Loop Diuretic Therapy in Heart Failure: The Need for Solid Evidence on a Fluid Issue

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ABSTRACT

Background: Heart failure (HF) is a common condition associated with substantial cost, morbidity, and mortality. Because results of clinical trials in the acute decompensated heart failure (ADHF) setting have been mostly neutral, loop diuretics remain the mainstay of treatment.
Hypothesis: Loop diuretic use may be associated with unfavorable outcomes.
Methods: A MEDLINE literature search was performed to identify articles relating to heart failure and loop diuretics. The current evidence on the risks and benefits of loop diuretics for the treatment of ADHF is reviewed.
Results: Loop diuretics are associated with symptomatic improvements in congestion, urine output, and body weight, but have shown no long-term mortality benefit. Loop diuretics, especially at high doses, are associated with worsened renal function and other poor outcomes.
Conclusions: Loop diuretics still prove useful in HF treatment, but risk-benefit analysis of these agents in the treatment of ADHF requires a well-designed prospective study.

Introduction

Acute decompensated heart failure (ADHF) constitutes the most common cause of hospitalization in the western world. Despite high in-hospital mortality rates, few studies have been conducted in the acute setting. Results of recent major clinical trials in ADHF were not encouraging.[1,2] Hence, loop diuretics have remained the mainstay of ADHF treatment.

Acute Pulmonary Edema

Dyspnea is the most common complaint of heart failure (HF) patients. While it arises from many different mechanisms, dyspnea is a manifestation of acute pulmonary edema (APE). APE is believed to occur primarily from the redistribution of intravascular fluid to the lungs, secondary to acutely elevated left ventricular (LV) filling pressures. This understanding has provided a basis for the management of APE, which entails reduction of LV preload and afterload, ventilatory support, and identification and treatment of underlying factors contributing to elevated LV filling pressures.

Loop diuretics improve clinical symptoms of dyspnea and signs of pulmonary edema by acutely decreasing LV preload, reducing wedge pressure, and increasing venous capacitance.[3] When used in combination with vasodilators, loop diuretics reduce ventricular cavity size and mitral regurgitation, resulting in increased forward cardiac output.[4]

Loop diuretics are routinely used as first-line agents to rapidly alleviate symptoms related to fluid overload. In the United States, loop diuretics were among the top 10% of the 200 most prescribed generic medications in 2008.[5] Despite their use for many decades, the recommendations by national guidelines remain largely supported by expert opinion and general consensus (Table 1).

Pharmacology of Loop Diuretics

Loop diuretics include furosemide, bumetanide, torsemide, and ethacrynic acid. Ethacrynic acid is the only one that lacks the sulfonamide moiety. They inhibit the $Na^+/K^+/2Cl^-$ cotransporter at the thick ascending limb of the loop of Henle, which is responsible for reabsorption of 20% to 30% of filtered sodium[6] (Figure 1). Loop diuretics inhibit sodium and water reabsorption as well as increase urinary excretion of chloride, calcium, and magnesium. They bind to the chloride binding site of the cotransporter on the luminal surface of epithelial cells; thus, they must reach the urine to be effective. Loop diuretics are highly protein bound and are primarily secreted through the organic-acid pathway into the tubular lumen.

Loop diuretics increase delivery of tubular fluid and electrolytes to the distal sites of hydrogen and potassium ion secretion, while plasma volume contraction increases aldosterone production. These effects promote sodium reabsorption at the distal tubules, thus increasing loss of potassium and hydrogen ions.[7] Nonosmotic vasopressin release and activation of the renin–angiotensin-aldosterone axis also enhance potassium and hydrogen excretion.[8]

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Table 1. Summary of Guideline Recommendations on Diuretic Therapy in Heart Failure

