Heart failure (HF) is a major and growing public health problem worldwide with high morbidity, mortality, and cost (1). Hospitalizations for acute decompensated heart failure (ADHF) have increased over time, and costs related to hospitalization account for ~75% of the total cost of HF care (2). Despite therapeutic advances in the care of chronic HF, the prognosis of patients with ADHF remains poor, with an in-hospital mortality rate of ~4% (3), 30-day rehospitalization rates of 23% (4), and a 6-month mortality rate approaching 20% in advanced HF (5)—with all event rates notably higher than those of myocardial infarction. Fluid retention and congestion are responsible for 90% of HF hospitalizations (1,3), and greater severity of congestion is associated with worse outcomes (6). Intravenous loop diuretics remain the first-line therapy for ADHF and are currently prescribed for ~90% of hospitalized ADHF patients (3). Despite the ubiquitous use of these agents, there are persistent uncertainties about appropriate dosing and the overall safety profile (7,8). Even with diuretic therapy, ~40% of hospitalized HF patients are discharged with unresolved congestion (9), with increased rehospitalization (10) and mortality (11) rates. There has been an increasing focus on an evidence-based approach to diuretic use in ADHF, as well as investigating alternative strategies to manage volume retention. Peripheral venovenous ultrafiltration (UF) has emerged as a potentially promising alternative to diuretic therapy in ADHF (12). This review summarizes the currently available data on the use of both loop diuretics and UF in ADHF and identifies challenges and unresolved questions for each approach.

**Loop Diuretics in ADHF**

**Pharmacology.** Loop diuretics inhibit the Na+/2Cl−/K+ cotransporter in the thick ascending loop of Henle, resulting in decreased urine sodium and chloride reabsorption with natriuresis and diuresis. The 3 commonly used loop diuretics all work via these same mechanisms, although pharmacologic differences may have clinical importance (Table 1) (13). The greater bioavailability of bumetanide and torsemide may offer more predictable diuresis, and the increased half-life of torsemide in the setting of renal, hepatic, and/or cardiac dysfunction may be advantageous for extended diuresis. The data comparing the loop diuretics are limited to small-scale, chronic HF studies with short follow-up and underuse of contemporary therapy as recently reviewed (14). These hypothesis-generating studies suggested potential benefits with torsemide compared with furosemide on neurohormonal activation, left ventricular remodeling, and fibrotic changes with resultant reduced hospitalizations, improved symptoms, and potentially reduced mortality (14). These findings would need to be confirmed in contemporary, adequately powered clinical trials.

Given the need for rapid onset of action, loop diuretics are typically given intravenously for hospitalized ADHF patients.
Intravenous (IV) administration of an effective dose of furosemide typically results in a diuretic effect within 30 min that peaks at 1 h (14). In HF, the dose–response curve shifts downward and to the right, thereby necessitating a higher dose to achieve the same effect (Fig. 1) (8,13). The sigmoid-shaped dose–response relationship demonstrates the importance of attaining a diuretic concentration on the steep part of the curve between the minimal effective dose and dose ceiling. With renal insufficiency, as seen in >50% of ADHF patients (15), organic anions compete with receptor sites for tubular transporters (16) and further increase dose requirements.

Although loop diuretics are commonly given by intermittent IV bolus, there are potential benefits of continuous infusion. Continuous infusion results in a more constant delivery of diuretic to the tubule, potentially reducing a post-diuretic “rebound” sodium retention and maintaining more consistent diuresis. Although a meta-analysis suggested greater urine output, shorter length of hospital stay, less renal impairment, and increased mortality, under-scoring the importance of effective decongestion in improving outcomes in ADHF (22,23).

**Safety.** Observational studies have shown associations between high doses of loop diuretics and adverse clinical outcomes (7,25–27). These observations are confounded by the fact that patients receiving higher doses of diuretics tend to have greater disease severity or comorbidity, making it impossible to establish whether the relationship between diuretic dose and outcomes is causal. Potential mechanisms for worse outcomes with loop diuretics include stimulation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (28–30), electrolyte disturbances, and deterioration of renal function (31,32)(Fig. 2). A recent analysis of the BEST (Beta-blocker Evaluation of Survival Trial) found that worsened mortality in association with high-dose loop diuretics was primarily limited to those patients with elevated blood urea nitrogen, suggesting a role for neurohormonal activation in observed increase mortality with loop diuretics (33). An animal study using a porcine

**Efficacy.** Loop diuretic use in ADHF generally improves dyspnea and decreases ventricular filling pressures (Fig. 2) (7,19). Loop diuretics may induce the synthesis of prostaglandins with vascular smooth muscle relaxation resulting in renal and pulmonary vasodilation (20,21). Although decades of clinical experience suggest that loop diuretics are generally effective at managing congestion in ADHF, recent studies suggested that the lack of adequate decongestion is more common than previously appreciated (22,23). The largest ADHF trial to date, the ASCEND-HF (Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure) trial (N = 7,141), demonstrated that standard ADHF care resulted in improved dyspnea at 24 h in 66% of patients (24). The lack of adequate symptom relief with diuretics has been associated with longer hospital stays and increased mortality, under-scoring the importance of effective decongestion in improving outcomes in ADHF (22,23).

