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

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Abstract

Acute decompensated heart failure (ADHF) is a common and highly morbid cardiovascular disorder. Most hospitalizations for ADHF are related to symptoms of congestion, and the vast majority of ADHF patients are treated with intravenous loop diuretics. Despite this nearly ubiquitous use, data supporting the safety and efficacy of loop diuretics in ADHF are limited, and controversy exists about the best way to use loop diuretics with regard to both dosing and means of administration (continuous infusion vs. intermittent boluses). We reviewed the data supporting the safety and efficacy of loop diuretics in patients with ADHF. A large body of observational literature suggests that loop diuretics, especially at higher doses, may be associated with increased mortality in patients with heart failure even after detailed adjustment for other measures of disease severity. Additionally, multiple small underpowered trials suggest that continuous infusion may be equivalent or superior to intermittent bolus dosing. In summary, there is a critical need to develop more robust data on the use of loop diuretics in ADHF. In that context, the NIH Heart Failure Clinical Research Network has begun the Diuretics Optimization Strategies Evaluation (DOSE) study, a multi-center, double-blind, randomized controlled trial that will enroll 300 patients with ADHF. The DOSE study will randomize patients using a 2 × 2 factorial design to low dose vs. high dose furosemide, and intermittent bolus vs. continuous infusion. Successful completion of the DOSE study will provide important data on the optimal clinical use of loop diuretics in ADHF.

Keywords

diuretics; acute decompensated heart failure; clinical trials

> "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 over age 65, accounting for over 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 AHF 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 and intermediate-term outcomes

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

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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 Acute Decompensated Heart Failure National Registry (ADHERE) demonstrate that approximately 90% of patients hospitalized with ADHF in the United Sates receive intravenous (IV) loop diuretics during the hospitalization[7]. This nearly ubiquitous use of loop diuretics in ADHF is understandable given that the vast majority of ADHF hospitalizations are related to volume overload and congestion[8], and decades of clinical observation has shown that intravenous 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 acute decompensated heart failure.[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, over 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 (RAAS) and the sympathetic nervous system (SNS), 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 RAAS and SNS 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 RAAS and SNS 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[17]. Administration of loop diuretics may lead to electrolyte imbalances (such hypokalemia, hyponatremia, and hypomagnesemia) that may exacerbate cardiac arrhythmias and increase the risk of sudden cardiac death[18, 19]. 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 beta-adrenergic responsiveness compared to placebo[20].

Clinically, multiple observations have suggested an association between diuretic use and worsening outcomes in patients with heart failure (Table 1)[19, 21–27]. In the Studies of Left Ventricular Function (SOLVD) 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[19]. Several other studies have identified an association between higher doses of diuretics in patients and adverse outcomes in with ADHF[26, 28] and advanced heart failure outpatients[24, 25, 27] and inpatients[23]. An analysis of data from the Digitalis Investigation Group (DIG) study used sophisticated propensity matching to control for baseline differences in patients taking diuretics compared to those who were not, and still found a 31% increased risk of death associated with diuretic use.[21] Most recently, analysis of the data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) 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)[23].

Although these observational data demonstrate an association between higher doses of diuretics and worse outcomes, all such data are highly confounded by indication, i.e., patients who receive higher doses of diuretics may do so because of greater disease severity compared to 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 multi-variable 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 intravenous 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 (VERITAS) and Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), in which treatment based primarily on loop diuretics was associated with rapid and substantial improvement of dyspnea[29, 30].

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 ESCAPE study, higher doses of intravenous loop diuretics were not associated with greater weight loss during the index hospitalization after adjustment for other measures[23]. Doses in published studies of intravenous furosemide in heart failure have ranged over 200 fold, from as low as 20 mg to as high as 4000 mg daily[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 in order 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 appears to be related to several underlying mechanisms.

As described above, loop diuretics activate both the RAAS and SNS, both of which tend to reduce renal blood flow and increase resorbtion 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[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 reabsorbtion of sodium and limit sodium excretion and diuresis.[34] The combined effects of heart failure, frequent concomitant renal insufficiency, and physiologic 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 acute decompensated heart failure.[35].

