Diuretic response in acute heart failure – pathophysiology, evaluation and therapy

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Nature Reviews Cardiology 2015;12(3):184-192
The administration of loop diuretics to achieve decongestion is the cornerstone of therapy for acute heart failure. Unfortunately, impaired response to diuretics is common in these patients and associated with adverse outcomes. Diuretic resistance is thought to result from a complex interplay between cardiac and renal dysfunction and specific renal adaptation and escape mechanisms, such as neurohormonal activation and the braking phenomenon. However, our understanding of diuretic response in patients with acute heart failure is still limited and a uniform definition is lacking. Three objective methods to evaluate diuretic response have been introduced, which all suggest that diuretic response should be determined based on the effect of diuretic dose administered. Several strategies have been proposed to overcome diuretic resistance, including combination therapy and ultrafiltration, but prospective studies in patients who are truly unresponsive to diuretics are lacking. An enhanced understanding of diuretic response should ultimately lead to an improved, individualized approach to treating patients with acute heart failure.
INTRODUCTION

Acute heart failure is one of the leading causes of hospital admission worldwide, and is associated with high morbidity, mortality, and rehospitalization.\textsuperscript{1,2} Most of the symptoms associated with acute heart failure are the result of excessive fluid retention, and loop diuretics are the treatment of choice to combat them. Loop diuretics are administered in up to 90\% of patients hospitalized for acute heart failure, despite the lack of evidence for outcome benefit.\textsuperscript{2,3} Poor response to diuretic therapy (that is, persistent signs and symptoms despite increasing doses of diuretic drug, known as diuretic resistance) frequently occurs in patients during hospitalization for acute heart failure, although the exact frequency is unknown owing to the lack of a standard definition.\textsuperscript{4} In two studies from 2014, a poor response to diuretics was more frequently found in patients with diabetes mellitus, reduced glomerular filtration rate (GFR) and high blood urea nitrogen levels, or low systolic blood pressure.\textsuperscript{5,6} Importantly, a poor diuretic response was independently associated with impaired symptom relief, a higher risk of in-hospital worsening of heart failure, increased mortality after discharge from hospital, and a threefold higher rate of rehospitalization, compared with patients with a good diuretic response. Moreover, an improved definition and quantification of diuretic response to loop diuretics has been called for by some clinicians.\textsuperscript{7} However, the pathophysiology behind diuretic resistance is not completely understood, and thought to result from the complex interplay between cardiac and renal dysfunction, specific renal adaptation, and escape mechanisms, such as the braking phenomenon.\textsuperscript{4} In this Review, we describe the pathophysiological background of diuretic resistance, the evaluation and definition of diuretic response, as well as current and future strategies to improve diuretic response in patients with acute heart failure.

PATHOPHYSIOLOGY

The cardiorenal system

The heart and kidney function together to regulate circulatory homeostasis via several mechanisms and feedback loops. In healthy individuals, glomerular filtration remains stable despite changes in volume and blood pressure. When triggered by sodium and volume overload, a rise in atrial pressure and release of natriuretic peptides facilitates renal sodium excretion via direct tubular effects and an increase in glomerular filtration rate.\textsuperscript{8–10} Concomitant suppression of the renin–angiotensin–aldosterone system (RAAS) contributes to stable blood pressure via systemic vasodilatation and renal sodium excretion by inhibiting the tubular effects of angiotensin II and aldosterone.\textsuperscript{11} Conversely, in a volume depleted state, increased RAAS activity contributes to the maintenance of blood pressure and renal sodium retention.\textsuperscript{11} Furthermore, angiotensin II induces renal efferent vasoconstriction,
helping to maintain renal filtration pressure and filtration rate despite decreasing arterial pressure. Activation of the sympathetic nervous system has a similar effect as, and is in part stimulated by, the RAAS. Moreover, the interaction of the cardiorenal system affects osmoregulation via effects on water diuresis. Under normal physiological conditions, the release of arginine vasopressin (an antidiuretic hormone) is stimulated by a high plasma osmolarity, which leads to renal water retention and restores normal osmolarity. However, during pronounced water volume disturbances, responses to volume depletion or overload can overcome the osmotic triggers, contributing to restoration of volume status at the expense of osmoregulation.

