Review article

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Diuretic therapy in heart failure: current controversies and new approaches for fluid removal

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Hospitalization for heart failure is a major health problem with high in-hospital and postdischarge mortality and morbidity. Non-potassium-sparing diuretics (NPSDs) still remain the cornerstone of therapy for fluid management in heart failure despite the lack of large randomized trials evaluating their safety and optimal dosing regimens in both the acute and chronic setting. Recent retrospective data suggest increased mortality and re-hospitalization rates in a wide spectrum of heart failure patients receiving NPSDs, particularly at high doses. Electrolyte abnormalities, hypotension, activation of neurohormones, and worsening renal function may all be responsible for the observed poor outcomes. Although NPSD will continue to be important agents to promptly resolve signs and symptoms of heart failure, alternative therapies such as vasopressine antagonists and adenosine blocking agents or techniques like veno-venous ultrafiltration have been developed in an effort to reduce NPSD exposure and minimize their side effects. Until other new agents become available, it is probably prudent to combine NPSD with aldosterone blocking agents that are known to improve outcomes.
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Introduction

Heart failure with volume overload account for 90% of the 1 million heart failure hospitalizations that occur annually in the United States [1,2]. The European scenario is equally alarming [3,4]. Despite improvements in primary prevention measures and disease management, this syndrome still represents a unique challenge for clinicians for both the high mortality and rehospitalization rates and the associated health costs [1–6].

Given the fact that the main reason for heart failure hospitalization appears to be dyspnea, as a result of pulmonary congestion, non-potassium-sparing diuretics (NPSDs) remain the cornerstone of heart failure therapy for they promptly and effectively resolve signs and symptoms of an acute decompensation and maintain an optimal fluid balance in the chronic setting [7,8]. Multiple data from international registries and large clinical trials demonstrate that more than 80% of patients were receiving NPSDs and, in the majority of cases, loop diuretics [1–6].

The acceptance of NPSDs into the heart failure treatment paradigm is largely based on clinical small, non-randomized studies conducted over the past 40 years without the benefit of large, multicenter randomized trials. As a result, the best strategy for their use (dose and modality of administration) is unclear. Consequently, although both the American and European guidelines recommend their use for the management of fluid overload or in asymptomatic patients with prior symptoms, these recommendations are mainly based on level C evidence [9,10].

There is growing literature showing an association between NPSD use and increased mortality and re-hospitalization in patients with both chronic and acute heart failure, particularly when high doses are administered. Retrospective analyses of large trials and multiple small studies lead to the hypothesis that NPSD may contribute to the high in-hospital and postdischarge event rates observed in this population.

Non-potassium-sparing diuretics and outcomes in heart failure

Small studies have associated loop diuretic therapy for heart failure with short-term adverse clinical outcomes,

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particularly at high doses, raising concerns about its toxicity [11,12].

Retrospective analyses of modern, large, randomized, multicenter trials and registries appear to support these results.

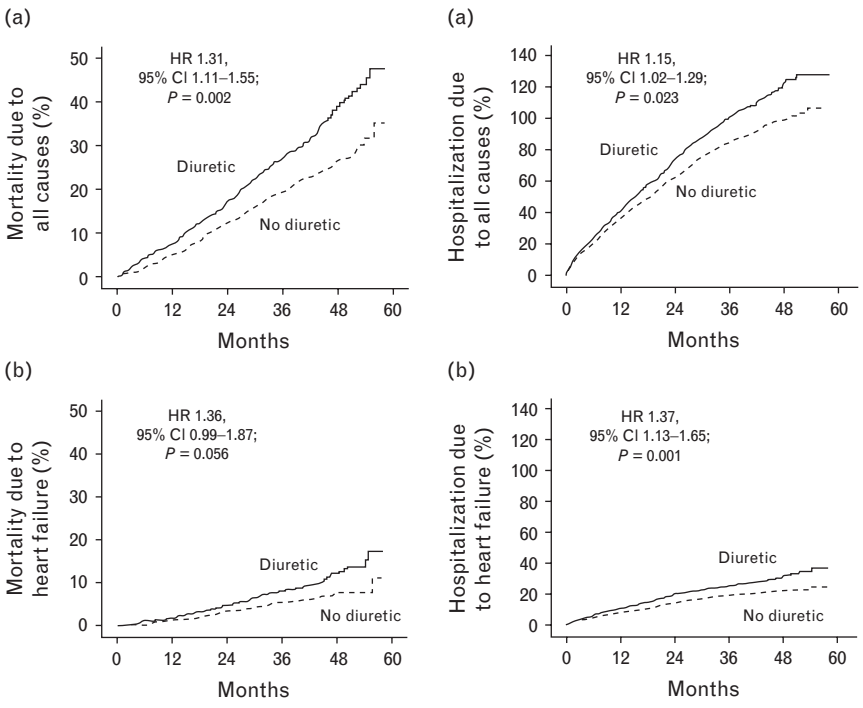
In fact, a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trial conducted on 6797 patients with documented left ventricular (LV) systolic dysfunction and an ejection fraction less than 36%, showed that patients receiving a NPSD at baseline were more likely to have an arrhythmic death compared with those who were not (3.1 vs. 1.7 arrhythmic deaths per 100 person-years). Similarly, all-cause and cardiovascular mortality rates were higher in patients receiving a diuretic at baseline (12.8 vs. 5.3 and 11.4 vs. 4.6 deaths per 100 person-years, respectively). Even after adjusting for potential confounders (disease severity, comorbid diseases and concomitant medication use), NPSD use remained significantly associated with arrhythmic death. Conversely, the use of potassium-sparing diuretic, alone or in combination with NPSDs was not independently associated with an increased risk of arrhythmic death [13].