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### Table 1 Pharmacokinetics of the Loop Diuretics

<table>
<thead>
<tr>
<th>Property</th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative IV potency, mg</td>
<td>40</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>10–100 (average, 50)</td>
<td>80–100</td>
<td>80–100</td>
</tr>
<tr>
<td>Oral to intravenous conversion</td>
<td>2:1</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Initial outpatient total daily oral dose, mg</td>
<td>20–40</td>
<td>0.5–1</td>
<td>5–10</td>
</tr>
<tr>
<td>Maintenance outpatient total daily oral dose, mg</td>
<td>40–240</td>
<td>1–5</td>
<td>10–200</td>
</tr>
<tr>
<td>Maximum daily intravenous dose, mg</td>
<td>400–600</td>
<td>10</td>
<td>200</td>
</tr>
<tr>
<td>Onset, min</td>
<td>30–60</td>
<td>30–60</td>
<td>30–60</td>
</tr>
<tr>
<td>Oral</td>
<td>5</td>
<td>2–3</td>
<td>10</td>
</tr>
<tr>
<td>Intravenous</td>
<td>1</td>
<td>1–2</td>
<td>1</td>
</tr>
<tr>
<td>Peak serum concentration after oral administration, h</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Affected by food</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Metabolism</td>
<td>50% renal conjugation</td>
<td>50% hepatic</td>
<td>80% hepatic</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>1.5–2</td>
<td>1</td>
<td>3–4</td>
</tr>
<tr>
<td>Normal</td>
<td>2.8</td>
<td>1.6</td>
<td>4–5</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2.5</td>
<td>2.3</td>
<td>8</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>2.7</td>
<td>1.3</td>
<td>6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6–8</td>
<td>4–6</td>
<td>6–8</td>
</tr>
<tr>
<td>Average duration of effect, h</td>
<td>4</td>
<td>4</td>
<td>19–23</td>
</tr>
</tbody>
</table>

Adapted, with permission, from Felker (13) and Wargo and Banta (14).
HF model showed that treatment with furosemide resulted in an increased progression of left ventricular systolic dysfunction (34).

Of particular interest is the association of higher diuretic dosing with worsening renal function (WRF) during ADHF hospitalization because WRF characterized by changes in creatinine and/or estimated glomerular filtration rate has been shown to be a predictor of poor outcomes (7,15). More recent data from several studies, however, have suggested that transient WRF during acute HF therapy may not affect post-discharge outcomes (35,36). Given that persistent congestion is itself a predictor of both WRF (37) and adverse outcomes (38), it would appear that transient WRF may be a reasonable trade-off in exchange for better decongestion. Understanding the optimal balance between the benefits of decongestion and the potential adverse effects of diuretics served as the rationale for the DOSE trial.

The DOSE trial. There is limited evidence to guide diuretic use as reflected in practice guidelines in which diuretic therapy is given a class I recommendation with a level of evidence based on expert opinion (39–41). The recently published DOSE trial is the largest prospective, double blind, randomized ADHF trial to evaluate initial diuretic strategies (18). Using a 2 × 2 factorial design, the DOSE trial randomized 308 ADHF patients to IV furosemide given as twice-daily boluses or continuous infusion and to either a low dose (IV dose numerically equivalent to the patient’s oral dose) or a high dose (2.5 times oral dose given intravenously) strategy. There was no significant difference in either of the co-primary endpoints of global assessment of symptoms (Fig. 3A) or change in serum creatinine over 72 h with diuretic administration by bolus or continuous infusion or with a low- versus a high-dose strategy. However, patients randomized to the higher dose strategy had more favorable outcomes with regard to several secondary measures, including relief of dyspnea, change in weight, and net fluid loss. These potential benefits were balanced by greater changes in renal function (Fig. 3B). Although the mean change in creatinine from baseline to 72 h was not significantly different between the low- and high-dose strategy, the high-dose approach was associated with a significantly higher proportion of patients experiencing transient WRF (increase in creatinine >0.3 mg/dl). Despite these changes in renal function, the higher dose group had fewer serious adverse events and no evidence of worse 60-day outcomes. Taken as a whole, the data suggest that higher doses of diuretics are likely to be more efficacious in relieving congestion than a low-dose strategy, at the cost of transient WRF that does not appear to have long-term consequences.