In patients with acute heart failure, a decrease in cardiac function causes reduced cardiac output and arterial underfilling, leading to decreased activation of arterial stretch receptors and resulting in compensatory systemic and intrarenal vasoconstriction. Decreased stretch of the glomerular afferent arteriole stimulates renin release, which leads to angiotensin II production. Angiotensin II release leads to afferent and efferent vasoconstriction, stimulation of sodium retention in the proximal tubule, and release of aldosterone. In turn, aldosterone increases sodium reabsorption in the collecting duct, resulting in extracellular fluid expansion and systemic congestion. In healthy individuals sodium delivery to distal renal tubules by increased vascular volume overcomes the sodium retaining effect of aldosterone (known as an aldosterone escape mechanism). This mechanism is impaired in patients with acute heart failure, in whom reduced renal blood flow forces continued sodium retention in response to aldosterone.

Heart failure also results in baroreceptor-mediated sympathetic nervous system activation that promotes vasoconstriction and contributes to further RAAS activation and renal sodium and water retention. The release of antidiuretic hormone exacerbates these effects. Furthermore, the protective effect of natriuretic peptides is diminished in patients with acute heart failure due to renal vasoconstriction, reduced sodium delivery, fewer active forms of natriuretic peptides, and downregulation of their receptors. In addition, adenosine (released in response to increased renal work load and high sodium concentration in the distal tubule) further reduces renal blood flow, stimulates proximal sodium reabsorption and through tubuloglomerular feedback further decreases GFR via the adenosine A1 receptor. In contrast to the adenosine A1 receptor, activation of the adenosine A2 receptor can increase renin secretion. The combination of these pathways creates a vicious circle that leads to further congestion and worsening heart failure.

A major symptom of heart failure is decreased organ perfusion. The kidney can compensate for a drop in renal blood flow by increasing the filtration fraction via angiotensin II-mediated efferent vasoconstriction and thereby preserve GFR. The combination of pump failure, neurohormonal activation, and therapies for heart failure, particularly angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers, can eventually overcome the kidney’s capacity to compensate for reduced perfusion. Additionally,
increased venous filling and abdominal pressures owing to ascites can increase renal afterload and intrarenal pressure, reduce the transrenal perfusion gradient (and thus renal perfusion pressure), increase renal interstitial pressure (directly opposing filtration pressure), and further contribute to renal insufficiency.25–27

**Mechanisms of diuretic resistance**

Diuretics are the first-line therapy for volume overload and aim to establish a negative sodium and consequently fluid balance. Poor response to diuretics is an important clinical problem in patients with acute heart failure and its underlying pathophysiological mechanisms are diverse.2,4

Regulation of renal sodium excretion involves several sequential transport mechanisms in the renal tubule.28 Diuretics act on specific sodium transport mechanisms, and are classified based on their tubular site of action (Figure 1). Acetazolamide and mannitol act on the proximal tubule, where up to two-thirds of the sodium load is filtered under physiological

![Figure 1](image)

**Figure 1. Diuretic therapy**

(1) Acetazolamide function in the proximal tubule by blocking carbonic anhydrase and decreasing NaHCO₃ excretion. (2) Mannitol functions in both the proximal tubule and the loop of Henle by increasing H₂O excretion. (3) Loop diuretics function in thick ascending limb of the loop of Henle by blocking the sodium-chloride-potassium cotransporter and increasing sodium, potassium, and chloride excretion. (4) Thiazide functions in the distal convoluted tubule by blocking the sodium-chloride transporter and increasing sodium chloride excretion. (5) Mineralocorticoid-receptor antagonists function in the collecting duct of the distal tubule and antagonize the aldosterone receptor, hence increasing sodium excretion and potassium retention.
Acetazolamide stimulates alkaline diuresis via bicarbonate excretion with sodium and potassium by inhibiting carbonic anhydrase in the proximal tubule. Mannitol is an osmotic diuretic that acts primarily on the loop of Henle and the proximal tubule by increasing the osmotic pressure of glomerular filtrate, thus inhibiting tubular reabsorption. Loop diuretics inhibit solute carrier family 12 member 1 (a sodium–chloride–potassium co-transporter) in the thick ascending limb of the loop of Henle, leading to decreased sodium and chloride reabsorption from the urine. Thiazide diuretics act on the distal convoluted tubule by blocking the sodium–chloride transporter in the distal tubule. Metolazone is a thiazide-like diuretic that exerts its effect in the distal tubule by inhibiting the reabsorption of sodium and chloride ions. Mineralocorticoid-receptor antagonists (MRAs; also known as aldosterone antagonists) act on the collecting duct by competitively antagonizing the mineralocorticoid receptor, thereby reducing sodium reabsorption.