Similarly, post-hoc analyses of the Digitalis Investigation Group (DIG trial) conducted on 6797 ambulatory patients with mild-to-moderate chronic heart failure demonstrated an association with NPSDs and increased risk of death, cardiovascular death, progressive heart failure death, sudden cardiac death and heart failure hospitalizations at 40 months of follow-up [14,15] (Fig. 1).

A large single-center study on 1354 advanced heart failure patients with a mean ejection fraction of 25% of any etiology and in New York Heart Association (NYHA) functional class III–IV, found a linear decrease in survival with increasing NPSD dose (83%, 81%, 68% and 53% for NPSD quartiles 0–40, 41–80, 81–160 and more than 160 mg, respectively). After extensive adjustment for important covariates, NPSD use remained an independent predictor of all-cause mortality [16] (Fig. 2). However, it should be emphasized that in this trial the highest NPSD dose quartile includes patients with lower ejection fraction, serum-sodium levels, hemoglobin levels and higher blood urea nitrogen and creatinine levels, all well-recognized negative prognostic factors in heart failure that may be potential confounding factors.

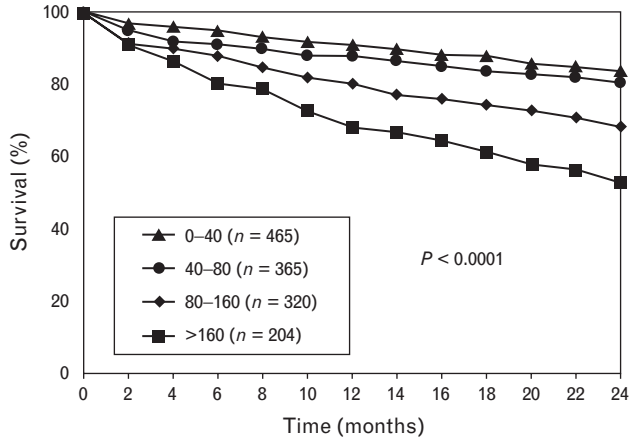
Again, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) investigators found a strong dose–response positive relationship between increasing NPSD dose (mainly furosemide) and 6-month mortality in 395 patients hospitalized for severe decompensated heart failure due to LV systolic dysfunction, particularly at a

Fig. 1



(Left) Kaplan–Meier plots for cumulative risk of mortality due to (a) all causes and (b) worsening heart failure; (right) Kaplan–Meier plots for cumulative risk of hospitalizations due to (a) all causes and (b) worsening heart failure in the DIG Trial [14]. CI, Confidence interval; HR, heart rate. Reprinted with permission.

Fig. 2



Kaplan–Meier survival estimates for loop-diuretic dose quartiles in patients with advanced systolic heart failure over 2-year follow-up in the study by Eshaghian *et al.* [16]. Reprinted with permission.

