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REVIEW

Volume Overload in Heart Failure: An Evidence-Based Review of Strategies for Treatment and Prevention

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Abstract

Acute decompensated heart failure is the leading cause of hospital admission in the United States, with a high risk of readmission within 30 days. Most acute decompensated heart failure admissions are driven by congestive signs and symptoms resulting from fluid and sodium overload. We reviewed the evidence base addressing the management and prevention of fluid overload in heart failure, focusing on recent clinical trials. All the references in this review were obtained through PubMed and had at least 1 of the following key words: *heart failure and volume overload, congestion, loop diuretics, thiazide diuretics, aldosterone antagonists, dopamine, cardiorenal syndrome, nesiritide, vasopressin antagonists, ultrafiltration, sodium restriction, fluid restriction, telemonitoring*, and *invasive hemodynamic monitoring*. We also reviewed relevant references cited in the obtained articles, especially articles addressing methods of treating or preventing volume overload in patients with heart failure.

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In the United States, 5.1 million Americans have heart failure (HF), and that number is expected to increase 46% by 2030.[1] Although treatments have improved, acute decompensated HF (ADHF) remains the leading cause of hospitalization, has a 50% 5-year mortality rate, and is costly, accounting for $30.7 billion in health care expenditures in 2012.[1] Heart failure occurs when cardiac output is insufficient to provide adequate blood flow to meet metabolic and circulatory demands. As a result, neurohormonal pathways are up-regulated, including the sympathetic nervous system, renin-angiotensin-aldosterone system, and vasopressin (or antidiuretic hormone) axis. Temporarily, mean arterial pressure and cardiac output increase to levels adequate for tissue perfusion; however, chronic neurohormonal activation is eventually deleterious, leading to salt and water retention and subsequent worsening of cardiac output.[2,3] Ultimately, excessive activation manifests with the familiar signs and symptoms of volume overload—the leading cause of ADHF hospitalizations.

In this review, we focus on treatments to remove excess fluid and prevent its accumulation in patients with HF, emphasizing recent clinical trials. All the references cited in this review have been obtained through PubMed using the following key words: *heart failure and volume overload, congestion, loop diuretics, thiazide diuretics, aldosterone antagonists, dopamine, cardiorenal syndrome, nesiritide, vasopressin antagonists, ultrafiltration, sodium restriction, fluid restriction, telemonitoring*, and *invasive hemodynamic monitoring*. We also reviewed relevant references cited in the obtained articles, especially articles addressing methods of treating or preventing volume overload in patients with HF.

STRATEGIES FOR FLUID REMOVAL

Diuretic Therapy

Diuretics are the mainstay of therapy in patients with congestive HF. Loop diuretics, which inhibit the Na-K-2Cl transport symporter, leading to decreased sodium absorption in the thick ascending loop of Henle, are most commonly used. If loop diuretics are not sufficient, additional synergistic diuretics that affect either the NaCl cotransporter (thiazides) or the renal mineralocorticoid receptor (aldosterone antagonists) are used.[4]

ARTICLE HIGHLIGHTS

- Although larger trials are needed, small studies suggest the superiority of torsemide compared with other available loop diuretics.
- Routine continuous intravenous infusion of loop diuretics offers no added benefits in removing fluid compared with intravenous bolus administration.
- Nesiritide and dopamine have limited, if any, roles in managing volume overload in patients with acute decompensated heart failure.
- Vasopressin antagonists may help decrease volume overload in patients with acute decompensated heart failure and hyponatremia.
- Ultrafiltration can remove fluid in diuretic-refractory patients, but clinical studies show no benefits compared with more intensive, optimal diuretic therapy regimens.
- Small observational and clinical studies have not shown a benefit in restricting sodium intake in patients with heart failure; further studies are required before a definitive conclusion can be reached.
- Implantable hemodynamic monitoring devices have a promising future, and their role in managing heart failure will continue to evolve in the next 5 to 10 years.

Loop Diuretics. Loop diuretics, which include furosemide, bumetanide, torsemide, and ethacrynic acid, are all generic. In the United States, furosemide was introduced much earlier than bumetanide and torsemide and is most commonly used. As a result, 87% of inpatients with ADHF are treated with furosemide, 3% with bumetanide, 0.4% with torsemide, and 10% with a combination of synergistic diuretics.[5]

Comparatively, loop diuretics are structurally similar, except for ethacrynic acid, which lacks a sulfa moiety. However, it is associated with a greater risk of ototoxicity, relegating its use to patients with allergies to sulfa-containing medications.[6,7] The other loop diuretics do have important differences in their pharmacokinetics (Table 1). For furosemide, the bioavailability ranges from 10% to 90%, with absorption decreasing in patients with severe ADHF-associated gut edema.[8,9] In contrast, bumetanide and torsemide are less affected by intestinal wall edema, allowing for higher and more predictable bioavailability ranging from 80% to 100%.[8,10] Once in the blood, concentration kinetics also differ; furosemide and bumetanide have half-lives of 1 to 3 hours and a 6- to 8-hour duration of action, and torsemide has a longer half-life at 4 to 6 hours, with a 12- to 18-hour duration of action.[8,11]

Compared with other loop diuretics, torsemide intrinsically blocks sympathetic nervous system and aldosterone activity, which may lead to favorable cardiac remodeling and decreased kaliuresis.[12-15] In an open-label, randomized controlled trial, patients treated with torsemide were found to have decreased myocardial fibrosis on 8-month endomyocardial biopsy specimens.[16] Although intriguing, only a few clinical outcome studies have subsequently compared torsemide with other loop diuretics. In an open-label trial, 234 hospitalized patients with ADHF were randomized to receive either furosemide or torsemide and continued the same diuretic treatment for 1 year. Despite being a sicker group (ie, more previous admissions for ADHF), the torsemide group had lower ADHF readmission rates (17% vs 32%) and spent fewer days in the hospital (106 vs 296 total days). In addition, the torsemide group had less fatigue but had no change in dyspnea.[17] In the outpatient setting, torsemide was examined in the TORIC (Torasemide in