Do higher doses of loop diuretics contribute to the development of the cardio-renal syndrome? In a retrospective analysis, Butler and colleagues 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 [22]. 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 vs. 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 intravenous loop diuretics (bolus dosing or continuous infusion). From a pharmacokinetic and pharmacodynamic perspective, there are potential benefits of continuous infusion as compared to intermittent bolus dosing. Bolus diuretic dosing may be associated with a higher rate of diuretic resistance due to prolonged periods of sub-therapeutic drug levels in the kidney. For example, giving an IV bolus of furosemide twice daily results in a 4–6 hour period of diuretic effect, followed by a 6–8 hour period of sub-therapeutic diuretic concentration during which sodium reabsorbtion in the kidney may rebound, especially in the face of inadequate dietary sodium restriction[33]. Continuous infusion results in a more constant delivery of diuretic to the tubule, potentially reducing this phenomenon. Additionally, continuous 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 [36–41]. 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[31] and identified studies including a total of 254 patients who met rigorous analytical 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 to intermittent bolus dosing. Notably, however, almost all the conclusions of this meta-analysis were driven by a single study by Licata and colleagues, which was substantially confounded by the use of hypertonic saline infusion in the continuous infusion group [48]. In their conclusions, the authors of the Cochrane analysis strongly emphasized the

overall poor quality of the available data and the need for methodologically sound and adequately powered randomized trials to definitively address this question[31].

In sum, almost all patients with ADHF are treated with a therapy (intravenous loop diuretics) about which there is substantial 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 DOSE 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 al 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[49].

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 (HFCRN) 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, in order 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), as compared to "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), as compared to twice daily bolus therapy in patients with ADHF

The co-primary endpoints 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 (1 × 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 in order 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. Based on 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 endpoint 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 endpoints 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. While 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[9]. 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 roughly 1 million yearly hospitalizations for ADHF in the United States annually.

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.

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Appendix

APPENDIX

Clinical sites and investigators participating in the Heart Failure Clinical Research Network:

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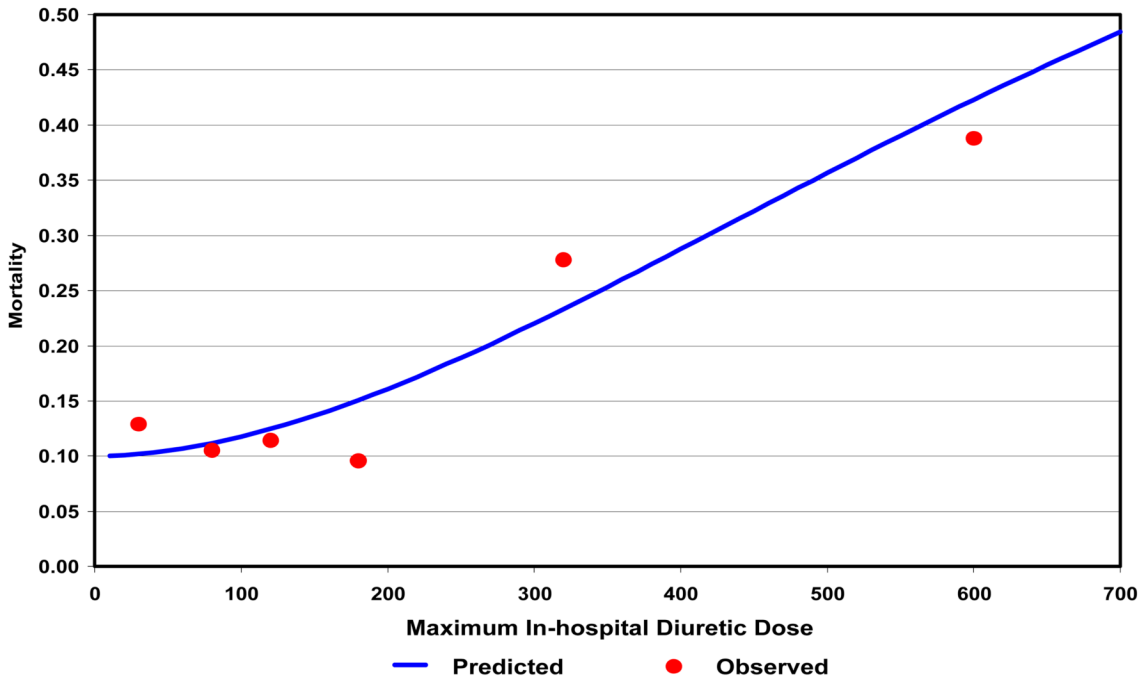

Figure 1.
Relationship between maximum in-hospital diuretic dose and mortality in the ESCAPE study (Reprinted from reference [23], with permission from Elsevier).