Table 1 Clinical outcomes by diuretic dose in the analysis of the ADHERE registry [18]

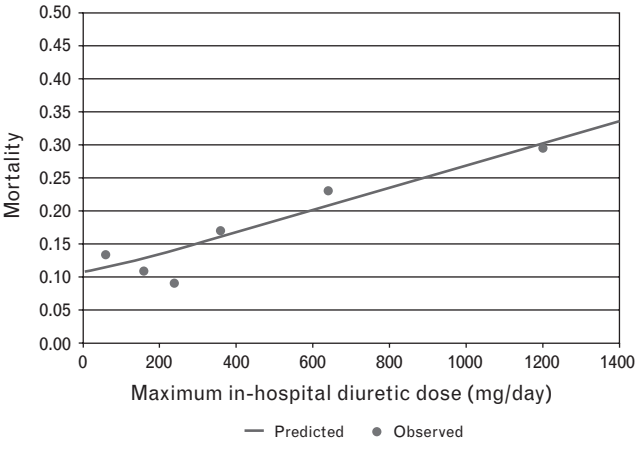
	Dose <160 mg ($n = 62\,866$)	Dose ≥160 mg ($n = 19\,674$)
Renal-related outcomes		
SCr change >0.5[a]	1876/37 137 (5.1)	982/12 005 (8.2)‡
Decrease in GFR >10 ml/min[a,b]	4805/21 807 (22.0)	2081/7886 (26.4)‡
Initiation of dialysis[a]	263/61 406 (0.4)	245/19 325 (1.3)‡
Hospital LOS (days), median [Q1, Q3]	4.0 [2.7, 6.1]	4.3 [2.9, 6.8]‡
Hospital LOS >4 days	31 041 (49.4)	10 801 (54.9)‡
ICU admissions	5106 (8.1)	1934 (98)‡
ICU/CCU LOS (days), median [Q1, Q3]	2.0 [1.0, 3.41]	2.1 [1.1, 3.8]*
ICU/CCU LOS >3 days	1475 (28.9)	621 (32.1)*
In-hospital mortality	1321 (2.1)	471 (2.4)**

CCU, coronary care unit; GFR, glomerular filtration rate; ICU, intensive care unit; LOS, length of stay; reprinted with permission; SCr, serum creatinine. ‡ Indicates the group is significantly different from the low–moderate IV diuretic group ($P < 0.0001$). * Indicates the group is significantly different from the low–moderate IV diuretic group ($P < 0.01$). ** Indicates the group is significantly different from the low–moderate IV diuretic group ($P < 0.05$). Figures in parentheses are percentages. [a] Excludes patient cases with LOS less than 24 h or creatinine more than 6 mg/dl. [b] Excludes patient cases with GFR more than 200 ml/min.

dose of about 300 mg/day of furosemide. Diuretic dose remained a significant predictor of mortality after adjusting for baseline variables that significantly predicted mortality [17] (Fig. 3).

Finally, the impact of intravenous loop diuretics on outcomes of patients hospitalized for acute heart failure has been recently explored by the Acute Decompensated Heart Failure national Registry (ADHERE) investigators who analyzed 62 866 patients receiving less than 160 mg and 19 674 patients at least 160 mg of furosemide. After risk and propensity adjustment, hospitalized heart failure patients receiving low-to-moderate doses of loop diuretics had lower hospital mortality, fewer instances of worsening renal function, lower intensive care unit (ICU) utilization and shorter length of hospital stay than patients treated with high-dose intravenous loop diuretics [18] (Table 1).

Fig. 3



Correlation between maximum in-hospital diuretic dose and mortality in the ESCAPE trial [17]. Reprinted with permission.

Torasemide attracted the attention of the scientific community for its better bioavailability and antialdosterone activity. In fact, in an open-label single center trial, 234 chronic systolic heart failure patients of any etiology were randomized to torasemide (20–80 mg) or furosemide (80–160 mg). After 1 year of follow-up patients in the torasemide group experienced fewer rehospitalization for heart failure or for all cardiovascular causes (32 vs. 17% and 59 vs. 44% respectively) [19].

The Torasemide in Congestive Heart Failure (TORIC) trial was an open-label, nonrandomized, postmarketing surveillance study conducted in 231 centers comprising 1377 NYHA Class II–III chronic stable heart failure patients. Each investigator enrolled a predetermined number of patients who were recruited in matched pairs with the same age, sex and NYHA class. In each pair, one patient received torasemide 10 mg and the other was allowed any other diuretic or diuretic combination therapy, including furosemide 40 mg daily, on top of standard medical therapy [angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), β-blockers and aldosterone-blocking agents]. After a 1-year follow-up patients in the torasemide group had a lower mortality rate (2.2 vs. 4.5%), a greater NYHA class improvement (45.8 vs. 37.2%) and fewer cases of hyponatremia (12.9 vs. 17.9%) [20]. Unfortunately, the wide inclusion criteria and the few exclusion criteria adopted in this study represent an important bias that needs to be taken into consideration.

