A
cute decompensated heart failure (ADHF) is the most
common cause of hospital admission in patients >65
years, accounting for >1 million hospitalizations, 6 million
hospital days, and $12 billion in costs annually in the United
States alone.1,2 The prognosis of patients admitted with
ADHF is dismal, with rates of rehospitalization or death
approaching 50% within 6 months.3,4 Despite these alarming
and oft-cited statistics, the development of new therapies in
ADHF has changed little over recent decades,5 and short-term
and intermediate-term outcomes have remained poor.6 In
addition to spurring the development of new therapies for
ADHF, these data suggest the need for an active reappraisal
of current therapy. This review will focus on the data (or lack
thereof) supporting the efficacy and safety of loop diuretics in
ADHF, discuss the challenges in performing clinical trials of
diuretics in ADHF, and describe an ongoing clinical trial
designed to rigorously evaluate optimal diuretic use in this
syndrome.

Loop diuretics are the foundation of current ADHF ther-
apy. Data from the ADHF National Registry demonstrate that
approximately 90% of patients hospitalized with ADHF in
the United States receive IV loop diuretics during the hospi-
talization.7 This nearly ubiquitous use of loop diuretics in
ADHF is understandable given that the majority of ADHF
hospitalizations are related to volume overload and congestion,8
and decades of clinical observation has shown that IV
administration of loop diuretics results in prompt diuresis and
relief of symptoms in most patients. Despite this breadth of
clinical experience, however, high quality data supporting the
safety and efficacy of loop diuretics in ADHF are sparse.
Accordingly, the most recent practice guidelines for ADHF
from the Heart Failure Society of America recommend loop
diuretics at “doses needed to produce a rate of diuresis
sufficient to achieve an optimal volume status.”9 Notably, this
guideline has the strongest level of recommendation (is
recommended) but the lowest level of evidence (C, based on
expert opinion only). Current guidelines from the American
College of Cardiology and the American Heart Association
do not address the treatment of ADHF.10 Although modern
phase II development programs for new drugs go to great
lengths to identify the range of doses that best balance safety
and efficacy, these fundamental clinical questions have not
been rigorously investigated for loop diuretics. Given the lack
of available evidence to guide diuretic therapy, it is not
surprising that practice patterns vary widely between physi-
cians and centers. In a study identifying unanswered ques-
tions in heart failure management, >50% of the questions
were related to the most appropriate use of diuretics.11

Safety of Loop Diuretics in ADHF
Several mechanistic considerations suggest the possibility
that loop diuretics may have detrimental effects in patients
with heart failure. Administration of loop diuretics to patients
with heart failure has been shown to activate the renin-an-
giotensin-aldosterone system and the sympathetic nervous
system, both of which are known to play a fundamental role
in heart failure progression.12–14 Although decreases in intra-
vascular volume from diuretic therapy contribute to renin-an-
giotensin-aldosterone system and sympathetic nervous sys-
tem activation, volume independent mechanisms also play a
role, including the direct stimulation of renin release by
blocking sodium chloride uptake at the macula densa and
upregulation of renin gene expression in the kidney.15 These
mechanisms may underlie the clinical observation that loop
diuretics are associated with increases in systemic vascular
resistance and may initially raise ventricular filling
pressures.16

Administration of loop diuretics to patients with heart
failure may result in a significant decrease in glomerular
filtration rate in some patients with heart failure, presumably
due to renin-angiotensin-aldosterone system and sympathetic
nervous system activation with related changes in renal blood
flow and glomerular filtration pressure.16 Paradoxically, some
patients with ADHF may have improvement in renal function
with diuretic therapy, potentially due to improvements in
functional mitral regurgitation with unloading or changes in venous or intra-abdominal pressure. Administration of loop diuretics may lead to electrolyte imbalances (such as hypokalemia, hyponatremia, and hypomagnesemia) that may exacerbate cardiac arrhythmias and increase the risk of sudden cardiac death. Although placebo controlled studies of diuretics in human with heart failure have not been performed, an animal study using a porcine heart failure model showed that treatment with furosemide resulted in an increased progression of left ventricular systolic dysfunction, increases in circulating aldosterone levels, and a greater down regulation of β-adrenergic responsiveness compared with placebo.

