clinically obtained laboratory values[a]
Standing weight at baseline and Hr6
Post-void residual at baseline and Hr6
6 h cumulative urine sodium (mmol)
Assessments unique to specific study visit
Visit 1
Clinical Assessment Survey
Visit 4
Clinical Assessment Survey
Visit 5
Clinical Assessment Survey
Concomitant medication list
Hospital discharge[a]
Weight
Discharge medications
Clinically obtained laboratory values (CBC, CMP, and LFTs) at discharge, peak, and nadir during hospitalization
Assessments of heart failure outcomes
All-cause mortality
First rehospitalization

CBC, complete blood count; CMP, complete metabolic panel; Hr6, Hour 6; LFTs, liver function tests.
[a]Generated during standard of care and collected from electronic medical record.

Serum and plasma are then centrifuged for 10 min at 4°C and 1500 *g*. Up to ten 0.5 mL aliquots from each serum and plasma collection, along with the plasma sample's buffy coat for DNA, are saved. After aliquoting, all blood and urine samples are stored at −80°C in continuously monitored freezers and registered in the biospecimen collection console of OnCore, a biospecimen management system integrated with the electronic medical record.

Study population

Beginning in 2015, the MDR Study aimed to enroll 200 participants. The overall cohort size was calculated to provide adequate power to validate our previously published loop diuretic natriuretic response prediction equation, a primary study question in *Table 1*.[42] Detecting a statistically significant difference (*P* %3C 0.05) with an area under the curve (AUC) of ≥0.8 with a power of 90% only requires 34 patients. As such, we focused rather on the size of the confidence interval of the AUC. With a population of 200 participants, there was 90% power to detect a 95% confidence interval error margin of 0.06 and 0.04 for an AUC of 0.8 and 0.9, respectively (α = 0.05). All other study question power calculations were performed as a derivative of this primary study population size.

We projected that ~50–66% of patients in the total cohort would qualify for the randomized sub-study (Visit 2). At 2 years of enrollment, only 26% (*n* = 60) of 228 enrolled participants were randomized in the sub-study. The Visit 2 enrollment target was modified to a goal of 100 patients with expansion of the total study population size to reach that goal. To date, the MDR Study has enrolled 460 total participants, with enrollment into the Visit 2 sub-study nearly complete. Enrollment is estimated to be completed by July 2020.

Discussion

The MDR Study will facilitate investigation into the multitude of clinical questions surrounding DR in ADHF. The central study goals are rapid identification of patients with DR and identification of DR mechanisms in ADHF. By developing the knowledge base and tools to rapidly identify DR, days of 'wasted' hospitalization with ineffective diuresis can potentially be avoided. Understanding the mechanism(s) of DR in patients with ADHF is a critical step in improving care in this population. As multiple medications with antagonistic activity at renal sodium transporters/channels are already available, knowledge of the nephron segment location and specific transporters responsible for DR can be immediately translated to patient care at low cost.

Limitations of the MDR Study are extensions of intentionally enrolling a heterogeneous, real-world cohort. In an effort to capture this population, patients hospitalized with ADHF are enrolled even if completion of all longitudinal assessment visits is not expected. Reasons for non-completion of all visits could be medical (e.g. worsening creatinine with cessation of IV diuretic therapy) or at the participant level (e.g. unlikely to return for an outpatient follow-up visit). Despite an intensely supervised 6 h urine collection, missing or spilled urine voids still infrequently occur. Missing voids are documented for inclusion in analyses. Study data that are generated during standard-of-care medical orders may be missing in some patients based upon unavailable data.

The MDR Study will provide a methodologically rigorous dataset and biorepository to study the mechanisms of DR longitudinally in a diverse real-world population of patients hospitalized with ADHF. The planned investigations will provide unique insight on the specific mechanisms of DR and impact of different diuretic strategies to restore diuretic response. The findings will provide critical information towards our understanding of DR in patients with ADHF on contemporary medical management.

Conflict of interest

J.M.T. reports grants and personal fees from Sequana Medical, BMS, 3ive Labs, Boehringer Ingelheim, Sanofi,

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