The experience with thiazide diuretics is often reported in the setting of advanced/stage IV heart failure patients who continue to be fluid overloaded despite optimal medical therapy. As a consequence, very limited data are available to assess their safety and efficacy. However, it appears that although hypotension and electrolyte disturbances are more often observed, metolazone usually administered in low doses (5 mg) in combination with loop diuretics can improve diuresis, even in patients with significant reduction in glomerular filtration rates (GFR) [21].

Although the retrospective nature of these data should be emphasized, taken together they suggest poor outcomes in a wide range of patients with acute and chronic heart failure treated with NPSDs, particularly when high doses are administered. To date, given the lack of large prospective randomized trials with torasemide and metolazone, no definitive conclusions can be made about the safety and efficacy of these drugs in the heart failure population.

An attempt to standardize the use of NPSDs in heart failure to provide practical recommendations for physicians has recently been proposed by the Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND-HF) Investigators [22] (Table 2). However, there is still an unmet need for clear dosing guidelines and follow-up criteria, particularly in the vulnerable postdischarge period in which the chronic oral diuretic dose is tailored according to physician's experience and patient's symptoms rather than on standardized protocols.

The potential mechanisms of myocardial and renal damage induced by non-potassium-sparing diuretics

Hypokalemia

NPSDs, particularly thiazides and furosemide, cause dose-dependent potassium depletion. Although severe hypokalemia (<3.0 mEq/l), is described in fewer than 10–15% of patients receiving high doses of a NPSD, nevertheless it may predispose to life-threatening ventricular arrhythmias [23,24].

Two factors appear to be responsible for the urinary potassium wasting: increased delivery of sodium and water to the aldosterone-sensitive potassium secretory site in the collecting tubules and increased secretion of aldosterone due to diuretic-induced volume depletion or as a result of the activation of neurohormones due to heart failure, particularly when intermittent bolus regimens are infused [25].

In the SOLVD analysis, NPSD produced a significant decrease in serum potassium and magnesium which are both likely to contribute to the almost doubled increased risk for arrhythmic death in the NPSD group, particularly in patients with LV systolic dysfunction secondary to ischemic disease. In addition, it should be recognized that the use of potassium-sparing diuretics, alone or in combination with NPSDs was not independently associated with increased risk of arrhythmic death in this trial [13].

In the earlier-mentioned study by Eshaghian *et al.* [16], the quartile with the highest NPSD dose (>160 mg) was associated with significantly increased 2-year all-cause mortality, death and urgent transplantation, progressive heart failure death and, interestingly, sudden death.

Thus, it appears that NPSD-induced hypokalemia may play a role in the increased mortality risk in patients with heart failure by increasing sudden death risk, particularly in patients with severe systolic dysfunction secondary to ischemic disease. For this reason, serum potassium concentration should be closely monitored during high-dose infusion and potassium supplementation administered if necessary.

Hypotension

Hypotension is common during NPSD therapy, as a result of rapid intravascular volume depletion and as a direct venodilatory effect leading to a decrease in preload [26,27].

This effect is likely to be enhanced in patients with heart failure, as they are preload dependent to maintain cardiac output. In addition, by impairing the constrictive effect of angiotensin II on the glomerular efferent arteriole the

Table 2 Diuretic dosing for acute HF according to the ASCEND-HF model [22]. Reprinted with permission

Creatinine clearance*	Patient	Initial IV dose†	Maintenance dose
>60 ml/(min 1.73 m^2)	New-onset HF or no maintenance diuretic therapy	Furosemide 20–40 mg 2–3 times daily	Lowest diuretic dose that allows for clinical stability is the ideal dose
	Established HF or chronic oral diuretic therapy	Furosemide bolus equivalent to oral dose	
<60 ml/(min 1.73 m^2)	New-onset HF or no maintenance diuretic therapy	Furosemide 20–80 mg 2–3 times daily	
	Established HF or chronic oral diuretic therapy	Furosemide bolus equivalent to oral dose	

* Creatinine clearance is calculated from the Cockroft–Gault or Modified Diet in Renal Disease formula. † Intravenous continuous furosemide at doses of 5 to 20 mg/h is also an option. HF, heart failure; IV, intravenous.

combination of NPSD and ACE inhibitors may decrease renal perfusion and consequently GFR.

Furthermore, hypotension may result in a decrease in coronary perfusion, particularly in patients with underlying coronary artery disease, representing approximately half of all heart failure patients. This may lead to myocardial injury and progression of LV dysfunction [28].