Clinically, multiple observations have suggested an association between diuretic use and worsening outcomes in patients with heart failure (Table 1). In the Studies of Left Ventricular Function Trial, use of a diuretic was associated with a 37% increase in the risk of arrhythmic death after controlling for multiple other measures of disease severity. Several other studies have identified an association between higher doses of diuretics and adverse outcomes in patients with ADHF and advanced heart failure outpatients and inpatients. An analysis of data from the Digitalis Investigation Group study used sophisticated propensity matching to control for baseline differences in patients taking diuretics compared with those who were not, and still found a 31% increased risk of death associated with diuretic use. Most recently, analysis of the data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness study demonstrated a nearly linear relationship between loop diuretic dose and mortality over 6 months of follow-up in patients hospitalized with advanced heart failure (Figure 1).

Although these observational data demonstrate an association between higher doses of diuretics and worse outcomes, all such data are highly confounded by indication (ie, patients who receive higher doses of diuretics may do so because of greater disease severity compared with patients who can be successfully treated with lower doses of diuretics). Although most (but not all) prior studies have found a persistent adverse effect of loop diuretics even after multivariable adjustment for other known predictors of mortality, such adjustment may be insufficient to completely eliminate confounding. Prospective, carefully controlled studies will be required to clarify whether there is a causal relationship between diuretic use and adverse outcomes, or alternatively if diuretic dosage is just a surrogate for disease severity.

### Efficacy of Loop Diuretics in ADHF

Administration of IV furosemide to patients with ADHF typically results in a prompt diuretic effect (within 30 minutes) that peaks at 1.5 hours. This effect leads to a decrease in ventricular filling pressures and improvement in symptoms in the majority of patients with ADHF. This observation has been confirmed in the placebo groups of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan, in which treatment based primarily on loop diuretics was associated with rapid and substantial improvement of dyspnea.

Despite this clinical efficacy, substantial questions remain about how to best use diuretics to treat volume overload in patients with heart failure. One major unanswered issue is the most appropriate dosing strategy for loop diuretics in ADHF. There are almost no data evaluating the relationship between diuretic dose and diuretic efficacy in ADHF. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness study, higher doses of IV loop diuretics were not associated with greater weight loss during the index hospitalization after adjustment for other measures. Doses in published studies of IV furosemide in heart
failure have ranged over 200-fold, from as low as 20 mg to as high as 4000 mg daily.\textsuperscript{31,32}

Several aspects of the pharmacology of loop diuretics may account in part for the observed variability in diuretic dosing for ADHF. Heart failure shifts the dose–response curve for loop diuretics downward and the right, necessitating a higher starting dose to achieve the same level of sodium excretion. Additionally, the “braking phenomenon,” characterized by a progressively diminishing response to diuretic therapy with ongoing treatment, is well recognized in heart failure patients and seems to be related to several underlying mechanisms. As described above, loop diuretics activate both the renin-angiotensin-aldosterone system and sympathetic nervous system, both of which tend to reduce renal blood flow and increase resorption of sodium in the proximal and distal tubule. Absolute or relative decreases in intravascular volume with ongoing diuretic therapy leads to a decrease in the amount of sodium filtered at the glomerulus and an increase in the amount of sodium reabsorbed.\textsuperscript{33} Chronic loop diuretic therapy also leads to structural changes in the kidney itself, particularly hypertrophy of the epithelial cells in the distal tubules, which enhance distal reabsorption of sodium and limit sodium excretion and diuresis.\textsuperscript{34} The combined effects of heart failure, frequent concomitant renal insufficiency, and physiological braking all contribute to the clinical phenomenon of diuretic resistance, in which patient have persistent evidence of volume overload but are progressively resistant to the effects of loop diuretics. When accompanied by worsening renal function, this has been termed the “cardio-renal syndrome,” and represents a major clinical challenge in the management of ADHF.\textsuperscript{35}