Organization	Acute Heart Failure	Strength of Recommendation	Chronic Heart Failure	Strength of Recommendation
American College of Cardiology/American Heart Association (2009)[36]	The hospitalized patient:	Class I; level of evidence B	Stage C and D HF patients:	Class I; level of evidence C
	Patients admitted with HF and with evidence of significant fluid overload should be treated with intravenous loop diuretics. Therapy should begin in the emergency department or outpatient clinic without delay, as early intervention may be associated with better outcomes for patients hospitalized with decompensated HF.		Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention.	
	When diuresis is inadequate to relieve congestion, as evidenced by clinical evaluation, the diuretic regimen should be intensified using either: Higher doses of loop diuretics; addition of a second diuretic (such as metolazone, spironolactone, or intravenous chlorothiazide); or continuous infusion of a loop diuretic.	Class I; level of evidence C		
European Society of Cardiology (2008)[37]	The symptomatic benefits and universal clinical acceptance of acute diuretic treatment has precluded formal evaluation in large-scale randomized clinical trials.	Class I; level of evidence B	Diuretics provide relief from the symptoms and signs of pulmonary and systemic venous congestion in patients with HF.	Class I; level of evidence B
	Patients with hypotension (SBP <90 mmHg), severe hyponatremia, or acidosis are unlikely to respond to diuretic treatment.	Class I; level of evidence B	Diuretics cause activation of the RAAS in patients with mild symptoms of HF and should usually be used in combination with an ACEI/ARB.	Class I; level of evidence B
	High doses of diuretics may lead to hypovolemia and hyponatremia, and increase the likelihood of hypotension on initiation of ACEIs or ARBS.	Class I; level of evidence B	The dose requirement must be tailored to the individual patient's needs and requires careful clinical monitoring.	Class I; level of evidence B

Table 1. (*continued*)

Organization	Acute Heart Failure	Strength of Recommendation	Chronic Heart Failure	Strength of Recommendation
	Alternative treatment options such as IV vasodilators may reduce the need for high-dose diuretic therapy.	Class I; level of evidence B		
Canadian Cardiovascular Society (2006)[38]	Patients with predominant volume overload should be given IV bolus(es) of furosemide. If the response is inadequate, combined IV boluses or infusion diuretics plus vasodilator therapy (IV nitroglycerin infusion started at 5 to 10 μg/min) should be given.	Class I, level of evidence B	A loop diuretic, such as furosemide, is recommended for most patients with HF and congestive symptoms. Once acute congestion is cleared, the lowest minimal dose should be used that is compatible with stable signs and symptoms.	Class I; level of evidence C
			For patients with persistent volume overload despite optimal other medical therapy and increases in loop diuretics, cautious addition of a second diuretic (eg, a thiazide or low-dose metolazone) may be considered as long as it is possible to closely monitor morning daily weight, renal function, and serum potassium.	Class IIb; level of evidence B
Heart Failure Society of America (2006)[39,40]	It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics—usually given intravenously rather than orally.	Strength of evidence B	Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms (orthopnea, edema, and shortness of breath) or signs of elevated filling pressures (jugular venous distension, peripheral edema, pulsatile hepatomegaly, and less commonly rales).	Strength of evidence A
	It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in intravascular volume, which may result in symptomatic hypotension and/or worsening renal function.	Strength of evidence C	Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present, particularly those with right-sided HF and refractory fluid retention despite high doses of other loop diuretics.	Strength of evidence C

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Table 1. (*continued*)

Organization	Acute Heart Failure	Strength of Recommendation	Chronic Heart Failure	Strength of Recommendation
	Careful repeated assessment of signs and symptoms of congestion and changes in body weight is recommended, because clinical experience suggests it is difficult to determine that congestion has been adequately treated in many patients.	Strength of evidence C	Diuretic refractoriness may represent patient noncompliance, a direct effect of diuretic use on the kidney, or progression of underlying cardiac dysfunction.	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; HF, heart failure; IV, intravenous; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

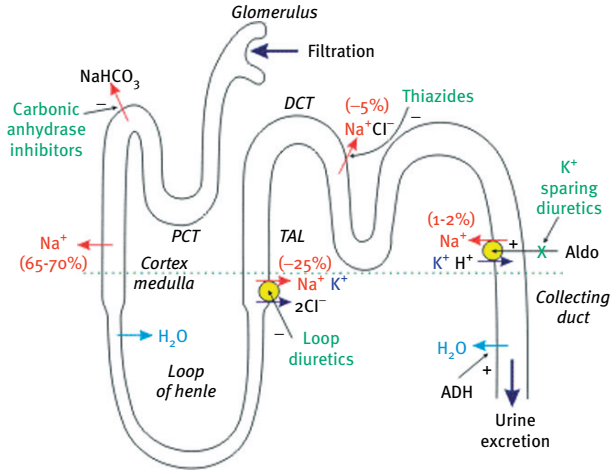

Figure 1. Action sites of diuretics. Abbreviations: ADH, antidiuretic hormone; CL^-; chloride ion; DCT, distal convoluted tubule; H^+, hydrogen ion; H_2O, water; K^+, potassium ion; NA^+, sodium ion; $NaHCO_3$, sodium bicarbonate; PCT, proximal convoluted tubule; TAL, thick ascending limb.