Fibrosis

NPSDs, particularly furosemide, can increase myocardial fibrosis [29,30]. Although the exact mechanism is unclear, it may represent an adjunctive mechanism leading to worsening heart failure and is likely a substrate for ventricular arrhythmias.

Conversely, potassium-sparing diuretics, such as spironolactone, eplerenone and canrenon, share antifibrotic and antiremodeling effects that account for the consistent reduction in cardiovascular morbidity and mortality in patients with advanced heart failure or heart failure following an acute myocardial infarction, by reducing sudden deaths [31–34]. Thus, these agents may help to reduce NPSD side effects (hypokalemia) at low doses and are likely to have a significant diuretic effect at high doses in an effort to minimize NPSD exposure [31–34].

Activation of neurohormones

Activation of the renin–angiotensin–aldosterone system and sympathetic nervous system by loop diuretics has been shown in small studies [35,36] to be associated with the progression of LV dysfunction.

These observations have been confirmed by a substudy of the SOLVD trial, showing that plasma concentrations of norepinephrine, atrial-natriuretic factor, arginine vasopressin, and renin activity were significantly higher in patients with LV dysfunction than in normal control individuals. Plasma renin activity was normal in patients with LV dysfunction without heart failure who were not receiving diuretics, and was significantly increased in those on diuretic therapy.

Furthermore, intermittent intravenous boluses have been associated with increased neurohormonal activation [37]. This may explain the paradoxical short-term abrupt increase in blood pressure and systemic vascular resistance, and the parallel decrease in cardiac index that sometimes is observed immediately after furosemide bolus injection [38]. Conversely, the use of a continuous infusion of a loop diuretic has been advocated both to reduce diuretic toxicity, by employing lower doses, and to increase efficacy after cardiac surgery and in the elderly with severe heart failure [39–42]. Although conflicting data have been published regarding the optimal diuretic infusion regimens [43,44], a Cochrane database review comprising eight trials involving 254 patients found that an increased diuretic effect and a better safety profile was observed with a continuous infusion of loop diuretics when compared with a bolus-dosing regimen [45]. Longer-acting loop diuretics (e.g. torasemide) produce less neurohormonal activation and may be used in these patients [46].

Cardiorenal syndrome

This can be defined as moderate or greater renal dysfunction that exists or develops in a patient with heart failure (in the presence of reduced or preserved systolic function) during treatment. Moderate renal dysfunction is defined, in turn, as a GFR of less than 59 ml/min/m^2 or an increase in serum creatinine of 0.3 mg/dl. This phenomenon occurs in approximately 20% of patients admitted for heart failure [47].

NPSD-induced renal insufficiency is mainly caused by decreased renal perfusion due to hypotension (decreased preload) and/or activation of the neurohormonal cascade leading to a 'vasomotor nephropathy' that is reversible, at least in the early phase [48]. This might be exacerbated by the concomitant administration of ACE inhibitors or ARB as part of the standard therapy for patients with heart failure. This mechanism may lead to diuretic resistance, particularly in patients with advanced LV dysfunction in whom neurohormones are already elevated. This often forces physicians to increase the diuretic dose or to use a combination of thiazides and loop diuretics, creating a vicious cycle leading to progressive renal impairment.

In fact, the presence of concomitant renal dysfunction is one of the strongest factors associated with higher mortality in patients with heart failure; in particular, it predicts death from progressive heart failure, suggesting that it is a manifestation of and/or a factor exacerbating ventricular dysfunction [49–53].

In an effort to improve diuretic effectiveness, it has been reported in relatively small randomized studies that the addition of a hypertonic saline solution in addition to NPSD (furosemide or torasemide) with an adequate potassium supplementation produced a greater daily diuresis and natriuresis in patients with refractory heart failure and possibly improved long-term mortality rates [54–55]. However, this combination therapy still needs to be validated in large trials.

The earlier-mentioned side effects should discourage the use of high-dose NPSDs in patients with heart failure in whom signs and symptoms are adequately controlled. If NPSDs are necessary, they should be used at the minimum efficacious dose (Table 2). In patients with acute decompensation, continuous infusion appears to be safer and more effective compared with intermittent boluses. Aldosterone-blocking agents and vasodilators should be taken into consideration as adjunctive treatment to resolve congestion and reduce NPSD dose.

New approaches to fluid removal in heart failure

Vasopressin antagonists

Vasopressin is a nonapeptide hormone that regulates vascular tone through V1 receptors located in the peripheral vasculature, and plasma osmolality via V2 receptors in the kidney, promoting water retention. Thus, reducing the effects of vasopressin appears to be an attractive therapeutic strategy to promote 'aquaresis' and correct hyponatremia [56].