TABLE 1. Loop Diuretic Comparison[a]

Characteristic	Furosemide	Bumetanide	Torsemide
FDA approval year	1966	1983	1993
Bioavailability (%)[8-10]	10-90	80-100	80-100
Half-life (h)[8,11]	1-3	1-3	4-6
Duration of action (h)[8,11]	6-8	6-8	12-18
Typical oral doses	40-160 mg 1-2 times per day Maximum: 600 mg/d	0.5-4 mg 1-2 times per day Maximum: 10 mg/d	20-80 mg/d Maximum: 200 mg/d
Cost ($/mo)[b]	14-40	30-75	60-90

[a]FDA = Food and Drug Administration.
[b]Wholesale prices from http://www.uptodate.com. Accessed February 10, 2015.

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Congestive Heart Failure) study, a nonrandomized, open-label, postmarketing, 1-year surveillance trial of 1377 patients that noted decreased overall mortality rates with torsemide use (2.2%) compared with other loop diuretic use (4.5%).[14] Forty-six percent of torsemide-treated patients also had improvements in New York Heart Association (NYHA) class compared with 37.2% with other diuretic treatments. Finally, adverse electrolyte changes were less, with 3% of the torsemide group requiring potassium supplementation compared with 30% with other diuretics. Because this was a retrospective, nonrandomized study, a prospective, randomized, unblinded study was subsequently performed in 237 outpatients. Compared with furosemide, torsemide improved symptoms (40.2% vs 30.7% improved NYHA class); however, there were no differences in hospitalization or mortality rates.[18]

In addition to the 4 "classic" loop diuretics, there is another, azosemide, with a longer duration of action. Theoretically, azosemide leads to decreased "rebound" activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system compared with shorter-acting diuretics. Clinically, 1 trial showed benefit in 320 patients with HF who were randomized to receive 2 years of treatment with 30 to 60 mg of azosemide vs 20 to 40 mg of daily furosemide, resulting in decreased HF hospitalization rates (hazard ratio, 0.53; P=.04), with no change in overall mortality rates.[19] This drug needs more study and is not currently available in the United States.

There remains a paucity of high-quality, double-blind, randomized controlled trial data despite the widespread use of loop diuretics. Comparative trials are urgently needed, especially for furosemide, bumetanide, torsemide, and azosemide. In the meantime, we suggest that the available evidence favors torsemide use.

With any loop diuretic, clinicians treating inpatients with ADHF must also decide on a method for intravenous administration—either continuous infusion or intermittent boluses. Compared with intermittent boluses, continuous delivery theoretically leads to lower peak concentrations, less renal dysfunction and neurohormonal activation, and decreased "rebound" sodium and water retention. However, few studies compared the 2 methods until the DOSE (Diuretic Strategies in Patients With Acute Decompensated Heart Failure) trial was published in 2011. This trial was a prospective, double-blind trial randomizing 300 patients to receive either continuous vs bolus furosemide therapy and high- vs low-dose furosemide strategies.[20] There were no differences in symptoms, creatinine levels, cystatin C levels, N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels, likelihood of a switch to oral diuretics at 48 hours, or hospital length of stay in the continuous and bolus arms. At 72 hours, patients treated with the high-dose strategy had more fluid loss (4899 mL vs 3575 mL; P=.001) and weight loss, improved dyspnea scores (P=.04), and a trend toward greater reduction in NT-pro-BNP levels (−1822 pg/mL vs −1194 pg/mL; P=.06). However, there were no differences in hospital length of stay, mortality, or 60-day readmission rates, and a greater proportion had an increase in creatinine concentration by more than 0.3 mg/dL (to convert to μmol/L, multiply by 88.4) (23% vs 14%; P=.04). Given the overall results of this well-conducted trial, there is no added benefit to routine continuous intravenous infusions over bolus administration of loop diuretics in the treatment of ADHF.

Thiazide Diuretics. Thiazide diuretics are typically used for hypertension treatment,[21] but they also can modestly affect volume removal. When added to a loop diuretic, the combination potentiates diuresis due to sequential receptor blockade in the ascending loop of Henle and the distal nephron.[22] Thiazides are especially useful in patients with long-term loop diuretic use because they help overcome the decreased loop diuretic response caused by hypertrophy of the loop of Henle and distal convoluted tubule.[23] Despite these well-known observations, studies supporting combination therapy include few patients and do not compare different therapy combinations.[24,25] Clinically, combination therapy can cause profound electrolyte abnormalities, especially hypokalemia, which requires close monitoring in the inpatient and outpatient settings.[26] Although there are no comparative data among the thiazide diuretics, metolazone and chlorothiazide tend to be favored, although hydrocholorothiazide and chlorthalidone can also be considered. We recommend metolazone, which should be administered infrequently (ie, 2.5-5 mg every 48 hours) owing to its long

half-life. For patients who cannot take oral medications, we favor chlorothiazide (250-500 mg twice daily), which is available in a more expensive intravenous formulation.

Aldosterone Antagonists. Table 2 summarizes the data for spironolactone, a nonselective mineralocorticoid receptor blocker, and eplerenone, a newer medication with minimal effects on sex steroid receptors.[27-29] In select patients, low-dose therapy decreases morbidity and mortality when added to standard HF medications owing to cardiac antifibrotic effects and beneficial cardiac remodeling.[30] Furthermore, higher-dose therapy leads to diuresis by blocking renal salt-retaining aldosterone receptors.[31] In contrast to low-dose therapy, high-dose therapy was evaluated in only 1 trial, which enrolled 100 patients with ADHF to receive either placebo or 50 to 100 mg of spironolactone. By the third day, treatment was associated with decreased edema, orthopnea, and NT-pro-BNP levels (2488 pg/mL vs 1555 pg/mL).[32] However, there were no differences in length of stay, and renal function worsened (20% in the spironolactone group had a ≥0.3 mg/dL rise in serum creatinine concentration compared with 4%), with no differences in serum potassium levels. Despite being the largest trial of its kind, this was a small study conducted at a single center in Portugal; the assessing physicians were not blinded to the treatment, and patient assignments were not randomized. Therefore, these results call for a definitive, larger, randomized controlled trial.