Delivery of diuretics to the site of action relies on several mechanisms (Figure 2). First, orally administered diuretics first must be absorbed in the gut to enter the bloodstream. In the presence of gastrointestinal oedema or gut hypoperfusion, absorption of orally administered diuretics is impaired, and might differ substantially between diuretics.
absorption of bumetanide and torsamide is likely to be better than that of furosemide under these conditions. Intravenous administration can overcome impaired absorption of orally administered diuretics. In patients with renal insufficiency or heart failure, a higher diuretic dose is required to achieve the same effects and, over time, increasing diuretic doses will become less effective.

Second, most loop diuretics (although interestingly bumetanide less so, because it can bind to plasma globulins), thiazide diuretics, metolazone, and acetazolamide are bound to plasma albumin. These diuretics act on their molecular target from the luminal side. Consequently, these drugs must be filtered by the glomerulus and actively secreted into the tubular lumen by the proximal tubule’s organic anion transporter in order to function. Hypoalbuminaemia, which is common in patients with heart failure, impairs the uptake and secretion of active furosemide and enhances conversion to its inactive form. Additionally, albumin lost into the tubule might bind furosemide and prevent it from acting on the sodium–chloride–potassium co-transporter. Coadministration of albumin and furosemide improves diuretic response in patients with cirrhosis, nephrotic syndrome, or chronic kidney disease, but no data are available in individuals with heart failure.

Third, patients with heart failure and chronic renal dysfunction have elevated levels of circulating organic acids, such as blood urea nitrogen, which competitively inhibit the organic anion transporter and further reduce diuretic availability at the site of action. RAAS and sympathetic nervous system activation lead to flow-dependent passive resorption of urea in the distal tubule; a concentration gradient created by increased sodium and water resorption in the proximal tubule results in diminished distal flow and increased reabsorption. High circulating blood urea nitrogen levels, therefore, not only contribute directly to diuretic resistance, but also reflect a kidney that is actively working to retain sodium and water. Consequently, in patients with heart failure, impaired absorption, decreased renal blood flow, azotaemia, hypoalbuminaemia, and proteinuria (resulting in reduced levels of active diuretics in the tubular lumen) might affect diuretic effectiveness.

At the onset of diuretic treatment, the natriuretic effect results in the intended negative sodium balance. The resulting decrease in extracellular volume triggers a homeostatic response, mediated by activation of the RAAS and sympathetic nervous system, leading to increased sodium retention at tubular sites not targeted by the specific diuretic. After several days, this homeostatic response counterbalances the diuretic effect of the drug, balancing sodium excretion and intake, and creating a new steady state with a lower extracellular volume. This braking phenomenon is an appropriate homeostatic response that prevents excessive volume depletion during continued diuretic therapy. However, in patients with pre-existent secondary hyperaldosteronism, such as those with heart failure, this phenomenon can be pronounced, causing rapid and abundant sodium reabsorption and contributing to diuretic resistance. Furthermore, persistent delivery of sodium or diuretics to the distal tubule leads to hypertrophy of the distal tubular cells, which bypasses
the proximal effect of the loop diuretic and results in enhanced sodium retention. Other noncardiac mechanisms resulting in a diminished response to diuretics, including reduced renal blood flow caused by renal artery stenosis or drug interactions, should also be considered when administering loop diuretics to patients.  

EVALUATING DIURETIC RESPONSE

No single accepted definition of diuretic resistance has been described. Of the several definitions proposed, the most frequently cited is ‘failure to decongest despite adequate and escalating doses of diuretics’. Less clinically applicable definitions that include variables not routinely obtained by clinicians have also been suggested (Box 1).