In ADHF, renal responsiveness to loop diuretics may be decreased. Patients with New York Heart Association (NYHA) class II or III HF have one-third to one-fourth the natriuretic response as compared with normal subjects. As HF severity increases, response to diuretics decreases even further. Experts suggest giving moderate doses more frequently to improve this.[6] Higher doses are required to overcome competitive inhibition by endogenous organic anions for the organic anion transporter and to obtain therapeutic urinary concentrations in HF patients with renal impairment.

Common adverse effects of diuretics are abnormalities in fluid and electrolyte homeostasis. When given to severe chronic HF patients, loop diuretics resulted in acute fall in stroke volume index, increase in LV filling pressure and systemic vascular resistance, as well as neurohormonal activation such as elevated plasma renin activity (PRA), plasma norepinephrine levels, and plasma arginine vasopressin levels.[8] In one early study, LV filling pressure and systemic vascular resistance were elevated 20 minutes after IV furosemide administration but returned nearly back to baseline after 1 to 2 hours.[8] These hemodynamic effects were attributed to vasoconstriction mediated by the renin-angiotensin-aldosterone system (RAAS).

When administered with thiazides, loop diuretics may substantially deplete potassium and magnesium. Patients should be closely monitored for higher risk of lethal arrhythmias. Loop diuretics block solute reabsorption at nephron sites that are important for concentrating the urine, and thus impair urinary concentrating ability. Thus, water is excreted in excess of sodium, which can help correct hyponatremia. However, loop diuretics impair the ability to dilute urine, which entails a risk of hyponatremia, particularly in patients who drink large amounts of hypotonic fluids.[9]

Pharmacokinetic and Pharmacodynamic Considerations in Heart Failure

The pharmacokinetic properties of furosemide differ from those of bumetanide and torsemide. Absorption of oral furosemide can be largely unpredictable between patients, ranging from 10% to 100%.[6] Furosemide is renally eliminated and excreted 50% unchanged. In renal disease, plasma half-life is prolonged due to decreased secretion and conjugation. In comparison, absorption of bumetanide and torsemide is much more predictable and complete, at 80% to 100%.[6] They are primarily hepatically metabolized at 50% and 80%, respectively. Plasma half-lives are not prolonged in renal insufficiency. HF patients treated with torsemide may require less hospitalization and have better quality of life than patients on furosemide.[10,11]

Pharmacokinetic properties of loop diuretics are altered in HF patients. Furosemide bioavailability is unlikely to be a problem in edematous disorders, as it remains fairly similar between patients with and without edema. However, patients with ADHF have longer time to peak concentrations and lower concentrations. As the extent of fluid overload increases, so do the alterations in pharmacokinetics. The delayed rate of absorption may be due to delayed gastric emptying and impaired gastrointestinal mobility or to edema of the gastrointestinal wall.[12]

Diuretic Resistance

In some patients, fluid overload persists despite higher diuretic doses. Diuretic resistance has been associated with worsened outcomes in HF patients. Patients requiring more intense therapeutic regimens generally seem sicker. A recent report demonstrated that such patients have increased risk of death, independent of usual prognostic factors.[13] Two types of diuretic resistance have been described. Short-term resistance, the "braking phenomenon," is a decrease in response after administration of the first dose.[6] The mechanism may be due to increased activity of angiotensin II or the sympathetic nervous system (SNS) as the body's physiologic response to curb excessive salt and fluid losses.[14] The second type of resistance occurs with long-term administration of loop diuretics. Solutes that escape from the loop of Henle concentrate in the distal segments of the nephron, resulting in distal tubule hypertrophy.[6] The hypertrophy increases distal tubular sodium reabsorption and decreased overall diuresis. Combination therapy with thiazide diuretics are commonly used to overcome this type of resistance. Thiazides block the sodium reabsorption at the distal tubule, thus maximizing furosemide effect.