Vasopressin Antagonists. Solute-free water diuretics, or aquaretics, work via vasopressin (antidiuretic hormone) antagonism and include lixivaptan, tolvaptan, and conivaptan. Although they are mostly used to correct hyponatremia, they have also been evaluated for ADHF treatment owing to their diuretic properties. For tolvaptan, it was first clinically evaluated in the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) study, in which 319 hospitalized patients with persistent congestive ADHF were randomized to receive tolvaptan (either 30, 60, or 90 mg/d) or placebo in addition to standard HF therapy. In the first 24 hours, there was a trend toward greater weight loss in the tolvaptan groups ($P<.08$ for all groups vs placebo) and increased

TABLE 2. Aldosterone Antagonist Comparison[a,b]

Characteristic	Spironolactone	Eplerenone	Evidence
Mechanism of action	Nonselective aldosterone receptor antagonist; structurally similar to progesterone	Selective aldosterone receptor antagonist with limited affinity for progesterone and androgen receptors	• 1999—RALES[28] - 1663 patients with NYHA III/IV class heart failure - Excluded creatinine >2.5 mg/dL; potassium >5 mmol/L. - Spironolactone associated with 11% absolute reduction in mortality and 35% reduction in hospitalization
Indication[c]	NYHA class II-IV CHF with EF ≤35% Essential hypertension	NYHA class II-IV CHF with EF ≤35% Essential hypertension	
Typical doses	25-100 mg/d (higher doses in patients with liver failure)	25-50 mg/d	• 2003—EPHESUS[27] - 3313 patients after AMI with EF <40% and CHF - Epleronone associated with reduced mortality (HR = 0.85), SCD, and hospitalization
Adverse effects	Antiandrogenic effects (dose-dependent incidence of gynecomastia, with 6.9%-10% experiencing this at doses >50 mg/d) Dysmenorrhea, amenorrhea Hyperkalemia	Selective binding to mineralocorticoid receptors results in minimal antiandrogenic effects Hyperkalemia	• 2011—EMPHASIS-HF[29] - 2737 patients with NYHA class II with EF <30% or EF <35% and widened QRS. - Epleronone associated with lower mortality (HR = 0.76) and hospitalizations
Cost ($/mo)[d]	45	125	

[a]AMI = acute myocardial infarction; CHF = congestive heart failure; EF = ejection fraction; HR = hazard ratio; NYHA = New York Heart Association; SCD = sudden cardiac death.
[b]SI conversion factor: To convert creatinine values to μmol/L, multiply by 88.4.
[c]Caution: estimated glomerular filtration rates less than 30 mL/min per 1.73 m^2 or potassium levels of 5.0 mmol/L or greater.
[d]Wholesale prices from http://www.uptodate.com. Accessed February 10, 2015.

serum sodium levels, with no adverse changes in potassium levels or renal function.[33] Subsequently, the much larger, double-blind, placebo-controlled, 4133-patient EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial revealed a benefit with tolvaptan therapy, leading to significant weight reduction and improved dyspnea scores in the first 24 hours, as well as decreasing edema by day 7.[34] Despite the short-term benefits, there were no long-term differences in all-cause mortality or hospitalizations at median follow-up of almost 10 months.

Similar to tolvaptan, lixivaptan has shown potential benefit in diuresis. In 1 study, 42 patients with mild-to-moderate HF were randomized to receive either placebo or 1 of 6 different doses of lixivaptan. There were significant and dose-related increases in urine volume at 24 hours, with the highest lixivaptan dose (400 mg) yielding an average of 3.9 L of urine output compared with 1.8 L with placebo ($P<.01$).[35] Because there are no large-scale trials, the Food and Drug Administration (FDA) has not yet approved lixivaptan and is awaiting data from the BALANCE (Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation) trial, which aims to enroll 650 patients with ADHF and a serum sodium level less than 135 mEq/L (to convert to mmol/L, multiply by 1.0).[36]

Compared with other "vaptans," conivaptan is unique because it is administered intravenously. Although there are no large studies, conivaptan can improve diuresis when added to loop diuretics. A pilot study in 170 hospitalized patients with worsening ADHF were randomized to receive conivaptan (loading dose plus 2 successive infusions of 40, 80, or 120 mg/d) or placebo in addition to standard loop diuretic therapy. At each dose range, initial urine output was significantly increased at 24 and 48 hours.[37] However, many patients had infusion-site phlebitis (17.5%-33%, depending on the dose), but there were no other adverse effects, such as changes in vital signs, electrolyte levels, or cardiac rhythms.

In summary, although vaptans may help in the short-term in patients with ADHF and hyponatremia, current studies suggest that they do not decrease mortality rates or have long-term benefits. If used, patients require close monitoring because antidiuretic hormone antagonists can lead to rapid increases in sodium levels.