**Box 1: Definitions of diuretic resistance**

<table>
<thead>
<tr>
<th>Definition</th>
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<tbody>
<tr>
<td>Persistent congestion despite adequate and escalating doses of diuretic with &gt;80 mg furosemide per day¹⁰⁷</td>
</tr>
<tr>
<td>Amount of sodium excreted as a percentage of filtered load &lt;0.2%¹⁰⁸</td>
</tr>
<tr>
<td>Failure to excrete at least 90 mmol of sodium within 72 h of a 160 mg oral furosemide dose given twice daily¹⁰⁹</td>
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</table>

In our experience, unresponsiveness to diuretic therapy leading to persistent signs and symptoms of congestion is usually considered diuretic resistance. Three objective methods to evaluate diuretic response have been introduced (Box 2).

**Box 2: Metrics of diuretic response**

<table>
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<tr>
<th>Metric</th>
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<tbody>
<tr>
<td>Weight loss per unit of 40 mg furosemide (or equivalent)⁵⁵¹</td>
</tr>
<tr>
<td>Net fluid loss per milligram of loop diuretic (40 mg of furosemide or equivalent) during hospitalization⁶</td>
</tr>
<tr>
<td>Natriuretic response to furosemide as the ratio of urinary sodium to urinary furosemide⁵²</td>
</tr>
</tbody>
</table>

These measures suggest that diuretic response should be determined based on the effect of diuretic dose administered.

Some investigators have tried to determine a quantitative measure of diuretic response, combining decongestive effect and diuretic dose. In this study, diuretic response was defined as weight loss from admission to day 4 per 40 mg furosemide (or equivalent). A poor diuretic response independently predicted heart failure rehospitalization (HR 1.58, 95% CI 1.24–2.01, \( P < 0.001 \)) and mortality (HR 1.73, 95% CI 1.40–2.12, \( P < 0.001 \)). This metric was investigated in the RELAX-AHF trial, which confirmed these findings (60-day cardiovascular death or heart failure rehospitalization: HR 1.86, 95% CI 1.20–2.88, \( P < 0.001 \)). Using weight change per unit of furosemide might provide an applicable metric to confirm that a patient is resistant to diuretics. Other investigators have used a similar metric to define diuretic response (termed ‘diuretic efficiency’) defined as net fluid loss per milligram of loop diuretic (40 mg of furosemide or equivalent) during hospitalization for acute heart failure,
dichotomizing above and below the median. Consistent with the results of other investigators, low diuretic efficiency was associated with worse long-term outcomes (HR 1.39, 95% CI 1.08–1.77, P = 0.007; HR 2.86, 95% CI 1.52–5.36, P <0.001). In both studies, poor diuretic response or efficiency was associated with renal impairment and higher blood urea nitrogen levels. However, diuretic response is not only a reflection of renal impairment, and poor diuretic response was also associated with more advanced heart failure, diabetes, and atherosclerotic disease.

Finally, a ratio of urinary sodium to urinary furosemide measured in spot urine samples was also examined. A poor response (<2 mmol/mg) was associated with impaired clinical outcomes (including death, cardiac transplantation, or rehospitalization owing to heart failure), which were independent of renal function, in patients with acute heart failure (HR 1.62, 95% CI 1.13–2.39, P = 0.008). Haemoconcentration has also been suggested as a practical and readily applicable strategy to assess diuretic response. The use of urinary sodium and chloride in patients with heart failure to assess decongestion has also been investigated. Decongestion was associated with reduced urinary sodium and chloride excretion per bumetanide dose. Given that urine measurements are not common practice in cardiology, this metric might be less applicable than other metrics, which are easier to obtain and so far have provided similar results to urine measurements. Ultimately, after extensive validation and investigation, the use of such metrics of diuretic response could be used to help to identify patients who might benefit from alternative decongestive therapies and to guide treatment selection.