Challenges of Diuretic Therapy

Diuretic resistance. In ADHF, diuretics may fail to adequately control salt and water retention despite dose escalation. This concept of diuretic resistance captures an ADHF subpopulation at high risk of morbidity and mortality (42). Several mechanisms contribute to this progressive diminution of loop diuretic efficacy (43). First, loop diuretics are “threshold drugs,” so an adequate dose is needed to achieve therapeutic effect. The shift of the dose–response curve in HF implicates insufficient dosing as a common cause of a lack of diuretic response. Differentiating diuretic resistance versus inadequate dosing is a well-recognized problem and is an area of ongoing research (44). Dose escalation beyond a patient’s previously recognized dose ceiling or a dose approaching the maximum recommended daily dose without incremental improvement in diuresis suggests diuretic resistance. An additional mechanism for diuretic resistance involves the “braking phenomenon” in which long-term loop diuretic administration results in a reduced natriuretic response. This phenomenon occurs due to a relative or absolute contraction of the extracellular fluid volume, resulting in reduced delivery of solute to the proximal tubule via the RAAS and sympathetic nerve–mediated mechanisms (45), as well as enhanced distal nephron solute reabsorption via adaptive epithelial hypertrophy and hyperfunction (46). Third, when the diuretic concentration in the tubular fluid decreases to below a therapeutic level, there is a period of post-diuretic sodium retention or “rebound” (8). Infrequent dosing may therefore lead to sodium retention that exceeds natriuresis, especially if dietary sodium intake is not restricted. Therefore, loop diuretics are generally more effective when given in several divided doses or continuously to limit this “rebound” effect.

Strategies for overcoming diuretic resistance. For patients with volume overload who are refractory to escalating doses of IV diuretics, several treatment options exist to try and enhance diuretic efficacy. Thiazide diuretics can be
effective adjuncts to loop diuretics (43). Thiazides are typically given as a single oral dose 1 h before loop diuretic dosing. Although this strategy can often be effective in overcoming diuretic resistance, careful monitoring of fluid status and serum electrolytes is critical. The combination of thiazides and loop diuretics can induce severe volume depletion or electrolyte disturbances including hypokalemia and hypomagnesemia with resultant increased risk of arrhythmias.

Aldosterone antagonists used at natriuretic doses may be another approach to overcome diuretic resistance (47). Although these agents are technically diuretics, they generally have little diuretic effect in patients with chronic HF at the standard doses (48). Much higher doses of spironolactone have been used in patients with cirrhosis, and small studies suggest that higher doses may be an adjunct to loop diuretics in achieving natriuresis (47). Because loop diuretics may worsen RAAS activation and secondary hyperaldosteronism, improved blockade of the sodium-retaining effect of aldosterone may enhance natriuresis (Fig. 2). Given the limited safety data available with this approach, such a strategy should only be undertaken with great care and close monitoring of volume status and electrolytes with concern for hyperkalemia.

Several HF trials have demonstrated positive results incorporating hypertonic saline solution (HSS) with loop diuretics (49–51). The largest of these was a 1,771-patient study of ADHF patients with diuretic resistance who were randomized to HSS (150 ml) plus twice-daily high-dose IV furosemide (250 mg) and a moderate sodium restriction (120 mmol) compared with the same diuretic regimen without HSS and a low sodium diet (80 mmol) (50). Those receiving HSS showed a significant increase in diuresis and shorter length of stay (3.5 vs. 5.5 days; p < 0.0001) with a favorable effect on creatinine clearance. During a mean follow-up of 57 months, the HSS and moderate sodium restriction group had reduced readmission (18.5% vs. 34.2%; p < 0.0001) and mortality (12.9% vs. 23.8%; p < 0.0001) rates. Hypothesized mechanisms for beneficial effects of low-volume HSS include restoration of effective arterial volume with improved neurohormonal inhibition and renal hemodynamic improvements as well as decreased
afterload, improved cardiac contractility, and enhanced diuretic responsiveness (50). These mechanisms are supported by data from small studies demonstrating that liberalization of dietary sodium in compensated HF patients may attenuate counterproductive neuroendocrine and hemodynamic responses, as recently reviewed (52). Given that ADHF patients have an excess of total body sodium, the efficacy of this counterintuitive therapeutic strategy as a method to suppress the body’s maladaptive responses and facilitate diuresis will need to be confirmed in more carefully controlled trials (53). Furthermore, how HSS administration would compare with alternative methods to improve intravascular volume such as albumin administration requires further investigation (54).