The EVEREST trials were randomized, double-blind, placebo-controlled programs that evaluated the short-term and long-term effects of 30 mg of the V2 antagonist tolvaptan when added to standard therapy in 4133 patients hospitalized with worsening heart failure and reduced ejection fraction. Tolvaptan produced a significant decrease in body weight that was associated with improvement in signs and symptoms of heart failure throughout hospitalization, without adversely affecting heart rate, blood pressure, or renal function. However, no differences were noted in terms of mortality and hospitalization between tolvaptan and placebo groups. As expected, hyponatremic patients improved or normalized their serum sodium in response to tolvaptan throughout the study. However, this improvement did not translate into improved clinical outcomes [57,58].

The efficacy and safety of the V1A/V2-receptor antagonist conivaptan in acute decompensated heart failure has been tested in a randomized, double-blind, placebo controlled, pilot study conducted on 170 hospitalized patients. Conivaptan (20-mg loading dose followed by 24-h continuous infusions of 40, 80 or 120 mg/day) significantly increased urine output more than placebo at 24 h; it was well tolerated and not associated with electrolyte or cardiac rhythm disturbances. However, these findings need to be confirmed in a large cohort of heart failure patients [59].

Adenosine antagonists

Adenosine 1 (A1) receptors located in the afferent arteriole and proximal tubule promote afferent arteriolar vasoconstriction and tubule-glomerular feedback, modulating GFR. A1-receptor antagonism induces diuresis and natriuresis without exerting adverse effects on cardiac and renal functions [60].

The PROTECT pilot study is a randomized, placebo-controlled, dose-finding study of the adenosine A1-receptor antagonist rolofylline conducted on 301 patients hospitalized for acute heart failure and renal impairment. Rolofylline 10, 20 or 30 mg was administered as a 4-h infusion for 3 days in addition to intravenous loop diuretics. Compared with placebo, rolofylline produced trends toward greater proportions of patients with marked or moderately improved dyspnea and fewer patients with worsening heart failure or renal function. Treatment with 30 mg was associated with a trend toward reduced 60-day mortality or readmission for cardiovascular or renal cause [61]. A large trial is now underway to confirm the beneficial results of this pilot study.

Ultrafiltration

This is defined as the production of plasma water from whole blood across a semipermeable membrane in response to a transmembrane pressure gradient generated by the hydrostatic pressure in the blood and filtrate compartments, and the oncotic pressure produced by plasma proteins [62].

The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial was designed to compare the safety and efficacy of veno-venous ultrafiltration and standard intravenous diuretic therapy for 200 hospitalized heart failure patients with at least two signs of hypervolemia. At 48 h, weight and net fluid loss were greater in the ultrafiltration group with similar dyspnea scores and episodes of hypotension. At 90 days, the ultrafiltration group had fewer rehospitalizations for heart failure. Changes in serum creatinine were similar in the two groups throughout the study. There was no correlation between net fluid removed and changes in serum creatinine in the ultrafiltration or in the intravenous diuretic group [63].

Theoretical advantages of this technique with respect to diuretic therapy include the rapidity of fluid removal, higher sodium clearance, decreased risk of electrolyte abnormalities and lack of neurohormonal activation. However, hemorrhage as a result of systemic anticoagulation, catheter-related complications, excess ultrafiltration resulting in hypotension, worsening renal function and membrane bioincompatibility represent potential barriers to the widespread use of ultrafiltration in heart failure patients [64].

Thus, although a promising technique, conclusive safety and efficacy data need to be confirmed in large clinical trials. In the meantime, extracorporeal ultrafiltration could be initiated in stable patients in whom other therapeutic options failed to resolve congestion.

Conclusion

Although prospective large, randomized trials to establish dose, modality of administration and safety are lacking, NPSDs are still the mainstay of the treatment for both acute and chronic heart failure patients, on the basis of their efficacy in providing prompt relief from signs and symptoms of congestion.

Even if a clear cause–effect correlation has never been demonstrated, recent data suggest that NPSD therapy may be associated with increased mortality in the heart failure population. Electrolyte imbalances, hypotension, activation of neurohormones and worsening renal function may explain these poor outcomes. Thus, given the lack of prospective data, it is prudent not to rely

exclusively on NPSD to treat signs and symptoms of heart failure. Implementing aldosterone blocking agents may help to improve outcomes by minimizing NPSD side effects at low doses (potassium depletion) and minimizing NPSD exposure when high doses are administered (diuretic effect).