Continuous Infusion vs Bolus Injection of Loop Diuretics

Bolus injections may also lead to acute tolerance, along with marked fluctuations in intravascular volume and increased toxicity from high peak serum levels.[15] Continuous infusion of loop diuretics decreases fluctuations in intravascular volume, providing relatively constant urine output. In a meta-analysis of 8 small, heterogeneous studies, continuous infusion resulted in greater urine volume and a better safety profile compared with intermittent bolus injections. Adverse events such as gout symptoms, hypotension, or ototoxicity were not reported with continuous infusion. Increases in serum creatinine were more common with bolus administration.[15]

Clinical Studies in Heart Failure

Many studies have investigated the relationship between diuretics and HF prognosis (Supporting Information Table 1). In an advanced systolic HF cohort, the highest diuretic dose quartile had significantly impaired survival compared with patients in the lowest quartile after 2 years. After adjustments for possible confounders, the highest diuretic quartile remained a significant predictor of mortality at years 1 and 2. The study showed a stepwise, dose-dependent effect of loops on mortality.[16] Another retrospective study evaluating the relationship of loop diuretic and angiotensin-converting enzyme (ACE) inhibitor doses with total and cause-specific mortality found similar results. High diuretic doses were independently associated with mortality, sudden death, and pump failure death.[13]

Two secondary subanalyses of the Digitalis Investigation Group (DIG) trial showed that chronic HF patients receiving diuretics had higher rates of mortality and hospitalization compared with patients without diuretics.[17,18] Patients were matched by their propensities to receive diuretics. Chronic diuretic therapy was associated with significant risk of all-cause mortality and HF hospitalizations.[17] When patients age $\geq$65 years were selectively analyzed, diuretic use was associated with increased risk of all-cause and cardiovascular mortality.[18]

Similar results have been found with in-hospital usage of loop diuretics and patient outcomes. Analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial database suggests a strong dose-response association between maximal in-hospital diuretic dose and mortality in hospitalized HF patients, especially when total daily doses of furosemide exceeded 300 mg. Even when inotrope usage was added to the model, diuretic dose continued to be a strong predictor of death.[19] In another study, a higher number of IV diuretic doses during hospitalization was associated with higher mortality and rehospitalization rates within 6 months after discharge. Using a regression model, number of IV diuretic doses and creatinine clearance were significant predictors for death.[20]

Increased risk for in-hospital mortality and renal failure have been seen with higher doses of IV loop diuretics compared with lower doses.[21] The duration of diuretic therapy may be a prognostic factor and predictor of morbidity by impacting hospital length of stay.[22] Hospital length of stay can be due to extent of congestion, but several actions exerted by parenteral diuretics may independently contribute to in-hospital complications.[22]

Loop diuretics have been associated with worsening renal function (WRF). However, elevated central venous pressure leading to venous congestion may be a stronger factor driving WRF in ADHF patients than intravascular volume depletion from diuretic overuse. In one study, ADHF patients were treated with IV or oral loop diuretics in combination with IV vasodilators (with or without inotropic agents). Patients who developed WRF had significantly greater central venous pressure on admission and after medical therapy. There were no differences in medication use, especially mean furosemide doses, between patients with and without WRF. Venous congestion, not diuretic

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use, was the strongest determinant for the development of WRF.[23]

Discussion

HF treatment has changed tremendously over the last 2 decades, most notably with medications that inhibit RAAS and SNS.[24] Loop diuretics have been utilized prior to our full understanding of the roles of RAAS and SNS in HF pathophysiology. While loop diuretics continue to be widely used for acute and chronic HF treatment, they can potentially exacerbate RAAS and SNS.

Pathologic neurohormonal changes, WRF, and increased mortality associated with diuretic use are partly due to SNS and RAAS stimulation in response to volume depletion[8] (Figure 2).[25] Plasma norepinephrine, atrial natriuretic factor, plasma arginine vasopressin, and PRA are significantly increased in patients with left ventricular dysfunction (LVD). However, PRA was normal in asymptomatic LVD patients not receiving diuretics, but was significantly increased ($P < 0.05$) in patients on diuretics.[26] This suggests that RAAS activation in moderate HF may occur in response to diuretic treatment rather than the disease process.[27] Diuretic withdrawal in stabilized systolic HF is associated with improvements in renal function parameters and some neurohormonal parameters like PRA.[28]

With the ever-changing understanding of HF pathophysiology, traditional therapies in ADHF need to be re-evaluated. Studies suggest that furosemide is overused. For example, IV furosemide is frequently administered to patients with respiratory distress in the ambulance setting.

