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Review article

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Decongestion in heart failure: medical and device therapies

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Abstract

Heart failure is a leading cause of hospitalization worldwide, and congestion is the predominant cause of heart failure symptoms and hospitalization. The primary therapy used to treat and prevent congestion has historically been loop diuretics. However, many patients are discharged from hospital with residual congestion, which is associated with persistent heart failure symptoms, adverse outcomes and hospital readmission. Multiple medical strategies and devices have been and are being investigated with the aim of improving decongestion and subsequent heart failure outcomes. Numerous questions exist about the design of clinical trials to test emerging medical and device therapies, including the magnitude of benefit on congestive, kidney and post-discharge outcomes relative to conventional decongestion practices, and how best to implement novel therapies. In this Review, we discuss emerging medical and device strategies targeting congestion in patients with heart failure.

Sections

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Key points

- Various medical and device strategies are under investigation to overcome barriers that limit decongestion in patients with acute decompensated heart failure.
- Medical strategies that optimize the use of existing diuretic therapies could have immediate, systemic effects on heart failure treatment, with limited risk or cost.
- Most devices under investigation are designed to improve the diuretic response indirectly by targeting a hypothesized haemodynamic mechanism; however, mechanistic data and clinical trials of drugs indicate that improving haemodynamics might have limited benefit.
- Barriers to the implementation of invasive devices include increased rates of adverse events from invasive procedures, cost, resource utilization and the requirement for provider expertise, limiting the pool of candidate patients.
- Randomized, controlled trials are needed to determine whether invasive devices can sufficiently improve decongestion and post-discharge outcomes compared with optimized medical therapy to offset their inherent risks and numerous barriers to widespread implementation.

Introduction

The prevalence of heart failure is rising worldwide, and approximately 25% of individuals will develop heart failure in their lifetime[1]. Likewise, hospitalizations for acute decompensated heart failure (ADHF) are rising and increasing in complexity[1,2]. Symptoms of congestion are the predominant reason for ADHF hospitalizations[3,4]. Congestion is defined as signs and symptoms of fluid accumulation in the intravascular and interstitial space owing to excessive salt and water retention by the kidney[5,6]. For decades, loop diuretics have been the predominant therapy to treat congestion in patients with ADHF and are the background standard-of-care therapy for ADHF in clinical trials[4,5,7]. However, approximately 25–30% of patients discharged after hospitalization for ADHF are recognized to have residual signs of congestion (and presumably more have unrecognized congestion), and inadequate decongestion is associated with a worse prognosis[3,8,9].

The reasons for inadequate decongestion are multifactorial and often not easily resolved. First, and perhaps foremost, consensus has not been reached on a clinically actionable decongestion end point. This situation is compounded by the high variation in the clinical assessment and treatment of congestion[4,10]. In addition, inaccurate measures of diuretic response (such as weight change, urine output and net input–output) can misinform clinicians[11,12]. Some degree of diuretic resistance is nearly ubiquitous in heart failure[13,14]. Although diuretic resistance can generally be overcome by escalating diuretic therapies, adequate titration is rarely standard in clinical practice[12,13,15]. Inadequate titration might stem from inaccurate measures of diuretic response, the cumbersome nature of continuous diuretic monitoring and titration, and a lack of knowledge and experience of such titration by many clinicians. In addition, worsening renal function is common in patients with ADHF, often causing clinicians to discontinue guideline-directed medical therapy (GDMT) and prematurely stop decongestion therapies even when persistent congestion is recognized[16–19]. For these reasons, decongestion strategies that achieve equivalent decongestion without worsening renal function are desired. Lastly, patient-related and system-related issues, such as a desire for short hospital stays and bed availability, might incentivize clinicians to discharge patients from the hospital prematurely when patient-reported symptoms of acute dyspnoea are resolved. Dyspnoea rapidly improves in the first hours of ADHF treatment despite persistent congestion, leading to the common teaching that only ~10% of the excess volume needs to be removed to improve ~90% of the dyspnoea[20,21].

Novel medical strategies and devices are being investigated to address these barriers and improve decongestion. Broadly, medical strategies include diuretic response-guided diuretic titration and combination diuretic therapies. Device therapies can be conceptualized as being either indirect or direct devices. Indirect devices are designed to improve natriuresis and diuretic response by correction of a hypothesized mechanism of cardiorenal interaction and/or diuretic resistance but do not directly remove salt or water from the body. Currently targeted mechanisms include reducing renal venous pressure, increasing renal arterial pressure, improving lymphatic flow and applying negative kidney pelvic pressure. By contrast, direct devices have a primary mechanism of action of directly removing salt and/or water from the body — for example, ultrafiltration, lymph removal, increased perspiration and automated administration of natriuretic pharmacotherapies.