However, if intravenous NPSD for an acute decompensation is required, the continuous infusion seems to be the safer modality of administration. Chronic maintenance dose during the post-discharge period still remains a challenge. Other NPSD such as torasemide and metolazone appear to be reasonable alternatives, however, their safety and efficacy in heart failure has not been extensively explored.

Vasopressin antagonists, adenosine antagonists and ultrafiltration appear to be promising but need further investigation.

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References

1 Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, *et al.* Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**:e21–e181.

2 Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol* 2008; **52**:428–434.

3 Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, *et al.* The EuroHeart Failure survey programme: a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003; **24**:442–463.

4 Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J* 2006; **27**:1207–1215.

5 Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MG, Abraham WT, *et al.*, for the ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; **149**:209–216.

6 Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, *et al.* Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. *Am Heart J* 2004; **148**:43–51.

7 Gheorghiade M, Shin DD, Thomas TO, Brandimarte F, Fonarow GC, Abraham WT. Congestion is an important diagnostic and therapeutic target in heart failure. *Rev Cardiovasc Med* 2006; **7**:S12–S24.

8 Shin DD, Brandimarte F, De Luca L, Sabbah HN, Fonarow GC, Filippatos G, *et al.* Review of current and investigational pharmacologic agents for acute heart failure syndromes. *Am J Cardiol* 2007; **99**:4A–23A.

9 Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, *et al.*, American College of Cardiology Foundation; American Heart Association. 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.

10 Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, *et al.*; ESC Committee for Practice Guidelines, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, *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 Heart J* 2008; **29**:2388–2442.

11 Cotter G, Weissgarten J, Metzkor E, Moshkovitz Y, Litinski I, Tavori U, *et al.* Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; **62**:187–193.

12 Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, *et al.* Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998; **351**:389–393.

13 Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation* 1999; **100**:1311–1315.

14 Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, *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.

15 Domanski M, Tian X, Haigney M, Pitt B. Diuretic use, progressive heart failure, and death in patients in the DIG study. *J Card Fail* 2006; **12**:327–332.

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 Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. 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.

18 Peacock WF, Costanzo MR, De Marco T, Lopatin M, Wynne J, Mills RM, Emerman CL, 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.

19 Murray MD, Deer MM, Ferguson JA, Dexter PR, Bennett SJ, Perkins SM, *et al.* Open label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. *Am J Med* 2001; **111**:513–520.

20 Cosin J, Diez J. Torasemide in chronic heart failure: results of the TORIC study. *Eur J Heart Fail* 2002; **4**:507–513.

21 Rosenberg J, Gustafsson F, Galatius S, Hildebrandt PR. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. *Cardiovasc Drugs Ther* 2005; **19**:301–306.

22 Ezekowitz JA, Hernandez AF, Starling RC, Yancy CW, Massie B, Hill JA, *et al.* Standardizing care for acute decompensated heart failure in a large megatrial: the approach for the Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND-HF). *Am Heart J* 2009; **157**:219–228.

23 Morgan DB, Davidson C. Hypokalemia and diuretics: an analysis of publications. *BMJ* 1980; **280**:905–908.

24 Dargie HJ, Cleland JG, Leckie BJ, Inglis CG, East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 1987; **75**:IV98–IV107.

25 Hropot M, Fowler N, Karlmark B, Giebisch G. Tubular action of diuretics: distal effects on electrolyte transport and acidification. *Kidney Int* 1985; **28**:477–489.

26 Bhatia ML, Singh I, Manchanda SC, Khanna PK, Roy SB. Effect of furosemide on pulmonary blood volume. *BMJ* 1969; **2**:551–552.

27 Dikshit K, Vyden JK, Forrester JS, Chaterjee K, Prakash P, Swan HJC. Renal and extrarenal haemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med* 1973; **288**:1087–1090.

28 Beohar N, Erdogan AK, Lee DC, Sabbah HN, Kern MJ, Teerlink J, *et al.* Acute heart failure syndromes and coronary perfusion. *J Am Coll Cardiol* 2008; **52**:13–16.

29 McCurley JM, Hanlon SU, Wei SK, Wedam EF, Michalski M, Haigney MC. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. *J Am Coll Cardiol* 2004; **44**:1301–1307.

30 Lopez B, Querejeta R, Gonzalez A, Sanchez E, Larman M, Diez J. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. *J Am Coll Cardiol* 2004; **43**:2028–2035.

31 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341**:709–717.