**TREATMENT OF PATIENTS**

Several treatment strategies have been proposed to overcome diuretic resistance. An approach to treat patients with acute heart failure who are also diuretic resistant is shown in Figure 3. Overall, we believe in an integrated, patient-tailored approach to improving biological availability of the drugs and counteracting maladaptive responses in patients who are diuretic resistant, which can be attempted using stepped pharmacological therapies, novel drugs, or mechanical fluid removal. Recommendations and scientific evidence for all the treatment options described below are presented in Table 1. Firstly, patient noncompliance to therapy should be ruled out by verifying medication intake and sodium restriction. Secondly, nonsteroidal inflammatory drugs should be discontinued, because they potentially lead to diuretic resistance by inhibiting prostaglandin G/H synthase 2 (also known as cyclo-oxygenase) and thereby interfere with prostaglandin synthesis, which antagonizes the natriuretic response to loop diuretics. Thirdly, switching to an alternative loop diuretic might be useful to achieve adequate absorption. For example, bumetanide and torasemide both have higher biological absorption than furosemide in patients with chronic heart
Chapter 2

In the TORIC study, which included outpatients with heart failure, torasemide treatment was associated with a significant improvement in NYHA class compared with furosemide or other diuretics (improvement of one grade in NYHA class 45.8% versus 37.2%; \( P < 0.001 \)). In a small meta-analysis of 2,025 patients, these findings were confirmed, suggesting a trend toward improvement in NYHA class with torasemide treatment. Adequate increasing doses of loop diuretics have to be prescribed to establish whether a patient truly has diuretic resistance. Finally, efficacy of diuretic therapy can be improved by switching from oral to intravenous administration to circumvent impaired enteral drug uptake in congested patients. The investigators of several small studies have suggested that continuous infusion improves diuresis, renal function, and leads to fewer adverse events compared with bolus injections. However, in the Diuretic Optimization Strategies Evaluation no differences in either treatment response or outcome in patients randomized to bolus versus continuous infusion were found, although diuretic doses and the incidence of worsening renal function were higher for patients in the bolus group. However, bolus dosing will not always be carried out as carefully in clinical practice as it was in the study, because this dosing strategy is usually driven by signs and symptoms and not by protocols.

Figure 3. An approach to treating patients with acute heart failure who are diuretic resistant. If a patient with acute heart failure is diuretic resistant, switch to an alternative loop diuretic. If symptoms persist, intravenously administer the drug before attempting a combination of diuretic therapies. In patients who are still diuretic resistant after these steps, alternative therapies might achieve decongestion.
### Table 1. Treating diuretic resistant patients with acute heart failure

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Author recommendations</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Loop diuretic</td>
<td>Increasing doses of loop diuretics are considered a first step</td>
<td>Felker et al.18</td>
</tr>
<tr>
<td>Switch loop diuretic</td>
<td>Switching to bumetanide or torasemide can improve bioavailability of loop diuretic</td>
<td>Vargo et al.20, Brater et al.33,49 Cosin et al.26, Bikdeli et al.57</td>
</tr>
<tr>
<td>Intravenous administration</td>
<td>Intravenous administration of loop diuretic strongly recommended to circumvent impaired enteral uptake</td>
<td>Dormans et al.38, Thomson et al.15, van Meyel et al.60, Felker et al.51</td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add thiazide</td>
<td>Improves sodium excretion by inhibiting distal sodium reabsorption, can be considered when increasing doses of intravenous loop diuretic are insufficient</td>
<td>Ellison,28 Kunau et al.,62 Channer et al.66</td>
</tr>
<tr>
<td>Add metalozide</td>
<td>Provides marked diuresis and can produce diuresis despite a low glomerular filtration rate</td>
<td>Ng et al.,64 Tilstone et al.65</td>
</tr>
<tr>
<td>Add acetazolamide</td>
<td>Increases diuresis; caution is recommended in patients with advanced renal failure owing to risk of concentration-dependent adverse effects</td>
<td>Brater et al.,66 Khan,67 Kassamali &amp; Sica,68</td>
</tr>
<tr>
<td>Add mannitol</td>
<td>In one study, mannitol improved diuresis</td>
<td>Turagam et al.,69</td>
</tr>
<tr>
<td>Add MRA at natriuretic doses</td>
<td>Associated with increased diuresis; can be considered in addition to combination therapy of loop and thiazide diuretics</td>
<td>RALES Investigators,72, van Vliet et al.,71 Ferreira et al.,77 Sigurd et al.,60 Olesen &amp; Sigurd,81</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Does not seem to improve diuretic response in acute heart failure and, therefore, has limited additive value in treating patients who are diuretic resistant</td>
<td>Elkayam et al.,84 Chen et al.,85 Triposkiadis et al.,89 Giamouzis et al.87</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>Improves diuresis and seems to be a safe alternative strategy in patients who are diuretic resistant</td>
<td>Paterna et al.,88 Licata et al.,89 Paterna et al.,90 Paterna et al.,91</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Studies on ultrafiltration have not demonstrated consistent improvement; ultrafiltration a last resort when other strategies have failed</td>
<td>Bart et al.,93 Costanzo et al.,94 Bart et al.,95</td>
</tr>
<tr>
<td><strong>Alternative therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Can increase urine output and might have additive value</td>
<td>Schrier et al.,83 Udelson et al.99</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>Does not increase urine output and is unlikely to have additive value</td>
<td>Gottlieb et al.100</td>
</tr>
<tr>
<td>Ularitide</td>
<td>Induces natriuresis and diuresis; the TRUE-AHF trial is ongoing</td>
<td>Valentin et al.102</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>Associated with symptom relief</td>
<td>Packer et al.104</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Addition of prednisone can result in marked diuresis; an alternative strategy that needs to be studied further</td>
<td>Liu et al.106</td>
</tr>
<tr>
<td>Rolofylline</td>
<td>Significant predictor of diuretic response and could help to overcome diuretic resistance</td>
<td>Valente et al.5</td>
</tr>
<tr>
<td>Serelaxin</td>
<td>No significant effect on diuretic response</td>
<td>Voors et al.,21 Metra et al.106</td>
</tr>
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Abbreviation: MRA, mineralocorticoid-receptor antagonist.
Combined diuretic therapy