In this Review, we discuss the challenges of designing ADHF clinical trials with decongestion end points, novel strategies to improve decongestion using current medical therapies and the increasing range of decongestion devices, including the underpinning pathological mechanisms that are targeted by these devices and practical considerations for their implementation.

End points in ADHF trials

Clinical trials with decongestion end points that are designed to test novel medical and device therapies for patients with ADHF present several challenges that are important in both trial design and result interpretation. Specifically, challenges include defining decongestion, the duration of intervention, inter-rater variation in congestion assessment, heterogeneity in the degree of volume overload between patients, participant selection criteria, inaccurate measures of diuretic response, and interpretation of changes in kidney function. Some of these challenges are discussed further below.

Defining decongestion

Defining and assessing congestion as an end point is much more complex than cardiovascular end points such as mortality or hospitalization. Volume assessment integrates multiple congestion measurements (such as signs, symptoms, laboratory measures, imaging and haemodynamic measurements), which often have limited internal agreement, into a fairly qualitative opinion on congestion status[4,10,22,23]. This process can lead to substantial variation both between clinicians and compared with 'gold-standard' assessments[24–27]. Importantly, no gold-standard assessment exists for volume status because it is multidimensional, volume goals can require individualization, and congestion can exist in one domain but not in another (such as pulmonary oedema or elevated filling pressures in the absence of oedema in the interstitial compartment). Possibly as a result of these complexities, targeting a single decongestion measurement, such as invasive haemodynamic

parameters or plasma levels of natriuretic peptides, has not demonstrated superiority over standard clinical evaluation[28,29]. Therefore, no one measure of congestion outperforms an aggregate clinical assessment. Despite these difficulties, objectively defining congestion at baseline and serially over time is crucial for clinical trials of decongestion strategies. Consequently, several expert consensus groups have designed assessments of congestion[22,30,31]. Each proposed congestion grading system includes multiple measures such as physical examination, laboratory values, imaging, symptoms and haemodynamic variables. However, the cited recommendations contain as many differences as similarities between assessments, and none has undergone prospective validation. No clear consensus exists on the preferred assessment of congestion. Given that congestion is multidimensional and many drugs and devices target different aspects of congestion, a unified definition of congestion might not be appropriate across all drugs and devices.

The differences in the congestion measures included and the numerical weighting assigned to signs and symptoms in congestion assessments used in different studies might have important implications for interpretation and prognosis. The definitions of congestion used in the DOSE[32] and CARRESS-HF[33] trials included orthopnoea and jugular venous pressure. The decongestion end point used in the ADVOR trial[34] focused entirely on extravascular measures of congestion (oedema, pleural effusion and ascites) and did not include jugular venous pressure or signs and symptoms of pulmonary congestion. After 72 h, 42% of patients in the ADVOR trial achieved decongestion compared with only 18% of patients in the high-dose group of the DOSE trial, despite substantially more urine output by patients in the DOSE trial[32,34]. These differences are unlikely to be a reflection of the intervention but are more likely to be attributable to factors such as the amount of congestion present at baseline in the participants, the different patient populations and differences in congestion assessment. In summary, the congestion end points in clinical trials of patients with ADHF require careful interpretation and direct comparison between trials with different definitions and different inclusion and exclusion criteria might not be possible.

Duration of intervention

Historically, clinical trials of decongestion therapies have been conducted for a fairly short duration (such as 3 days) despite heterogeneity in the amount of hypervolaemia between patients, with a sizable proportion of patients requiring intravenous diuretic therapy for residual congestion after the end of the intervention period[32,34–37]. This situation provides the opportunity for the control group to 'catch up' with the intervention group in the subsequent days before discharge from hospital and might partly explain the lack of significant differences in many trials of decongestion in terms of length of hospital stay, decongestion status at discharge from hospital or post-discharge outcomes[32,34,36,37]. Therefore, researchers conducting trials with decongestion end points should strongly consider continuing the therapy until clinical decongestion is complete, rather than for a fixed time, to understand the true therapeutic value of the investigational approach.