Dopamine

Intravenous dopamine induces natriuresis and diuresis by increasing renal vasodilatation and blood flow through activation of renal-specific dopamine (DA) DA_1 and DA_2 receptors[38] and inhibition of proximal tubular Na^+/H^+ and Na^+K^+ATPase pumps.[39] Dopamine purportedly selectively activates receptors in a dose-dependent manner, with low doses (2-5 μg/kg per minute) predominantly affecting DA_1 and DA_2 receptors and higher doses activating β and then α vasoreceptors.[38] This physiologic finding inspired the concept of using low-dose ("renal-dose") dopamine to enhance diuresis in ADHF; however, this strategy has been clinically disappointing. Multiple systematic reviews have noted no meaningful benefits with low-dose dopamine therapy.[40,41] A 2005 meta-analysis of 61 trials encompassing 3259 patients showed no differences in mortality, need for renal replacement therapy, or adverse events. In this study, urine output increased 24% in the first 24 hours.[42]

Because only 1 small study included in these reviews specifically included patients with HF,[43] 3 studies were conducted evaluating low-dose dopamine for ADHF treatment. A retrospective study assessed 116 patients receiving furosemide by continuous infusion coupled with low-dose dopamine or bolus intravenous furosemide alone.[44] The patients in the dopamine/continuous furosemide arm had improved renal function, greater diuresis, fewer inpatient hospital days, and reduced 30-day readmission rates. However, the 2 groups had significantly different baseline characteristics, including worse renal function and a higher rate of aldosterone antagonist treatment in the dopamine group. The subsequent DAD-HF (Dopamine in Acute Decompensated Heart Failure) study was the first to prospectively randomize patients with ADHF to receive either high-dose intravenous furosemide (20 mg/h) or low-dose intravenous furosemide (5 mg/h) coupled with 8 hours of low-dose dopamine (5 μg/kg per minute).[45] There were no differences in diuresis, dyspnea scores, inpatient hospital days, mortality rates, renal function, or rehospitalization rates in the 60 patients enrolled in the study. Three years later, the ROSE-AHF (Renal Optimization Strategies Evaluation in

Acute Heart Failure) trial supplanted DAD-HF as the largest randomized trial of low-dose dopamine in the HF population.[46,47] In this trial, 360 patients with ADHF and renal dysfunction were randomized to receive diuretics with placebo, low-dose dopamine (2 μg/kg per minute), or low-dose nesiritide for 72 hours. Compared with DAD-HF, ROSE-AHF used dopamine for longer (although at a lower dose), had no variations in diuretic dosing between the groups, and had a much larger study size. In the end, dopamine therapy did not affect urine output or renal function and at 60 days led to no differences in mortality or unscheduled outpatient or inpatient HF-related appointments.

Based on the previously mentioned trials, dopamine's effect of renal vasodilation has not led to clinical benefits, perhaps due to variability in pharmacologic levels and heterogeneous responses to dopamine. Even in healthy individuals, a stable infusion dose of 3 μg/kg per minute of dopamine leads to unreliable dopamine plasma concentrations, varying between 1800 and 18,300 ng/L.[48] In patients with renal failure, dopamine's renal vasodilatory effects are blunted and instead paradoxically increase renal resistance indices.[49] Similarly, patients with ADHF have reduced effects with dopamine infusion, requiring much higher—than-expected doses (4-6 μg/kg per minute) to augment peak renal blood flow and reduce renal vascular resistance. Furthermore, the sickest patients (NYHA class IV) have no dopamine-associated changes in renal vascular resistance or the fraction of cardiac output dedicated to renal perfusion.[50] Therefore, dopamine's pharmacologic effects seem least effective in patients with severe ADHF or renal failure, likely at least partly explaining the observed lack of clinical benefit.

As summarized in Table 3, the routine use of dopamine for augmented diuresis or renal protection is not supported by recent studies. In patients with HF and reduced ejection fraction, it is reasonable to use dopamine only transiently to increase blood pressure and cardiac output.

Nesiritide

The effects of BNP seem perfectly tailored to therapeutic exploitation: augmented natriuresis, sympatholysis, antiproliferative effects, and renin-angiotensin-aldosterone system inhibition. Based on 2 trials showing a reduction in pulmonary capillary wedge pressure and improvement in dyspnea after 3 hours of therapy,[51,52] synthetic BNP (nesiritide) was approved by the FDA in 2001 for clinical use.

A year later, the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy With Dobutamine or Nesiritide Therapy) trial was published, which showed symptomatic improvements with nesiritide compared with dobutamine, with lower rates of ventricular arrhythmias.[53] By 2004, nesiritide was in widespread use in various off-label clinical settings despite the lack of documented clinical benefits. These settings included prolonged infusions in patients awaiting heart transplants, 1-time doses given as first-line therapy for ADHF in the emergency department, and intermittent, scheduled injections in outpatient infusion clinics in patients with chronic HF.[59] However, 2 meta-analyses published in 2005 noted increased renal failure, hypotension, and mortality rates in patients treated with nesiritide, prompting further studies.[54,55]

The first subsequent randomized study, the FUSION II (Second Follow-up Serial Infusions of Nesiritide) trial, showed no clinical benefits with serial outpatient nesiritide infusions.[56] Then, 2 large-scale trials evaluated inpatient nesiritide therapy. The first, the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure) trial, randomized 7141 patients to receive nesiritide (0.01 μg/kg per minute for at least 24 hours and up to 7 days) or placebo therapy.[57] There were no significant improvements in self-reported dyspnea rates at 6 and 24 hours and no differences in death or HF hospitalization rates.[58] However, nesiritide use led to more adverse events, especially hypotension (26.6% vs 15.3%; $P \leq .001$). The second trial, the previously mentioned ROSE-AHF study,[47] specifically targeted patients with ADHF and renal failure. Compared with placebo use, low-dose (0.005 μg/kg per minute) nesiritide therapy was not associated with improvements in urine output, renal function, symptoms, mortality rates, or rehospitalization rates. In addition, nesiritide therapy led to higher symptomatic hypotension rates.