If escalating intravenous doses of loop diuretics are insufficient, combination therapy with two classes of diuretic drugs might improve diuretic efficacy. The addition of a thiazide diuretic enhances sodium excretion by inhibition of distal sodium reabsorption, and prevent post-diuretic sodium retention after cessation of loop diuretic activity because thiazides have a longer half-life than loop diuretics. Potential adverse effects of combination therapy include hypokalaemia, hyponatraemia, dehydration, worsening renal function and metabolic acidosis; careful monitoring of patients receiving these drugs is, therefore, required. Addition of metozalone to a loop diuretic results in marked diuresis and is especially useful in patients with renal failure, because metozalone can produce diuresis despite a low GFR.

Given that a large amount of sodium is reabsorbed in the proximal tubule, adding a diuretic that functions in this location might be beneficial to patients. In healthy volunteers, addition of acetazolamide to furosemide showed a minor additive effect on diuresis. In one study, an additional effect of acetazolamide in correcting metabolic acidosis and increased diuresis when used intermittently in combination with furosemide and spironolactone therapy in patients with congestive heart failure was reported. Given that acetazolamide is cleared by the kidney, caution is recommended in patients with advanced renal failure owing to the risk of concentration-dependent adverse effects. Another option for combined therapy is mannitol. Investigators reported effective diuresis in 80.3% of 122 patients with acute heart failure treated with furosemide–mannitol infusion, although the study had no control group. To date, studies to evaluate combination therapy in patients with heart failure and who are diuretic resistant are scarce, and evidence remains inconclusive. Two trials (DIURESIS-CHF and CLOROTIC) to investigate combination therapy in patients with acute heart failure are ongoing and planned, respectively. However, diuretic resistance is not explicitly defined as an inclusion criterion in either study.

Adding a natriuretic dose of an MRA to diuretics might also help to overcome diuretic resistance by blocking the mineralocorticoid receptor and thereby prevent excess sodium reabsorption in the collecting duct caused by secondary hyperaldosteronism. MRAs at low doses are guideline-recommended therapy in heart failure and significantly improve survival. The dose-finding Randomized Aldactone Evaluation Study revealed that higher doses of spironolactone (50–75 mg daily) had natriuretic effects, compared with doses of 12.5 mg or 25 mg daily, which had no natriuretic effect. In two small, single-centre studies of 100 and 21 patients, respectively, high-dose spironolactone was associated with increased diuresis or earlier resolution of symptoms and signs of congestion. A common adverse effect of high-dose MRAs is hyperkalaemia; new MRA drugs with a reduced risk of causing electrolyte disturbances are currently being investigated. Addition of high-dose MRAs can be considered even in addition to combination therapy with loop and thiazide diuretics.