Measures of diuretic response

Diuretic response is commonly used to measure the efficacy of a decongestion therapy, particularly with indirect devices designed to augment the diuretic response[38–42]. Changes in urine output relative to an earlier control period can be confounded by changes in diuretic dose, neurohormonal changes, and adaptations to the earlier diuretic period causing substantial variation in diuretic response over time, or simply by bed rest. In a trial of diuretic response in which patients were randomly assigned to simulated activities of daily living (intermittent sitting and slow walking) or supine recumbency (bed rest) for 90 min, bed rest significantly increased urine volume by 162% and natriuresis by 178%[43]. Therefore, increases in diuretic response or reductions in filling pressures in single-group, uncontrolled studies must be interpreted with caution. The Cancion system (Orqis Medical) provides a cautionary example. Early non-randomized studies of the Cancion system reported improved pulmonary capillary wedge pressure and kidney function compared with measurements taken before implantation, similar to the data available for many emerging devices[44]. However, a subsequent large, randomized controlled trial was stopped early because of an inability to demonstrate a benefit of the Cancion system on pulmonary capillary wedge pressure, decongestion end points or serum creatinine levels in the setting of excess adverse bleeding events in the device group[44,45].

Changes in kidney function

The interpretation of changes in kidney function in patients with ADHF is complex[46]. Approximately 20% of patients with ADHF have substantial improvement in kidney function during decongestion, which is paradoxically associated with increased risks of rehospitalization and death[47–49]. Given that, by definition, an improvement in organ function cannot be the cause of the worsened outcomes, this finding illustrates the fallacy of concluding from association studies that worsening renal function is causal for worsened outcomes. The finding also emphasizes the problem of reducing the assessment of kidney function during decongestion therapy to one measure (change in serum creatinine level) that is confounded by numerous variables. Importantly, in the setting of positive therapeutic interventions that achieve decongestion or optimize GDMT, worsening renal function is associated with neutral or improved survival[16,50–52]. As a result, small improvements or worsening of serum creatinine levels cannot be assumed either to result from the intervention or to be an indicator of therapeutic success or failure. Therefore, change in kidney function is not an appropriate measure of efficacy in trials of decongestion therapies.

Considering these complexities, clinical trialists of decongestion devices and strategies in patients with ADHF should, when feasible, consider continuing the intervention until intravenous diuretic therapy for decongestion is completed rather than for a fixed duration of the investigational therapy; ensure that diuretic response and congestion are measured objectively and that control therapies have similar exposures that modify diuretic response such as bed rest; use substantial deterioration in kidney function (that is, a doubling of serum creatinine level or the need for renal replacement therapy) as a safety criterion and not as an efficacy measure; and, ideally, power for and incorporate hard clinical outcomes as primary end points to determine whether decongestion with the intervention improves outcomes after discharge from hospital. The final point is crucial for higher-risk devices because multiple trials of decongestion therapies have improved diuresis or congestion, with no improvement in post-discharge outcomes[32,34,36,37]. Although patients with ADHF require decongestion regardless of the effect on post-discharge outcomes, how decongestion therapies are prioritized will depend on their capacity to improve hard clinical outcomes. The substantially increased cost, resource use and rate of complications associated with invasive devices need to be justified by improved longer-term clinical outcomes and not simply by decongestion-based outcomes (Box 1).

Box 1 | Optimizing decongestion in acute decompensated heart failure

Emerging medical and device strategies can be implemented to improve decongestion in acute decompensated heart failure.

- Use a standardized assessment of congestion that is translatable across clinical trials and hospitals.
- Set a specific, objective decongestion target (for example, a net negative target for urine or sodium output) for the next 12–24 h to guide the initial diuretic strategy and further diuretic titrations.
- Rapid titration of diuretics and addition of combination diuretic therapies as needed to meet decongestion targets.
- Strategies that improve the monitoring and titration of existing diuretic therapies have the lowest barriers to implementation and should be integrated into the electronic health record.
- Patients who are refractory to these less invasive and less resource-intensive strategies could be candidates for invasive devices to improve decongestion if future randomized controlled trials demonstrate efficacy and safety.

Optimization of existing medical therapy

The existing diuretic armamentarium consists of numerous, inexpensive therapies with generally additive natriuretic efficacy (Fig. 1). Natriuresis is an important metric for decongestion therapies because sodium is the pathophysiological mediator of congestion, and natriuresis is an independent prognostic risk factor for in-hospital and post-discharge outcomes in patients with ADHF[53–56]. The major clinical trials of medical therapies for ADHF with decongestion primary outcomes that have informed the use of diuretics are summarized in Table 1.