Although there may remain a yet-undiscovered niche use, the ASCEND-HF and ROSE-AHF trials indicate no current role for nesiritide in augmenting urine output or renal function in patients with ADHF. Nesiritide

TABLE 3. Summary of Mechanisms of Action and Recent Evidence for Dopamine and Nesiritide in ADHF

Therapy	Mechanisms of action	Evidence
Dopamine	• Increased cardiac inotropy and chronotropy through stimulation of β-receptors • At lower doses, increase in renal blood flow via renal arterial vasodilation mediated by stimulation of DA_1 and DA_2 receptors[38] - In patients with ADHF and renal failure, may have no effect or actually be deleterious to renal blood flow[49,50]	• 2001-2002—Two systematic reviews[10,40] - No difference in mortality or renal function • 2010—DAD-HF[45] - 60 patients with ADHF - Dopamine at 5 μg/kg per minute for 8 h vs placebo - No differences in diuresis, dyspnea scores, inpatient hospital days, mortality, renal function, or rehospitalization rates • 2013—ROSE-AHF[46,47] - 360 patients with ADHF and renal failure - Dopamine at 2 μg/kg per minute or nesiritide for 72 h vs placebo - For dopamine vs placebo: no difference in renal function, urine output, 60-d mortality, or heart failure events
Nesiritide	• Recombinant human brain natriuretic peptide • Augmented natriuresis, sympatholysis, antiproliferative effects, and RAAS inhibition	• 2000 (VMAC study) and 2002[51,52] - Nesiritide for 3 h vs placebo - Reduction in PCWP and dyspnea scores in the nesiritide group • 2002—PRECEDENT[53] - 255 patients randomized to receive nesiritide or dobutamine - Less ventricular tachyarrhythmias with nesiritide • 2005—Two meta-analyses[54,55] - Increased renal failure, hypotension, and mortality rates with nesiritide • 2008—FUSION II[56] - No clinical benefit to outpatient nesiritide infusion • 2011—ASCEND-HF[57,58] - 7141 patients randomized to receive nesiritide or placebo - No difference in dyspnea, death, or heart failure hospitalization - More hypotension in the nesiritide arm • 2013—ROSE-AHF[46,47] - 360 patients with ADHF and renal failure - Dopamine or nesiritide (0.005 μg/kg per minute) for 72 h vs placebo - For nesiritide vs placebo: no difference in urine output, renal function, symptoms, 60-d mortality, or rehospitalizations

ADHF = acute decompensated heart failure; PCWP = pulmonary capillary wedge pressure; RAAS = renin-angiotensin-aldosterone system.

should be used only after proven treatment strategies have not improved symptoms (and then only in select inpatients who are not hypotensive or in cardiogenic shock), and expectations for therapeutic success should be tempered by knowledge of these recent negative clinical studies. Table 3 summarizes the pharmacologic properties of nesiritide and the relevant clinical trials.

Ultrafiltration

Although first considered in 1908, venovenous ultrafiltration (UF) was not used in the HF population until low-impact devices were developed. Modern UF machines typically use 2 peripheral venous catheters, thus avoiding the complications of large-bore central venous access.[60] These catheters are attached to a machine with 2 pumps and a blood filter circuit. Within a minute, blood rapidly circulates through a special filter, sheds excess water and salt through aquapheresis, and then returns back to the patient. By design, UF machines are relatively easy to use, do not require intensive care unit or dialysis center monitoring, and have limited settings focused on adjusting the rate of isotonic fluid removal (which is usually restricted to a maximum of 0.5 L/h). Ultrafiltration is very effective at removing fluid, averaging 4.7 L for a single session, 7.1 L in 2 sessions, and 8.6 L during a hospitalization.[61-63]

Early on, several smaller studies suggested a promising future for UF.[63-65] By 2005, larger trials emerged, which are summarized in Table 4. The first study was the RAPID-CHF (Relief for Acutely Fluid-Overloaded Patients With

TABLE 4. Summary of Mechanisms of Action and Recent Evidence for UF in ADHF

Mechanisms of action	Evidence
• Venovenous removal of isotonic fluid • Greater net loss of sodium; less neurohormonal activation • Adjustable rate of volume removal, leading to greater control	• 2005—RAPID-CHF[61] - 40 patients with ADHF and renal failure to single UF session vs usual care - UF group with significantly more volume removal and improved dyspnea score; no difference in 24-h weight loss and renal function • 2007—UNLOAD[66,67] - 200 patients with ADHF to UF and intravenous diuretics - UF group with greater weight loss, better dyspnea score, and lower rehospitalizations and 90-d unscheduled visits - UF compared with continuous diuretic infusion showed similar fluid loss; however, associated with fewer rehospitalizations • 2012—CARRESS-HF[68] - 188 patients with ADHF and worsened renal failure - UF compared with stepped pharmacologic therapy shows no significant weight loss but worse renal function and higher serious adverse event rates

ADHF = acute decompensated heart failure; UF = ultrafiltration.

Decompensated Congestive Heart Failure) trial, which randomized 40 patients with concomitant renal insufficiency to receive a single 8-hour UF session or usual care.[61] The UF group lost more volume (4.7 L vs 2.8 L; *P*=.001) and had less dyspnea. Adding a second UF session was even more effective, with continued higher volume removal at 48 hours (8.4 L vs 5.4 L; *P*=.012). Subsequently, the 200-patient UNLOAD (Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF) trial demonstrated similar results, with the UF group having greater mean ± SD weight loss (5.0±3.1 kg vs 3.1±3.5 kg; *P*=.001) and water removal (4.6 L vs 3.3 L; *P*=.001) at 48 hours but with no differences in dyspnea.[66] By 90 days, the UF group had a mean ± SD lower risk of HF rehospitalization (0.22±0.54 vs 0.46±0.76; *P*=.022) and fewer unscheduled clinic visits (21% vs 44%; *P*=.009). There were no differences in renal function or mortality rates.[67]