32 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.*, Eplerenone post-acute myocardial infarction heart failure efficacy and survival study investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**:1309–1321.

33 Brandimarte F, Blair JE, Manuchehry A, Fedele F, Gheorghiade M. Aldosterone receptor blockade in patients with left ventricular systolic dysfunction following acute myocardial infarction. *Cardiol Clin* 2008; **26**:91–105.

34 Boccanelli A, Mureddu GF, Cacciatore G, Latini R, Masson S, Porcu M, *et al.* Antiremodeling effect of aldosterone receptors blockade with canrenone in mild chronic heart failure (AREA IN CHF): final results. *Eur J Heart Failure* 2009; **11**:68–76.

35 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.

36 Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CR, Hamer J. Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. *Br Heart J* 1979; **42**:316–325.

37 Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, *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.

38 Francis GS, Siegel RM, Goldsmith SR. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. *Ann Intern Med* 1985; **103**:1–6.

39 Martin SJ, Danziger LH. Continuous infusion of loop diuretics in the critically ill: a review of the literature. *Crit Care Med* 1994; **22**:1323–1329.

40 Gulbis BE, Spencer AP. Efcacy and safety of a furosemide continuous infusion following cardiac surgery. *Ann Pharmacother* 2006; **40**:1797–1803.

41 Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; **28**:376–382.

42 Howard PA, Dunn MI. Aggressive diuresis for severe heart failure in the elderly. *Chest* 2001; **119**:807–810.

43 Cioffi G, Tarantini L, Pulignano G, Del Sindaco D, De Feo S, Opasich C, *et al.* Prevalence, predictors and prognostic value of acute impairment in renal function during intensive unloading therapy in a community population hospitalized for decompensated heart failure. *J Cardiovasc Med* 2007; **8**:419–427.

44 Howard PA, Dunn MI. Effectiveness of continuous infusions of loop diuretics for severe heart failure. *J Cardiovasc Med* 2006; **7**:5–10.

45 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.

46 Reddy P, Mooradian AD. Diuretics: an update on the pharmacology and clinical uses. *Am J Ther* 2009; **16**:74–85.

47 Gheorghiade M, Pang P. Acute heart failure syndromes. *J Am Coll Cardiol* 2009; **53**:557–573.

48 Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, *et al.* The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail* 2002; **8**:136–141.

49 Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, Krumholz HM. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail* 2003; **9**:13–25.

50 Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, *et al.* Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004; **147**:331–338.

51 Schrier RW. Role of diminished renal function in cardiovascular mortality. *J Am Coll Cardiol* 2006; **47**:1–8.

52 Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000; **35**:681–689.

53 Mahon NG, Blackstone EH, Francis GS, Starling RC III, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. *J Am Coll Cardiol* 2002; **40**:1106–1113.

54 Paterna S, Fasullo S, Di Pasquale P. High-dose torasemide is equivalent to high-dose furosemide with hypertonic saline in the treatment of refractory congestive heart failure. *Clin Drug Investig* 2005; **25**:165–173.

55 Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, *et al.* Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003; **145**:459–466.

56 Goldsmith SR, Gheorghiade M. Vasopressin antagonism in heart failure. *J Am Coll Cardiol* 2005; **46**:1785–1791.

57 Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, *et al.*, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 2007; **297**:1332–1343.

58 Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, *et al.*, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007; **297**:1319–1331.

59 Goldsmith SR, Elkayam U, Haught WH, Barve A, He W. Efficacy and safety of the vasopressin V1A/V2-receptor antagonist conivaptan in acute decompensated heart failure: a dose-ranging pilot study. *J Card Fail* 2008; **14**:641–647.

60 Dohadwala MM, Givertz MM. Role of adenosine antagonism in the cardiorenal syndrome. *Cardiovasc Ther* 2008; **26**:276–286.

61 Cotter G, Dittrich HC, Weatherley BD, Bloomfield DM, O'Connor CM, Metra M, Massie BM, Protect Steering Committee, Investigators, and Coordinators. The PROTECT pilot study: a randomized, placebo-controlled, dose-finding study of the adenosine A1 receptor antagonist rolofylline in patients with acute heart failure and renal impairment. *J Card Fail* 2008; **14**:631–640.

62 Costanzo MR. Ultrafiltration in the management of heart failure. *Curr Opin Crit Care* 2008; **14**:524–530.

63 Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, *et al.*, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007; **49**:675–683.

64 Kazory A, Ross EA. Contemporary trends in the pharmacological and extracorporeal management of heart failure: a nephrologic perspective. *Circulation* 2008; **117**:975–983.