Early studies showed that low-dose dopamine increases the glomerular filtration rate and renal blood flow in stable HF patients (55,56), but contemporary randomized studies are generally lacking. The DAD-HF (Dopamine in Acute Decompensated Heart Failure) study investigated 60 patients randomized to high-dose furosemide (continuous infusion at 20 mg/h) or low-dose furosemide plus low-dose dopamine (continuous infusions at 5 mg/h and 5 μg/kg/min, respectively) for 8 h (57). WRF occurred more frequently in the high-dose diuretic arm (30% vs. 9%; p = 0.04), but there was a similar length of stay and 60-day mortality/rehospitalization. Overall, a low-dose loop diuretic combined with low-dose dopamine was as effective as high-dose furosemide infusion in terms of urine output and dyspnea relief with an improved renal function profile. However, based on the DOSE trial, the higher incidence of WRF in the nondopamine arm could have been attributed to the high-dose diuretic regimen rather than a benefit from dopamine in the low-dose diuretic arm. The ongoing ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure, NCT01132846) study comparing low-dose nesiritide, low-dose dopamine, and placebo as adjuncts to loop diuretics in patients with ADHF and renal dysfunction will shed light on the relative efficacy and safety of these approaches.

**UF in the Management of HF**

Ultrafiltration allows for the extracorporeal removal of plasma water from whole blood across a semipermeable membrane in response to a transmembrane pressure gradient. UF in its different forms has been used for decades in refractory edema (58). The recent development of venovenous peripheral UF has positioned UF on the forefront as an alternative to loop diuretics in ADHF. Contemporary UF devices allow for the removal of fluid at the bedside using peripheral IV access without specialized personnel (59).

**Pathophysiology of UF**

Ultrafiltration offers a mechanism for relatively rapid and controlled treatment of volume overload, with volume removal rates as high as 500 ml/h. A potential advantage of UF over loop diuretics is that the ultrafiltrate is isotonic, whereas the urinary output with loop diuretics is hypotonic, and therefore UF removes more sodium (and less potassium) than diuretics for an equivalent volume loss (60). If fluid removal does not exceed the interstitial fluid mobilization rate of approximately 15 ml/min, then the intravascular volume can be preserved with UF, potentially interrupting the vicious cycle of neurohormonal activation and renal impairment that can occur with loop diuretics (61). This hypothesis is supported by data demonstrating that patients receiving UF have lower plasma renin, norepinephrine and aldosterone levels as long as 90 days after treatment compared with those receiving diuretics (62). Most studies investigating neurohormonal activation generally preceded the routine use of beta-blockers or contemporary angiotensin-converting enzyme inhibitors, and the potential neurohormonal benefits of UF in the contemporary ADHF patient are ill-defined. Nonetheless, small studies suggest that UF improves pulmonary and
peripheral edema, lung function, and hemodynamics without adverse effects on renal function (61–64). Favorable hemodynamic changes with UF may result in improved renal function and restoration of diuretic responsiveness (63,65). The avoidance of electrolyte abnormalities may also account for improved outcomes (12,66).

**Practical Aspects of UF Therapy**

Venovenous UF can be performed via either central or peripheral vascular access as long as there are 2 catheters or 2 lumens that can provide 10 to 40 ml/min of blood flow. The UF procedure uses a transportable UF console along with a disposable, single-use extracorporeal blood circuit (Fig. 4) (67). Full anticoagulation therapy with continuous infusion of heparin is recommended to preserve filter function. Fluid removal rates are set by the provider and range from 10 to 500 ml/h; typical rates for volume removal in clinical studies have been approximately 250 ml/h (12,68). The fluid removal rate is re-evaluated over time to confirm adequate plasma refill using serial clinical parameters and potentially serial hematocrit measurements (63). Care must be taken that removal of intravascular volume does not exceed the capillary refill rate because this can lead to further RAAS activation, hypotension, and renal injury (61,69). Typical treatments last for 24 h, although more extended periods are possible. The benefits of repeated UF sessions either during hospitalizations or as an outpatient management strategy are unknown. Patients with poor venous access, hypercoagulable states, hypotension, advanced renal disease, and cardiogenic shock and those requiring inotropic support are generally not suitable for UF therapy.