Despite these promising results, the trials were criticized because the usual care groups were not aggressively treated with diuretics as most received only double their outpatient diuretic regimen. For the subset treated more aggressively, diuretic therapy was similar to UF in reducing fluid (−4.6 L vs −3.9 L) and weight (5.0 kg vs 3.6 kg).[66] In response, the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial was then performed, which randomized 188 patients with ADHF, worsened renal function (creatinine level ≥0.3 mg/dL from baseline), and persistent intravascular congestion to receive UF or diuretic therapy.[68] In contrast to previous trials, usual care patients were initially treated with high-dose loop diuretics and then received additional thiazide diuretics, inotropes, or vasodilators if urine output was inadequate. As a result, there were no differences in mean ± SD weight loss at 96 hours (5.5±5.1 kg vs 5.7±3.9 kg; *P*=.58), but the UF group had more serious adverse events (72% vs 57%; *P*=.03), mainly due to bleeding and catheter-related complications, and worsened mean ± SD serum creatinine levels (0.23±0.7 mg/dL vs −0.04±0.53 mg/dL; *P*=.003). Aside from the use of more intensive medical therapy, the enrollment of only patients with evidence of worsened renal function (cardiorenal syndrome) in CARRESS-HF may explain the disparate results between it and the UNLOAD studies.

In conclusion, UF is effective in removing fluid in patients with ADHF but is associated with increased risks, mainly due to vascular access complications (vein access, bleeding, trauma, and infection). Based on the current evidence, UF is similarly efficacious to optimally dosed diuretic therapy, costs more, and requires close patient supervision. Therefore, UF should not be initially considered, although it may prove useful in diuretic-refractory patients with ADHF. Because equipoise exists regarding appropriate use of UF in ADHF, a larger, 800-patient, randomized controlled trial was undertaken, but it was terminated due to patient recruitment challenges.[69]

PREVENTIVE STRATEGIES

Fluid and Salt Restriction

Neurohormonal imbalances created by HF lead to an inability to excrete sodium and water. Therefore, conventional wisdom has advised limiting the intake of both because one cannot accumulate what one does not ingest. Early studies suggested that patients with HF on high-salt diets have an inability to augment ventricular contractility, plasma natriuretic factors, and urine sodium excretion.[70] However, these responses seem to be different in patients treated with typical modern pharmacologic therapies (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists). In fact, 1 study showed that these patients have similar responses to controls when exposed to high salt loads, augmenting the cardiac index and stroke volume while decreasing peripheral vascular resistance and suppressing angiotensin II and norepinephrine levels. Moreover, continued high-salt diet exposure did not lead to ADHF.[71] In contrast, sodium restriction led to no change in NYHA classifications but increases in aldosterone, norepinephrine, and dopamine levels.

Regarding clinically relevant outcomes, recent studies also contradict commonly held beliefs correlating increases in sodium intake (and, therefore, total body fluid retention and increased weight) with ADHF. In 1 study, patients presenting to the emergency department with HF did not consume more high-sodium food in the preceding 3 days.[72] In another study, most patients (~54%) did not have a significant change in weight before developing ADHF.[73] In yet another study, which collected data from implantable hemodynamic monitoring systems in patients with HF, weight gain did not precede ADHF; instead, most had increased intracardiac filling pressures first.[74]

Intriguingly, 2 randomized controlled trials evaluating different sodium intake diets also suggested no benefit to sodium restriction. In the first trial, recently admitted patients randomized to the less-restricted diet (2.8 g) had fewer readmissions at 180 days (8% vs 26%) and lower plasma renin, aldosterone, and BNP levels compared with patients randomized to the more sodium-restricted diet (1.8 g/d).[75] However, this trial required unusually high doses of furosemide (250-500 mg twice daily) and unrealistically limited fluid intake to 1000 mL/d. A subsequent trial by the same group randomized patients to receive 1.8 g vs 2.8 g of sodium per day and 1 L vs 2 L of fluid per day and used lower doses of furosemide (125-250 mg twice daily). Again, higher sodium intake was associated with decreased readmissions at 180 days (adjusted odds ratio of 2.46) and improved neurohormonal markers.[76] In contrast to the previously mentioned trials, a recent cohort study evaluated sodium intake over 6 days in 123 patients with systolic HF and found that patients in the highest tertile of sodium consumption had a higher risk of mortality and all-cause hospitalizations (combined adjusted hazard ratio of 2.55 vs the lowest tertile).[77] These patients also had higher total daily fluid intake (2.4 L vs 2 L).

In the inpatient setting, sodium restriction also may not be beneficial. One study randomized 75 patients with ADHF to a fluid- or sodium-restricted diet (800 mL/d or 800 mg/d, respectively) or an unrestricted diet for 3 days.[78] There were no differences in dosages of loop diuretics and no differences in length of stay, renal function, clinical congestion, body weight, or readmission rates. However, perceived thirst was significantly worse in the sodium- and fluid-restricted groups.

Finally, a research team evaluated combining high-dose furosemide with high-dose hypertonic saline (150 mL of 1.4%-4.6% saline) in patients with diuretic-refractory ADHF, randomizing 107 patients to receive this unique therapy vs high-dose furosemide (500-1000 mg/d) therapy alone. The group receiving hypertonic saline had improved diuresis, natriuresis, and renal function, with lower readmission (47% vs 79%) and mortality (45% vs 87%) rates during the 48-month follow-up period.[79] Of note, the patients in both groups received far higher doses of intravenous furosemide (500-1000 mg/d) than is usual; thus, this trial needs to be replicated with standard diuretic treatments before endorsing hypertonic saline therapy.

Previously, the American Heart Association, the European Society of Cardiology, and the Canadian Cardiovascular Society had recommended sodium and water restriction in patients with HF. However, given the previously noted data and a recent Cochrane Review citing the potential for increased harm,[80] the most recent American College of Cardiology/American

Heart Association guidelines do not endorse any specific level of sodium or fluid intake in patients with stage C and D HF.[81] Because this is controversial,[82] well-conducted large-scale trials are needed to definitively determine the role of sodium and water in patients with HF.

Monitoring Strategies

There is a strong interest in the early detection of ADHF because early treatment can prevent morbidity and hospitalizations.[83] Therefore, considerable research has focused on invasive and noninvasive early-warning monitoring methods.