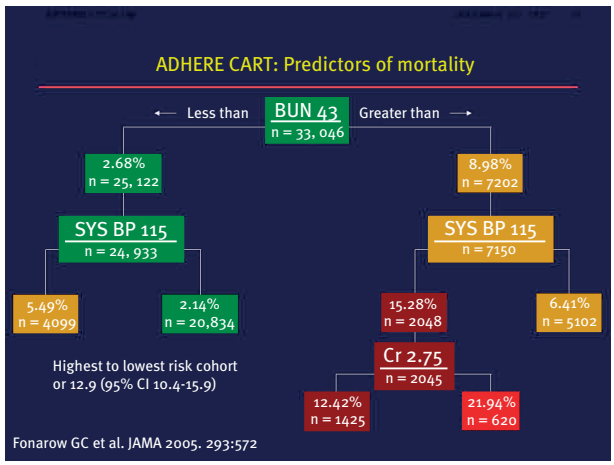

Figure 2. Relationship of renal hypoperfusion, systolic blood pressure, and in-hospital mortality in acute decompensated heart failure.[25] Abbreviations: ADHERE CART, Acute Decompensated Heart Failure National Registry classification and regression tree; BUN, blood urea nitrogen; CI, confidence interval; Cr, serum creatinine; n, number of patients; OR, odds ratio; SYS BP, systolic blood pressure. Reprinted with permission.

However, one study found that 40% of patients were eventually diagnosed with conditions in which furosemide was not medically indicated. Furosemide was considered inappropriate in 42% of the patients and potentially harmful in 17%.[29] Similar findings of unclear indications of diuretic use are also common in the chronic-care facility, and withdrawal of these agents is often successful.[30] Misdiagnosis leading to inappropriate diuresis can result in increases in morbidity.[31]

The safety of loop diuretics as determined by large, randomized, controlled studies is still unknown. This is partly explained by difficulties in designing trials and recruiting patients in acute decompensation,[32] the heterogeneity of the ADHF population, and the lack of consensus on meaningful clinical endpoints, such as improvement of dyspnea or mortality.[33] An attempt to randomize ADHF patients to diuretics or placebo is also viewed as unethical, as many consider it a medical emergency sufficiently frightening to the patient and accompanying persons. Most physicians are resistant to the idea of not intervening and reluctant to obtain informed consent for a clinical trial in emergent or urgent settings. The thought of a patient dying with untreated HF regardless of the evidence for benefit or harm of a particular treatment is usually regarded as unacceptable; the pressure to act becomes irresistible. These barriers hinder the possibility of such studies.

Many small studies have demonstrated that loop diuretics are beneficial, but these were conducted prior to the era of neurohormonal blockade (see Supplemental Table 2 online). Not only did these trials use different types and dosages of loop diuretics, they were inadequately powered to draw conclusions regarding patient outcomes. Many studies were confounded by co-interventions like inotropes and thiazides. There is considerable interest in looking at the relationship between loop diuretic dose and outcomes in HF patients on current medical therapy. A prospective, randomized clinical study sponsored by the National Heart, Lung, and Blood Institute, Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure (The DOSE-AHF), is underway to compare the safety and efficacy of loop diuretics at high vs low doses and in 2 to 3 separate doses vs 1 continuous infusion.[34]

With increasing concerns in recent years, we have to be cognizant about liberal use of loop diuretics.[21] Loop diuretics should be used modestly, with constant dosage adjustment and with regular clinical assessment. Although literature supports several strategies for volume management, removal of excess extracellular fluid with diuretics is still the mainstay of ADHF therapy. Salt restriction should be emphasized, knowing that an increase of daily dietary sodium intake of as little as 10 to 100 mEq results in a 2-kg weight gain and changes in RAAS and SNS activity.[35]

Conclusion

Diuretics have been widely used in HF despite evidence of harm. They have not been tested in randomized, long-term outcome trials, mainly because of the ethical challenges mentioned above. Even with today's focus on evidence-based medicine, secondary sources of information serve as guides for making decisions. This is clearly evidenced by the paucity of level-A recommendations on diuretic use in the most updated guidelines for ADHF treatment (Table). Aside from augmenting urine output, few studies have demonstrated any material benefit of diuretics in HF. In the era of neurohormonal blockade, loop diuretic therapy needs to be clearly defined.