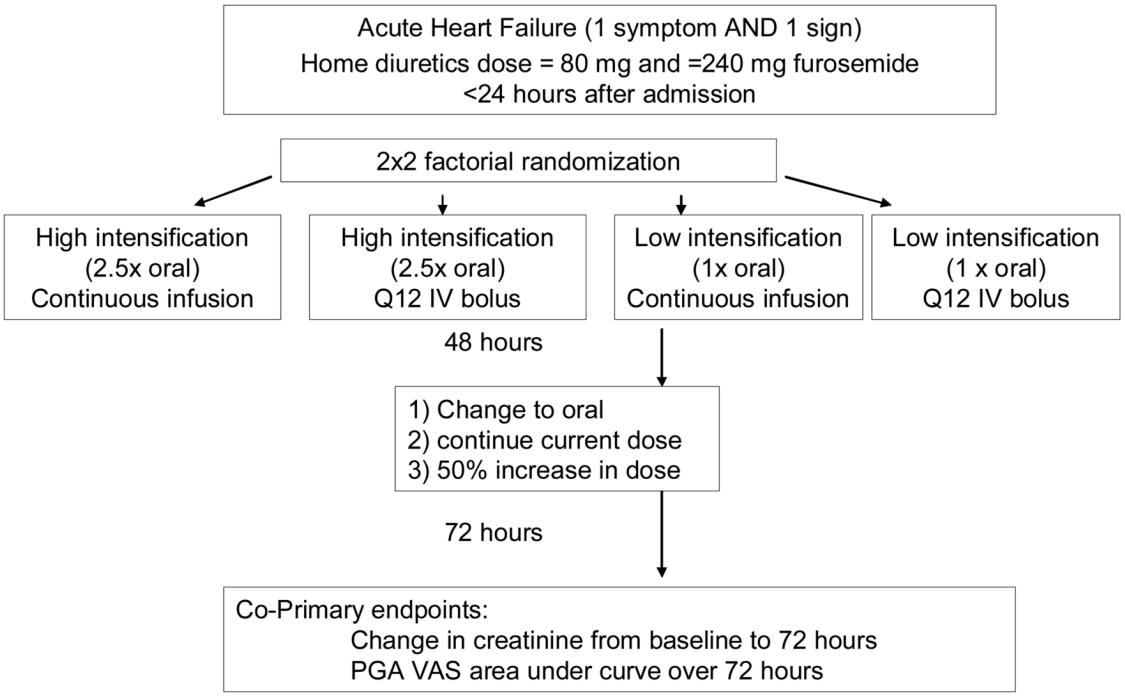

Figure 2.
Study Schema for DOSE Study. ADHF=acute decompensated heart failure. PGA=patient global assessment, VAS=visual analog scale, AUC=area under the curve

Table 1

Observational Studies of Diuretics and Outcomes in Heart Failure

Study	Population	N	Comparison	Endpoint	Risk	95% CI
SOLVD[19]	LV dysfunction with or without HF	6797	Oral diuretics vs. none	Mortality	1.37	1.08–1.73
DIG[21]	chronic HF	2782	Oral diuretics vs. none	Mortality	1.31	1.11–1.55
Butler[22]	ADHF	382	Dose of IV loop diuretics	worsening renal function (Δ 0.3mg/dl)	1.04 per 20 mg increment of furosemide	1.004–1.076
ESCAPE[23]	Advanced HF inpts	395	Dose of IV loop diuretics	Mortality	1.15 per doubling of dose	1.025–1.28
Eshaghian[24]	Advanced HF outpts	1354	Dose of oral diuretics	Mortality	3.4 per quartile of dose	2.4–4.7
Neuberg[25]	chronic HF	1153	Diuretic oral dose (<> 80 mg furosemide)	Mortality	1.37 for dose above median	not provided, p=0.004
Philbin[26]	ADHF	1150	# of IV diuretic doses	In-hospital mortality	1.11 per # of doses	1.06–1.17
Mielniczuk[27]	chronic HF	183	oral diuretic dose	HF events	1.53 for dose > 80mg	0.58–4.03

Table 2

Randomized Trials of bolus vs. continuous infusion of diuretics in heart failure

Study	N	Design	Intervention	Duration	Endpoint(s)	Findings
Aaser[42]	8	randomized, cross-over, unblinded	Continuous infusion vs. BID IV bolus	24 hrs	Urine output	bolus better
Dormans[44]	20	randomized, cross-over, unblinded	continuous infusion vs. single IV bolus	24 hrs	Urine output	infusion better
Kramer[45]	8	randomized, cross-over, unblinded	continuous infusion vs. single IV bolus	24 hrs	Urine output	no difference
Lahav[46]	9	randomized, cross-over, unblinded	Continuous infusion vs. q8 hr bolus	48 hrs	Urine output	infusion better (trend)
Licata[48]	107	randomized, single blind	Continuous infusion + hypertonic saline vs. Q12 bolus	6–12 days	Urine output at 24 hours LOS Mortality	infusion better on all endpoints
Pivac[43]	20	randomized, single blind, crossover	Q12 4 hour “infusion” vs. Q12 bolus	24 hrs	Urine output	infusion better
Schuller[47]	33	randomized, unblinded	continuous infusion vs. bolus	72 hrs	mortality	No difference