Do higher doses of loop diuretics contribute to the development of the cardio-renal syndrome? In a retrospective analysis, Butler et al\textsuperscript{22} identified higher loop diuretic dosage as an independent predictor of worsening renal function in ADHF even after controlling for disease severity and the degree of diuresis. As with the relation between diuretic dose and mortality described above, however, it may be impossible to completely adjust for other confounders of disease severity that could effect both diuretics requirements and the risk of worsening renal function. Thus, it remains unknown whether higher diuretic requirement are simply a marker for higher risk or whether higher doses of loop diuretics contribute directly to the development of the cardio-renal syndrome in patients with ADHF.

Are there Safer Ways to Use Diuretics? Bolus Versus Infusion

The concerns about safety and efficacy described above suggest the need to identify the better strategies for using loop diuretics in ADHF. In addition to the questions about dosing described above, ongoing uncertainty exists about the optimal route of administration of IV loop diuretics (bolus dosing or continuous infusion). From a pharmacokinetic and pharmacodynamic perspective, there are potential benefits of continuous infusion when compared with intermittent bolus dosing. Bolus diuretic dosing may be associated with a higher rate of diuretic resistance due to prolonged periods of subtherapeutic drug levels in the kidney. For example, giving an IV bolus of furosemide twice daily results in a 4- to 6-hour period of diuretic effect, followed by a 6- to 8-hour period of subtherapeutic diuretic concentration during which sodium reabsorption in the kidney may rebound, especially in the face of inadequate dietary sodium restriction.\textsuperscript{33} Continuous infusion results in a more constant delivery of diuretic to the tubule, potentially reducing this phenomenon. Additionally, contin-
uous infusion is associated with lower peak plasma concentrations, which may be associated with a lower incidence of other side effects such as ototoxicity, especially at higher doses.

Multiple small studies have evaluated the role of continuous infusion of loop diuretics in patients with heart failure. These studies have been underpowered to address clinical questions and have generally lacked methodologic rigor. A recent meta-analysis from the Cochrane Collaboration comprehensively evaluated the available literature to address this question and identified studies including a total of 254 patients who met rigorous analytic standards (Table 2). In general, continuous infusion was associated with greater urine output, shorter length of hospital stay, less impairment of renal function, and lower mortality when compared with intermittent bolus dosing. Notably, however, almost all the conclusions of this meta-analysis were driven by a single study by Licata et al., which was substantially confounded by the use of hypertonic saline infusion in the continuous infusion group. In their conclusions, the authors acknowledged that careful, evidence-based investigation of their mechanical ventilation and of myocardial infarction.

In light of the uncertainty about loop diuretics, the optimal dosing strategy, and the best route of administration, the National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network has undertaken a multicenter, randomized, controlled trial of loop diuretic strategies in ADHF, the Diuretic Optimization Strategies Evaluation (DOSE) study (clinicaltrials.gov, NCT00577135). DOSE will randomize 300 patients hospitalized with ADHF and signs and/or symptoms of congestion in a 2×2 factorial design, to test the following hypotheses:

1. That “low intensification” furosemide therapy (1× the chronic oral dose) will be more efficacious (with regard to relief of symptoms) and safer (with regard to changes in renal function), when compared with “high intensification” furosemide therapy (2.5× the chronic oral dose) in patients with ADHF.
2. That continuous infusion diuretic therapy will be more efficacious (with regard to relief of symptoms) and safer (with regard to renal function), when compared with twice daily bolus therapy in patients with ADHF.