References

1. Cuffe MS, Califf RM, Adams KF Jr, et al; for OPTIME-CHF Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–1547.
2. Mebazaa A, Nieminen MS, Packer M, et al; for SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA*. 2007;297:1883–1891.
3. Silke B. Central hemodynamic effects of diuretic therapy in chronic heart failure. *Cardiovasc Drugs Ther*. 1993;7(Suppl. 1):45–53.
4. Stevenson LW, Brunken RC, Belil D, et al. Afterload reduction with vasodilators and diuretics decreases mitral regurgitation during upright exercise in advanced heart failure. *J Am Coll Cardiol*. 1990;15:174–180.
5. *Drug Topics* magazine. Table of top 200 generic drugs by total prescriptions, 2008. http://drugtopics.modernmedicine.com/top200gen. Accessed September 24, 2009.
6. Brater DC. Diuretic therapy. *N Engl J Med*. 1998;339:387–395.
7. Rocco TP, Fang JC. Pharmacotherapy of congestive heart failure. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. New York, NY: McGraw-Hill; 2006; 874.
8. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med*. 1985;103:1–6.
9. Nicholls MG. Interaction of diuretics and electrolytes in congestive heart failure. *Am J Cardiol*. 1990;65:E E 17–23.
10. Müller K, Gamba G, Jaquet F, Hess B. Torasemide vs. furosemide in primary care patients with chronic heart failure NYHA II to IV—efficacy and quality of life. *Eur J Heart Fail*. 2003;5:793–801.
11. Murray MD, Deer MM, Ferguson JA, et al. Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. *Am J Med*. 2001;111:513–520.
12. Brater DC. Pharmacokinetics of loop diuretics in congestive heart failure. *Br Heart J*. 1994;72:S40–S43.
13. Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J*. 2002;144:31–38.
14. Kramer BK, Schweda F, Riegger GA. Diuretic treatment and diuretic resistance in heart failure. *Am J Med*. 1999;106:90–96.
15. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev*. 2005;3:CD003178.
16. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol*. 2006;97:1759–1764.
17. Ahmed A, Husain A, Love TE, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J*. 2006;27:1431–1439.
18. Ahmed A, Young JB, Love TE, Levesque R, Pitt B. A propensity-matched study of the effects of chronic diuretic therapy on mortality and hospitalization in older adults with heart failure. *Int J Cardiol*. 2008;125:246–253.
19. Hasselblad V, Gattis Stough W, Shah MR, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail*. 2007;9:1064–1069.
20. Philbin EF, Cotto M, Rocco TA Jr, Jenkins PL. Association between diuretic use, clinical response, and death in acute heart failure. *Am J Cardiol*. 1997;80:519–522.
21. Peacock WF, Costanzo MR, De Marco T, et al; for ADHERE Scientific Advisory Committee and Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *Cardiology*. 2009;113:12–19.
22. Wright SP, Verouhis D, Gamble G, Swedberg K, Sharpe N, Doughty RN. Factors influencing the length of hospital stay of patients with heart failure. *Eur J Heart Fail*. 2003;5:201–209.
23. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589–596.
24. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429–1435.
25. Fonarow GC, Adams KF Jr, Abraham WT, et al; for ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293:572–580.
26. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990;82:1724–1729.
27. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J*. 1987;57:17–22.
28. Galve E, Mallol A, Catalan R, et al. Clinical and neurohumoral consequences of diuretic withdrawal in patients with chronic, stabilized heart failure and systolic dysfunction. *Eur J Heart Fail*. 2005;7:892–898.
29. Jaronik J, Mikkelson P, Fales W, Overton DT. Evaluation of prehospital use of furosemide in patients with respiratory distress. *Prehosp Emerg Care*. 2006;10:194–197.
30. Van Kraaij DJ, Jansen RW, Gribnau FW, Hoefnagels WH. Use of diuretics and opportunities for withdrawal in a Dutch nursing home population. *Neth J Med*. 1998;53:20–26.
31. Mosesso VN Jr, Dunford J, Blackwell T, Griswell JK. Prehospital therapy for acute congestive heart failure: state of the art. *Prehosp Emerg Care*. 2003;7:13–23.
32. Poole-Wilson PA. Treatment of acute heart failure: out with the old, in with the new. *JAMA*. 2002;287:1578–1580.
33. Komajda M, Follath F, Swedberg K, et al. The EuroHeart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J*. 2003;24:464–474.
34. National Institutes of Health, Clinical Trials Web site. Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure (The DOSE-AHF Study). http://www.clinicaltrials.gov/ct2/show/NCT00577135?term=DOSE-AHF&rank=1. Accessed September 24, 2009.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20771

