Advances in Heart Failure

Loop Diuretics in Acute Decompensated Heart Failure
Necessary? Evil? A Necessary Evil?

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“In times of great danger, you are permitted to walk with the devil until you have crossed the bridge.” —Bulgarian proverb

Acute 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 therapy. 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 hospitalization.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 physicians and centers. In a study identifying unanswered questions 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-angiotensin-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 intravascular volume from diuretic therapy contribute to renin-angiotensin-aldosterone system and sympathetic nervous system 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.13

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

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*Clinical sites and principal investigators participating in the Heart Failure Clinical Research Network are listed in the Appendix.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(Circ Heart Fail. 2009;2:56-62.)

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Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.108.821785
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 in patients 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.

### Table 1. Observational Studies of Diuretics and Outcomes in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>End Point</th>
<th>Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies of Left Ventricular Function</td>
<td>Left ventricular dysfunction with or without HF</td>
<td>Oral diuretics vs none</td>
<td>Mortality</td>
<td>1.37</td>
<td>1.08–1.73</td>
</tr>
<tr>
<td>Digitalis Investigation Group</td>
<td>Chronic HF</td>
<td>Oral diuretics vs none</td>
<td>Mortality</td>
<td>1.31</td>
<td>1.11–1.55</td>
</tr>
<tr>
<td>Butler et al</td>
<td>ADHF</td>
<td>Dose of IV loop diuretics</td>
<td>Worsening renal function (change of 0.3 mg/dl)</td>
<td>1.04 per 20-mg increment of furosemide</td>
<td>1.004–1.076</td>
</tr>
<tr>
<td>Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness</td>
<td>Advanced HF in-patients</td>
<td>Dose of IV loop diuretics</td>
<td>Mortality</td>
<td>1.15 per doubling of dose</td>
<td>1.025–1.28</td>
</tr>
<tr>
<td>Eshaghian et al</td>
<td>Advanced HF out-patients</td>
<td>Dose of oral diuretics</td>
<td>Mortality</td>
<td>3.4 per quartile of dose</td>
<td>2.4–4.7</td>
</tr>
<tr>
<td>Neuberg et al</td>
<td>Chronic HF</td>
<td>Diuretic oral dose (&lt;80 mg furosemide)</td>
<td>Mortality</td>
<td>1.37 for dose above median</td>
<td>Not provided, P=0.004</td>
</tr>
<tr>
<td>Philbin et al</td>
<td>ADHF</td>
<td>No. of IV diuretic doses</td>
<td>In-hospital mortality</td>
<td>1.11 per No. of doses</td>
<td>1.06–1.17</td>
</tr>
<tr>
<td>Mielniczuk et al</td>
<td>Chronic HF</td>
<td>Oral diuretic dose</td>
<td>HF events</td>
<td>1.53 for dose &gt;80 mg</td>
<td>0.58–4.03</td>
</tr>
</tbody>
</table>
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 to 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. 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. 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.

Do higher doses of loop diuretics contribute to the development of the cardio-renal syndrome? In a retrospective analysis, Butler et al 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. Continuous infusion results in a more constant delivery of diuretic to the tubule, potentially reducing this phenomenon. Additionally, conti-
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.42–48 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 question31 and identified studies including a total of 254 patients who met rigorous analytic standards (Table 2).42–48 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,48 which was substantially confounded by the use of hypertonic saline infusion in the continuous infusion group. In their conclusions, the authors of the Cochrane analysis strongly emphasized the overall uncertainty regarding the best dosing strategy and route of administration, and for which observational data raise concerns about the overall safety. This suggests the need for an adequately powered, carefully controlled clinical study to address the balance between safety and efficacy of various dosing and mode of administration strategies for loop diuretics in ADHF—a “phase II development program” for furosemide.

Is it Possible to Study Diuretics in ADHF? Design of the Diuretic Optimization Strategies Evaluation Study

Despite the meager data on which current clinical practice is based, diuretics are seen as so fundamental to ADHF management that careful, evidence-based investigation of their use is challenging. Placebo controlled trials of diuretics in highly symptomatic patients with ADHF have been appropriately deemed unethical. One strategy for investigating optimal diuretic therapy is to evaluate differing doses or combinations with other agents. Cotter et al49 compared a vasodilator focused strategy (high dose nitrates with low dose diuretics) to a diuretic focused strategy (high dose diuretics and low dose nitrates) in patients with ADHF and acute pulmonary edema and found that the vasodilator focused strategy led to significantly lower incidence of the need for 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.

Table 2. Randomized Trials of Bolus Versus Continuous Infusion of Diuretics in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Intervention</th>
<th>Duration</th>
<th>End Point(s)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaser et al42</td>
<td>8</td>
<td>Randomized, cross-over,</td>
<td>Continuous infusion vs BID IV bolus</td>
<td>24 hours</td>
<td>Urine output</td>
<td>Bolus better</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dormans et al44</td>
<td>20</td>
<td>Randomized, cross-over,</td>
<td>Continuous infusion vs single IV bolus</td>
<td>24 hours</td>
<td>Urine output</td>
<td>Infusion better</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kramer et al45</td>
<td>8</td>
<td>Randomized, cross-over,</td>
<td>Continuous infusion vs single IV bolus</td>
<td>24 hours</td>
<td>Urine output</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lahav et al46</td>
<td>9</td>
<td>Randomized, cross-over,</td>
<td>Continuous infusion vs Q8 bolus</td>
<td>48 hours</td>
<td>Urine output</td>
<td>Infusion better(trend)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licata et al48</td>
<td>107</td>
<td>Randomized, single blind</td>
<td>Continuous infusion + hypertonic saline vs Q12 bolus</td>
<td>6–12 days</td>
<td>Urine output at 24 hours LOS Mortality</td>
<td>Infusion better on all end points</td>
</tr>
<tr>
<td>Pivac et al43</td>
<td>20</td>
<td>Randomized, single blind,</td>
<td>Q12 4-hour infusion vs Q12 bolus</td>
<td>24 hours</td>
<td>Urine output</td>
<td>Infusion better</td>
</tr>
<tr>
<td></td>
<td></td>
<td>crossover</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schuller et al47</td>
<td>33</td>
<td>Randomized, unblinded</td>
<td>Continuous infusion vs bolus</td>
<td>72 hours</td>
<td>Mortality</td>
<td>No difference</td>
</tr>
</tbody>
</table>

For example, LAPMA may lead to a phase II development program for furosemide. LAPMA (loop diuretics) can be administered as a “phase II development program.”
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 (! oral dose for “low intensification,” and 2.5! 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 chose 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, Min-
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Sources of Funding

The Heart Failure Clinical Research Network is funded by the National Heart, Lung, and Blood Institute.

Disclosures

None.

References


**KEY WORDS: diuretics ▶ heart failure ▶ trials**
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Circ Heart Fail. 2009;2:56-62
doi: 10.1161/CIRCHEARTFAILURE.108.821785

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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