The coprimary end points will be improvement in symptoms (based on the area under the curve of the patient global assessment using a visual analog scale) from randomization to 72 hours, and the change in serum creatinine between randomization and 72 hours. Given the subjective nature of the evaluation of clinical symptoms, the DOSE study will use a double-blind, double dummy design to minimize bias. All patients will receive both a continuous infusion and intermittent IV boluses, one of which will contain furosemide and the other a saline placebo. A flow chart of treatment assignment and study timeline for the DOSE study is shown in Figure 2.
The design of the DOSE study has several notable challenges that are worthy of comment. With regard to dosage, the investigators recognized that what constitutes a high dose or low dose of diuretics for an individual patient differs based on patient-specific factors such as baseline renal function and chronic diuretic dose. Therefore, assigned diuretic dosing will be based on the chronic oral diuretic dosage (1x oral dose for “low intensification,” and 2.5x oral dose for “high intensification”). In clinical practice, diuretic strategies are continually reassessed and adjusted based on the clinical condition of the patient and the response to therapy. This creates a substantial tension between the desire to adjust the diuretic dose frequently and the need to have patients continue on their assigned treatment to evaluate the differences between therapies. To provide an opportunity to adjust diuretic dosing within the context of the study protocol, an adjustment in diuretic dosing is permitted by the study protocol at 48 hours from the time of randomization. On the basis of the clinical assessment of the patient at that time, the treating physician may choose to:

- Maintain current strategy without change
- Increase dose by 50% (while remaining blinded)
- Change to oral diuretics (dose at physician discretion)

Patients requiring additional open label diuretics, IV vasoactive agents, or mechanical support during the randomization period will meet the secondary end point of “worsening or persistent heart failure.” Conversely, patients may develop signs or symptoms of excessive diuresis (such as hypotension or worsening azotemia) that necessitate holding or discontinuing diuretics before completion of the randomization period. This will be captured as a “treatment failure” only if it requires specific intervention beyond simply holding diuretics. As this is a randomized trial comparing initial diuretic strategies, in all cases the interpretation of the primary end points with regard to both symptom relief and renal function will be on an “intention to treat” basis. All subjects will undergo serial measurement of cardiac and renal biomarkers throughout the index hospitalization and during follow-up. The DOSE study is currently enrolling patients at 9 regional clinical centers in the United States and Canada.

Conclusions

ADHF has emerged as one of the most important clinical syndromes in cardiovascular medicine in terms of incidence, morbidity, and costs. Although loop diuretics are the mainstay of therapy for ADHF, much uncertainty remains about the safety and efficacy of various doses as well as means of administration. Although observational data can provide clues to the safety and efficacy of therapies, a true assessment of the risks and benefits can only be achieved with an appropriately powered, prospective randomized clinical trial. Despite the challenges of performing rigorous randomized trials of diuretic therapy, we suggest that a therapy provided routinely to almost all patients with ADHF should be held to a higher level of evidence than expert opinion only. The DOSE study is attempting to address the critical question of how best to use loop diuretics in patients with ADHF and signs and symptoms of volume overload. Successful completion of the DOSE study will identify the optimal initial strategy of loop diuretics in this patient population, which will be broadly representative of the 1 million annual hospitalizations for ADHF in the United States.

In addition to the obvious clinical benefit of defining the best strategy for diuretic therapy, data from the DOSE study will help establish a standard for optimal background therapy against which future ADHF therapies can be compared. Defining the optimal strategy for diuretic administration will therefore not only impact current clinical care but will aid in the development and evaluation of new ADHF therapies moving forward.

Appendix

Clinical sites and investigators participating in the Heart Failure Clinical Research Network are as follows: Network Chair: Eugene Braunwald, MD; National Heart, Lung, and Blood Institute Project Officers: Alice Mascette, MD, Robin Boineau, MD; Data Coordinating Center: Kerry Lee, PhD, Duke Clinical Research Institute, Durham, NC; Principle Investigators and Clinical Centers: David Bull, MD, University of Utah Health Sciences Center, Salt Lake City, Utah; Steven Goldsmith, MD, University of Minnesota, Minn-
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None.

References


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