35. Cody RJ, Covit AB, Schaer GL, Laragh JH, Sealey JE, Feldschuh J. Sodium and water balance in chronic congestive heart failure. *J Clin Invest*. 1986;77:1441–1452.
36. Hunt SA, Abrahams WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009;53:e1–e90.
37. European Society of Cardiology, Heart Failure Association of the ESC (HFA), European Society of Intensive Care Medicine (ESICM), et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008;10:933–989.
38. Arnold JM, Liu P, Demers C, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. *Can J Cardiol*. 2006;22:23–45.
39. Heart Failure Society of America. Evaluation and management of patients with acute decompensated heart failure. *J Card Fail*. 2006;12:e86–e103.
40. Heart Failure Society of America. Heart failure in patients with left ventricular systolic dysfunction. *J Card Fail*. 2006;12:e38–e57.

References for Supporting Information Tables 1 and 2

41. Domanski M, Norman J, Pitt B, et al. Diuretic use, progressive heart failure, and death in patients in the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol*. 2003;42:705–708.
42. Paterna S, Parrinello G, Cannizzaro S, et al. Medium term effects of different dosage of diuretic, sodium, and fluid administration on neurohormonal and clinical outcome in patients with recently compensated heart failure. *Am J Cardiol*. 2009;103:93–102.
43. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67.
44. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J*. 2004; 147:331–338.
45. Walma EF, Hoes AW, van Dooren C, et al. Withdrawal of long-term diuretic medication in elderly patients: a double blind randomised trial. *BMJ*. 1997;315: 464–468.
46. De Jonge JW, Knottnerus JA, van Zutphen WM, et al. Short term effect of withdrawal of diuretic drugs prescribed for ankle oedema. *BMJ*. 1994;308:511–513.
47. Burr ML, King S, Davies HE, et al. The effects of discontinuing long-term diuretic therapy in the elderly. *Age Ageing*. 1977;6: 38–45.
48. Myers MG, Weingert ME, Fisher RH, et al. Unnecessary diuretic therapy in the elderly. *Age Ageing*. 1982;11:213–221.
49. Barr CS, Lang CC, Hanson J, et al. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1995;76: 1259–1265.
50. Sherman LG, Liang CS, Baumgardner S, et al. Piretanide, a potent diuretic with potassium-sparing properties, for the treatment of congestive heart failure. *Clin Pharmacol Ther*. 1986;40:587–594.
51. Cheitlin MD, Byrd R, Benowitz N, et al. Amiloride improves hemodynamics in patients with chronic congestive heart failure treated with chronic digoxin and diuretics. *Cardiovasc Drugs Ther*. 1991;5:719–725.
52. Richardson A, Bayliss J, Scriven AJ, et al. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. *Lancet*. 1987;2:709–711.
53. Nordrehaug JE, Omsjø IH, Vollset SE. A 3-month double-blind cross-over study of the effect of benazepril and hydrochlorothiazide on functional class in symptomatic mild heart failure. *J Intern Med*. 1992;231:589–594.
54. Cowley AJ, Stainer K, Wynne RD, et al. Symptomatic assessment of patients with heart failure: double-blind comparison of increasing doses of diuretics and captopril in moderate heart failure. *Lancet*. 1986;2:770–772.
55. Boccanelli A, Zachara E, Liberatore SM, et al. Addition of captopril versus increasing diuretics in moderate but deteriorating heart failure: a double-blind comparative trial. *Postgrad Med J*. 1986;62(Suppl. 1):184–187.
56. Sievert H, Offermann T, Hopf R, et al. Basic therapy of chronic heart failure with digitalis or diuretics [in German]? *Dtsch Med Wochenschr*. 1989;114:363–367.