In clinical practice, no clear consensus on combination therapy exists and implementation is mostly determined by personal experience. We do not intend to use combination...
therapy for outpatients based on the potential complications, which mean that daily monitoring of laboratory values and hydration status is required. Several strategies can be used to prevent or overcome electrolyte disturbances. Hypokalaemia can be avoided by the co-administration of a low-dose potassium-sparing MRA or potassium sparing diuretic. Tolvaptan, a vasopressin V2 receptor blocker, has a potential role in the prevention of hyponatraemia. Overall, combination treatment requires careful follow-up and a tailored approach for each patient.

**Dopamine**

Addition of low-dose dopamine (<3 μg/kg/min) to diuretic therapy has been suggested as a method to improve renal blood flow, thereby preserving renal function and improving diuresis. Investigators in the Renal Optimization Strategies Evaluation tested whether addition of low-dose dopamine (2 μg/kg/min), low-dose nesiritide (a synthetic B-type natriuretic peptide; 0.005 μg/kg/min), or placebo, to diuretic therapy enhanced decongestion and preserved renal function in patients with acute heart failure and renal dysfunction. However, neither dopamine nor nesiritide had a significant effect on urine volume (placebo: 8,296 ml; dopamine: 8,524 ml; nesiritide: 8,574 ml) or level of cystatin C (placebo: 0.11 mg/l; dopamine: 0.12 mg/l; nesiritide: 0.07 mg/l), suggesting no added benefit to diuretic therapy. In a subsequent study, investigators in the prematurely discontinued, small-scale Dopamine in Acute Decompensated Heart Failure II trial confirmed these findings, despite promising results from the previous Dopamine in Acute Decompensated Heart Failure I study. The results of these studies suggest that dopamine does not improve diuretic response in patients with acute heart failure. Despite the lack of evidence, low-dose dopamine is still often used in clinical practice because this drug is thought to stimulate diuretic response by improving renal function, and might be beneficial in patients for whom other strategies have failed.

**Hypertonic saline**

Intravenous hypertonic saline, co-administered with diuretics, has been suggested as a way to improve diuresis, by mobilizing extravascular fluid into the intravascular space resulting in increased cardiac output, renal blood flow, and quick excretion of excess volume. In several small studies of no more than 107 patients, increased diuresis and clinical improvement in patients with acute heart failure was observed with addition of hypertonic saline. In the largest study to date (the SMAC-HF trial, including 1,771 patients, increased diuresis and natriuresis, and reduced rehospitalization rates (18.5% versus 34.2%; P <0.001), were observed in the patients treated with intravenous furosemide and hypertonic saline, compared with those who received furosemide alone. These promising results suggest that hypertonic saline is a safe alternative strategy to improve diuretic response in patients with acute heart failure. However, most experience comes from only a limited number of studies.
and, therefore, prospective trials in patients who are truly diuretic resistant are needed to establish the role of hypertonic saline.

Ultrafiltration

Ultrafiltration is an effective method for fluid removal that filters plasma water directly across a semipermeable membrane using a pressure gradient, which yields an ultrafiltrate that is iso-osmotic compared with plasma. In two randomized, controlled trials (RAPID-CHF and UNLOAD) to compare diuretic therapy and ultrafiltration, greater fluid removal was observed in the ultrafiltration groups, although weight loss after 24 h did not differ in RAPID-CHF (P = 0.24), and dyspnoea scores were similar in UNLOAD (P = 0.35). Interestingly, ultrafiltration was associated with significant reductions in rehospitalization for heart failure (18% versus 32%; P = 0.037) and fewer unscheduled hospital visits (21% versus 44%; P = 0.009); unfortunately these results were not adjudicated. In the CARRESS-HF study, the investigators examined the use of ultrafiltration in 188 patients with acute heart failure and cardiorenal syndrome. Patients were randomly assigned to receive stepped diuretic therapy or fixed-rate ultrafiltration in a 1:1 ratio (n = 94 per group). Ultrafiltration was inferior to pharmacological therapy, primarily owing to an increase in the creatinine level in the ultrafiltration group (+0.23 ± 0.70 versus –0.04 ± 0.53 mg/dl; P = 0.003), along with more adverse events (72% versus 57%; P = 0.03). However, not all patients in the ultrafiltration group received ultrafiltration therapy, and the fixed rate of fluid removal in the ultrafiltration arm has been questioned. So far, ultrafiltration has not been studied specifically in patients with diuretic resistance. In our opinion, ultrafiltration is a last resort when increasing doses of intravenous loop diuretics, combination therapy or hypertonic saline strategies have failed to overcome diuretic resistance and, even then, only in selected patients who are truly diuretic resistant. Multiple studies on ultrafiltration in heart failure are ongoing, but a phase III outcome trial (AVOID-HF) was terminated owing to recruitment problems. Unfortunately, none of the studies explicitly addresses diuretic resistance in patients.