Noninvasive Strategies. Telemonitoring allows for remote monitoring of weights and symptoms, ideally prompting rapid therapeutic changes in the outpatient setting. One of the earliest large randomized controlled trials to show benefit enrolled 280 outpatients with NYHA class III and IV symptoms. Clinicians were required to review proprietary home monitoring system data daily and adjust medications accordingly. Telemonitoring led to unexpectedly lower mortality rates (absolute risk reduction = 10.3%; P=.003), although there were no differences in 6-month hospitalization rates, the primary end point.[84]

Subsequent well-conducted trials have not shown benefits in morbidity or mortality rates. The Tele-HF (Telemonitoring to Improve Heart Failure Outcomes) trial used a different telemonitoring system that required patients to report daily symptoms and weights. These data were reviewed by clinicians who adjusted patients' HF medications. Because this required considerable effort (reviewing >3 data reports per week), adherence was only 55% in the telemonitoring group, likely explaining the lack of differences in 6-month readmission or death rates.[85] Another trial, the TIM-HF (Telemedical Interventional Monitoring in Heart Failure) trial, prospectively evaluated telemedical management in 710 patients with NYHA class II and III HF. Despite using a more sophisticated system, which automatically transmitted 3-lead electrocardiographic data, blood pressure, and daily weights, there were no differences in mortality or HF hospitalization rates.[86]

Given the limited value of telemonitoring, manufacturers have developed alternative monitoring devices. One noninvasive device uses multiple sensors to detect changes in thoracic electrical impedance and then performs impedance cardiography (ICG) to estimate aortic blood flow and other hemodynamic parameters.[87] In the PREDICT (Prospective Evaluation of Cardiac Decompensation in Patients With Heart Failure by Impedance Cardiography Test) trial, 212 patients with HF underwent biweekly clinical assessments and ICG measurements for 26 weeks. Researchers synthesized the ICG data to develop a composite score highly predictive of clinical events in the ensuing 14 days.[88] Now, ICG is being further evaluated in the PREVENT-HF (Prevention of Heart Failure Events With Impedance Cardiography Testing) trial, which will determine whether ICG analysis can help prevent hospitalizations.[89] Another strategy uses the VeriCor left ventricular end diastolic pressure (LVEDP) monitor (VeriCor Medical Systems), which noninvasively measures radial artery blood pressure and lung pressures during the Valsalva maneuver to estimate LVEDP.[90] In a recent trial, 25 hospitalized patients were randomized to treatment guided by VeriCor monitor—estimated LVEDP levels, and another 25 were treated based on clinical signs alone. The intervention group had lower LVEDPs at hospital discharge (19.7 mm Hg vs 25.6 mm Hg; P=.01) as well as decreased rehospitalization rates (16% vs 48% at 1-year follow-up).[91] These results are encouraging; however, a larger randomized controlled trial is needed to fully evaluate the VeriCor system before recommending widespread use.

Invasive Monitoring. Compared with noninvasive devices, implantable hemodynamic monitors (IHMs) have the ability to continuously monitor real-time cardiac hemodynamics. In theory, IHM can help practitioners adjust HF medications and optimize intravascular fluid status in inpatient and outpatient settings. The first IHM device, Chronicle (Medtronic Inc), was similar to a single-lead pacemaker. Essentially, a pressure-monitoring transvenous lead was positioned in the right ventricular outflow tract that then transmitted data to a subcutaneously placed device. While promising, the COMPASS-HF (Chronicle Offers Management to Patients With Advanced Signs and Symptoms of Heart Failure) trial showed no advantage to IHM-guided therapy compared with optimal medical management.[92] A subsequent trial, REDUCEhf

(Reducing Events in Patients With Chronic Heart Failure), which combined Chronicle technology with an implantable cardiac defibrillator, also showed no benefits.[93] With this combined device, there were also safety concerns because the increased complexity resulting from implanting 2 separate leads in the right ventricular led to an intolerably high risk of IHM lead failure (4% at 4 years).

Another means of invasive monitoring was studied in FAST (Fluid Accumulation Status Trial), a prospective, double-blind study evaluating intrathoracic impedance measurements in predicting HF events.[94] Patients with previously implanted cardioverter defibrillators received a software update (OptiVol; Medtronic Inc) that recorded intrathoracic impedance. The sensitivity of the software to predict HF events was superior compared with that of following changes in weight (76% vs 23%; $P<.001$). The FAST trial prompted the DOT-HF (Diagnostic Outcome Trial in HF) trial, which randomized 335 patients with HF to receive ambulatory management based on intrathoracic impedance via OptiVol or usual care.[95] No clinical benefits were observed with OptiVol-guided therapy; in fact, there were increased ambulatory visits and HF hospitalizations. Of note, this trial was terminated early owing to slow enrollment, with only 355 patients enrolled in a planned 2400-patient study.

In contrast to the previously mentioned IHM devices, the CardioMEMS device (St Jude Medical) is associated with clinical improvements. This device is implanted in the pulmonary artery and measures pressure waveforms in the distal pulmonary artery. In the CHAMPION-HF (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Subjects) trial, the device was implanted in 550 patients with NYHA class III HF, who were then randomized to a treatment group, which allowed clinicians to use device data for management, or a control group.[96] CardioMEMS monitoring led to a 28% reduction in HF-related hospitalizations at 6 months and a 37% reduction during follow-up. The intervention group had shorter hospital stays (2.2 days vs 3.8 days) and an improved quality of life. Most importantly, the device was safe, without significant adverse events. Despite controversy about whether this trial adequately blinded CardioMEMS output in the control group, the FDA approved CardioMEMS in 2014.