**Outcomes with UF in HF.** Early studies were of small sample size, included highly selected patient populations, and had short follow-up (61,62,64). The impact of UF on symptoms, renal function, and post-discharge outcomes was recently examined in the RAPID-CHF (Relief for Acutely
Fluid-Overloaded Patients with Decompensated Congestive Heart Failure) and UNLOAD (Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized with Acute Decompensated Heart Failure) trials.

The RAPID-CHF trial was a small proof-of-concept trial of 40 patients with ADHF randomized to a single 8-h session of UF or to usual care (68). For the primary endpoint of weight loss at 24 h, there was no significant difference between UF and usual care. However, fluid removal after 24 h was significantly greater with UF. Dyspnea and HF symptoms at 48 h were also significantly improved in the UF group compared with those receiving usual care.

The UNLOAD trial is the largest trial to date investigating UF in ADHF (12). This unblinded trial randomized 200 patients with ADHF to either UF or loop diuretic therapy within 24 h of hospitalization. The UNLOAD trial studied UF as primary therapy (i.e., the protocol did not require failure of initial diuretic therapy for entry). The co-primary endpoints of the UNLOAD trial were weight loss and dyspnea relief at 48 h. The UF group had greater weight loss (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; p = 0.001), but there was no difference in the patient-reported outcome of dyspnea. Notably, the UNLOAD trial showed a decrease in rehospitalization for HF with UF compared with diuretic therapy (hazard ratio: 0.56; p = 0.04) (Fig. 5). There was significantly less hypokalemia with UF compared with diuretics, and other safety parameters (including serum creatinine change) were similar in the 2 study arms. Although the potential effect of primary UF on reduction of HF rehospitalization is intriguing, this must be balanced by the recognition that this was a secondary endpoint and based on a relatively small number of events (16 of 86 UF patients vs. 28 of 87 usual care patients; p = 0.04). Furthermore, this small, unblinded study with short follow-up may have been confounded by unintentional bias because HF rehospitalizations were investigator reported, and criteria for rehospitalization were not presented.

The economic impact of UF as an initial strategy for ADHF remains uncertain. Although up-front costs may be greater with UF than with diuresis, total longitudinal costs could be lower if length of hospital stay is reduced and/or rehospitalization rates are decreased (12,66). A cost-consequences decision model analysis found that despite a reduction in rehospitalization with UF, it was unlikely to result in cost savings from a societal level (70). However, these calculations were based on recently developed UF devices and proprietary supplies. Another recent review on the financial implications of UF in HF highlighted the high costs of disposable materials and staff training (71). Production of lower cost UF supplies and streamlined training could shift the cost–benefit analysis. Further analysis of the economic aspects of UF therapy will be an important step in defining the role for UF before broad clinical application.

At present, current guidelines recommend UF therapy only for patients who have not responded to initial medical therapy (Class IIa, Level of Evidence: B) (39,40). The reduction in rehospitalization with UF therapy as seen in the UNLOAD trial will need to be confirmed in larger, appropriately powered studies before primary UF therapy can be considered a first-line treatment. The role of UF as a treatment for the so-called cardiorenal syndrome is also currently under investigation in the National Institutes of Health-sponsored CARRRESS study (Effectiveness of Ultrafiltration in Treating People With Acute Decompensated Heart Failure and Cardiorenal Syndrome, NCT00608491), which is randomizing patients with ADHF, WRF, and persistent volume overload to a strategy of UF versus stepped pharmacological management with a primary endpoint of the change in serum creatinine and change in weight considered as a bivariate endpoint at 96 h.

**Conclusions**

Congestion and volume retention are the hallmark of HF, and loop diuretic therapy plays a central role in their treatment. Although many unanswered questions remain about the best approach for using diuretics, their demonstrated efficacy in relieving congestion and the long clinical experience suggest that they will remain an important part of the ADHF armamentarium. The results of the DOSE trial suggest that previous concerns about the safety of high-dose diuretics may not be valid, especially if more effective decongestion can be achieved. Peripheral venous UF represents one of the most promising novel approaches to volume management in ADHF. Potentially, UF may allow for more effective removal of sodium and fluid without the electrolyte abnormalities or neurohormonal activation seen with diuretics, with improved quality of life and reduced rehospitalization rates. The optimal method for achieving successful decongestion while minimizing changes in renal function and neurohormonal activation remains an area of intensive ongoing research, which will provide greater insight into the best practices for the management of ADHF.
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Key Words: heart failure ▪ loop diuretics ▪ ultrafiltration ▪ volume retention.