Alternative therapies

Various intravenous agents have been investigated in acute heart failure, and although none has shown convincing survival benefits to date, several have mechanisms of action that might be helpful in overcoming diuretic resistance. The vasopressin V1 receptor blocker, tolvaptan, is effective at increasing sodium concentrations in patients with hyponatraemia, increases urine output in patients with symptomatic heart failure and might, therefore, have additive value in patients who are diuretic resistant. Synthetic natriuretic peptides have also been developed and investigated in patients with heart failure. Nesiritide, approved by the FDA in the USA for relief of heart failure symptoms (class Ila, level of evidence C), but not by European regulators owing to a lack of efficacy, did not increase urine output in patients with acute heart failure, and is, therefore, unlikely to have additive value in patients
with diuretic resistance.\textsuperscript{101} Ularitide is a synthetic form of the hormone urodilatin, a human endogenous natriuretic peptide expressed in the kidney, and induces natriuresis and diuresis by binding to specific natriuretic peptide receptors.\textsuperscript{102} Ularitide might have therapeutic advantages in acute heart failure and specifically in patients who are diuretic resistant, and is being investigated in the ongoing TRUE-AHF trial.\textsuperscript{103} Levosimendan is a phosphodiesterase inhibitor with vasodilator and positive inotropic properties, which enables rapid and durable symptom relief in acute heart failure and has positive effects on renal function, and which could help to treat symptoms in patients who are diuretic resistant.\textsuperscript{104}

In a small study of 13 patients with acute heart failure, addition of prednisone in individuals with diuretic resistance led to marked diuresis, significant weight loss (9.39 ± 3.09 kg; \(P<0.01\)), and improved renal function (GFR 33.63 ± 15.87 ml/min/1.73m\(^2\); \(P<0.01\)).\textsuperscript{105} Further studies are needed to confirm these findings.

Finally, treatment with the adenosine A\(_1\) antagonist rololfylline was a significant predictor of diuretic response (\(t\)-statistic = −3.091; \(P=0.002\) in multivariate models) due to greater weight loss, possibly owing to improved renal perfusion or direct diuretic effects.\textsuperscript{5} In some patients with poor diuretic response, inhibition of adenosine A\(_1\) might help to overcome diuretic resistance, although the adverse effect profile of rololfylline, in addition to lack of efficacy, has led to discontinuation of its development. Serelaxin is a human recombinant of the vasodilator relaxin-2, with systemic and renal effects.\textsuperscript{106} Although no significant effect of serelaxin on diuretic response has been observed, this drug might have beneficial effects that can prevent organ damage in patients with acute heart failure who are diuretic resistant.\textsuperscript{51,106}

**CONCLUSIONS**

Impaired diuretic response is a common problem in patients with acute heart failure and strongly associated with poor in-hospital and post-discharge clinical outcomes. Quantitative measures for diuretic response have been proposed, but need to be validated in other populations of patients with acute heart failure. In addition to establishing the value of diuretic response metrics as prognostic markers, early identification of patients at risk of a poor diuretic response might allow the initiation of therapies to modify their response. Prospective studies using a validated metric of diuretic response to identify patients who are diuretic resistant are a necessary first step towards determining the best strategies for overcoming diuretic resistance, and consequently determining whether such metrics lead to improved outcomes. Such strategies could ultimately result in a better, individualized approach to treating patients with acute decompensated heart failure, for whom no evidence-based therapies currently exist.
REFERENCES

1. McMurray, J. J. et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur. Heart J. 33, 1787–1847 (2012).


42. Phakdeekitcharoen, B. & Boonyawat, K. The added-up albumin enhances the diuretic effect of furosemide in patients with hypoalbuminemic chronic kidney disease: a randomized controlled study. BMC Nephrol. 13, 92 (2012).