Although CardioMEMS is the only FDA-approved device, several other IHMs are currently under development. Two notable IHMs are HeartPod (St Jude Medical) and a system developed by Remon Medical Technologies. In brief, HeartPod monitors left atrial pressures and is currently being evaluated in a large randomized controlled trial.[97] In a pilot trial, 40 patients with NYHA class III or IV HF had an average reduction in left atrial pressures from 17.6 mm Hg in the first 3 months to 14.8 mm Hg; however, the study was underpowered to detect clinical differences.[98] The other device (Remon Medical Technologies) has shown promise in a pilot trial and is currently being evaluated in the PAPIRUS III (Monitoring Pulmonary Artery Pressure by Implantable Device Responding to Ultrasonic Signal) trial.[99] All in all, IHM devices have a promising future, and we believe that their role in managing HF will continue to evolve as more devices are studied and come to market. Table 5 summarizes the data available for the various preventive strategies.

CONCLUSION

Volume overload remains a vexing clinical problem. Previously, clinicians relied on physiologic and pharmacologic principles to guide them in treating and preventing volume overload in these patients. However, as this review illustrates, high-quality clinical trials have provided evidence to guide clinicians in the day-to-day treatment of patients with ADHF. Intriguing small studies have hinted that perhaps not all loop diuretics are created equal and call for larger rigorous clinical trials. Large, well-conducted clinical trials evaluating nesiritide and dopamine suggest that neither drug has a major role in ADHF management. Ultrafiltration remains a promising modality for fluid removal for diuretic-refractory patients, but clinical studies do not suggest benefit for most patients compared with optimal diuretic therapy. The age-old principle of sodium restriction has been called into question by observational and clinical studies, and further prospective investigation is required. Finally, we are at the dawn of the era of invasive hemodynamic monitoring for HF management. However, as we evaluate this exciting new technology, we must remember that it is our duty to

TABLE 5. Summary of Preventive Strategies and Recent Evidence

Intervention	Evidence	Recommendations
Low-sodium diet	• 2009[76] - A 410-patient RCT comparing 1.8 g/d of sodium vs 2.8 g/d of sodium and 1-L fluid restriction vs 2-L fluid restriction - Decreased readmissions at 6 mo in the group with liberal sodium intake • 2011[77] - A 123-patient prospective, nonrandomized observational study in the ambulatory setting - Higher mortality and increased hospitalizations in the higher-sodium group	• Most recent ACC/AHA guidelines do not endorse specific restrictions[81] • Large-scale RCTs are necessary
Telemonitoring	• 2003—WHARF[84] - RCT with 280 patients with NYHA class III and IV symptoms - Proprietary telemonitoring system showed lower mortality rates but no differences in 6-mo hospitalization rates • 2007—Tele-HF[85] - RCT with >1600 patients randomized to telemonitoring (patient reported symptoms and weights) or usual care - No difference in 6-mo readmission or mortality in the intervention arm; of note, only 55% adherence in the telemonitoring group • 2011—TIM-HF[86] - 710-patient RCT evaluating a telemonitoring system that automatically transmitted 3-lead electrocardiographic data, blood pressure, and daily weights - No reductions in HF hospitalizations and no mortality benefit	• Telemonitoring systems have not shown clinical benefit
ICG (noninvasive)	• 2004—PREDICT trial[88] synthesized ICG data to develop composite score that can predict patients with high risk of clinical decompensation in the short-term (2 wk) • PREVENT-HF trial[89] is ongoing to determine utility of ICG in preventing hospitalizations	• More trials are necessary before using this system is practice
VeriCor LVEDP monitor (noninvasive)	• 2011[90] - A small RCT (50 patients) - Lower LVEDPs at discharge and lower rehospitalization rates at 1 y when using VeriCor system to guide therapy	• Larger RCT is needed before recommending widespread use
IHMs	• 2008—COMPASS-HF[92] - Chronicle device: implantable hemodynamic monitor in the RV outflow tract - No significant clinical benefit • 2011 DOT-HF[95] - Randomized 335 patients to receive management based on intrathoracic impedance via OptiVol device or usual therapy - No mortality benefit; increased visits and hospitalizations in intervention arm REDUCE-HF[93] - Hemodynamic sensor implanted in the RV outflow tract along with ICD - Study stopped early due to high incidence of device failure CHAMPION-HF[96] - Randomized 550 patients to receive implantable CardioMEMS-guided therapy or standard therapy - A 28% reduction in HF hospitalizations at 6 mo and shorter hospital stays in the intervention arm	• CardioMEMS was FDA approved in 2014 • Multiple trials are ongoing evaluating other IHM devices

ACC = American College of Cardiology; AHA = American Heart Association; FDA = Food and Drug Administration; HF = heart failure; ICD = implantable cardioverter defibrillator; ICG = impedence cardiography; IHM = implantable hemodynamic monitor; LVEDP = left ventricular end diastolic pressure; NYHA = New York Heart Association; RCT = randomized controlled trial; RV = right ventricular.

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ensure that it meets the same standard we require of all other therapies: sound clinical evidence suggesting benefit in treating or preventing volume overload in patients with HF.

Abbreviations and Acronyms: **ACC** = American College of Cardiology; **ADHF** = acute decompensated heart failure; **AHA** = American Heart Association; **AMI** = acute myocardial infarction; **CHF** = congestive heart failure; **DA** = dopamine; **EF** = ejection fraction; **FDA** = Food and Drug Administration; **HF** = heart failure; **HR** = hazard ratio; **ICD** = implantable cardiac defibrillator; **ICG** = impedence cardiography; **IHM** = implantable hemodynamic monitor; **LVEDP** = left ventricular end diastolic pressure; **NT-pro-BNP** = N-terminal of the prohormone brain natriuretic peptide; **NYHA** = New York Heart Association; **PCWP** = pulmonary capillary wedge pressure; **RAAS** = renin-angiotensin-aldosterone system; **RCT** = randomized controlled trial; **RV** = right ventricular; **SCD** = sudden cardiac death; **UF** = ultrafiltration

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