Loop diuretics

Intravenous loop diuretics are recommended by international guidelines as the first-line therapy to treat congestion in patients with ADHF via diuresis and natriuresis[4,5,7]. Despite decades of experience, clinical questions about the optimal use of loop diuretics remain[13]. Of these questions, the issue of loop diuretic escalation to overcome diuretic resistance is perhaps the most important. The dose–response curve for loop diuretics has a sigmoidal shape for sodium excretion along a logarithmic scale of diuretic concentration, which is shifted rightwards and downwards in patients with ADHF[13]. Diuretic resistance is the manifestation of this rightwards shift in most patients with ADHF, especially with chronic use of loop diuretics and clinically significant kidney disease[13,57,58]. To illustrate, intravenous administration of 40 mg of furosemide to a healthy volunteer saturates the sodium–potassium–chloride cotransporter (NKCC2), increasing sodium exit from the loop of Henle by 20–25% and producing a natriuresis of ~20% of filtered load, measured as the fractional excretion of sodium[59,60]. However, in patients with heart failure, a median intravenous dose of furosemide of 160 mg (interquartile range 40–270 mg), a dose that is commonly thought to achieve the maximal effect of the drug, increased sodium exit from the loop of Henle by only 12.6 ± 10.8%[61]. This cause of diuretic resistance can be partially mitigated by administering higher doses of the loop diuretic to achieve a therapeutic concentration on the shifted dose–response curve. Sequential titration of the diuretic up to very high doses (such as 500 mg of intravenous furosemide equivalents) linearly and significantly increased the peak fractional excretion of sodium in patients with ADHF[57]. In addition to increasing the peak natriuresis, larger doses of diuretic increase the time during which the levels of diuretic exceed the therapeutic threshold, thereby also increasing the total natriuresis and diuresis. When a therapeutic intravenous dose of a loop diuretic is identified, the dose should be administered with a frequency to achieve the target amount of decongestion for the day. Patients with ADHF who do not have diuretic resistance can have a substantial spontaneous natriuresis during the 'off-diuretic' periods, contributing meaningfully to the total daily natriuresis[62]. By contrast, post-diuretic sodium excretion during the off-diuretic period is often minimal in patients with diuretic resistance[56,62]. Therefore, these patients require more frequent bolus dosing of the loop diuretic (for example, every 6–8 h) or high-dose continuous intravenous infusion of the loop diuretic to achieve a net negative daily sodium balance because natriuresis primarily occurs when therapeutic levels of the drug are present in these patients.

SGLT2 inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors should be initiated early during hospitalization for ADHF or continued during hospitalization if already prescribed[63]. SGLT2 inhibitors are GDMT across the ejection fraction spectrum and are safe in both hospitalized and ambulatory patients[5,7,64]. In patients with ADHF, SGLT2 inhibitors augment the response to intravenous diuretic[64]. SGLT2 inhibitors induce modest natriuresis by inhibiting SGLT2 and by reducing transport through the sodium–hydrogen exchanger 3 (NHE3), which is the transport pathway responsible for a large proportion of tubular sodium reabsorption[65–67]. Therefore, SGLT2 inhibitors have the dual benefits of acutely augmenting decongestion when given in combination with intravenous loop diuretics and optimizing long-term GDMT, reducing morbidity and mortality as early as 30 days after discharge from hospital[5,7,63,64,68] (Table 1). In addition, SGLT2 inhibitors can minimize the adverse effects of loop diuretics by lowering plasma uric acid levels and preventing kidney magnesium and potassium wasting during loop diuretic therapy[67,69,70]. In patients with euvolaemia, the immediate natriuretic effect of SGLT2 inhibitors rapidly diminishes owing to compensatory sodium reabsorption in the distal tubules, which prevents lethal hypovolaemia from natriuresis and reconciles the short-term diuretic benefit of the drugs with their excellent safety profile in patients with chronic heart failure[67].

Acetazolamide

In the ADVOR trial[34], empirically combining acetazolamide (a carbonic anhydrase inhibitor) with low-to-moderate dose intravenous loop diuretics improved the primary end point of the decongestion score and resulted in an additional ~500 ml of urine output and ~100 mmol natriuresis over 2 days compared with loop diuretic monotherapy. However, no significant improvement occurred in the outcomes of rehospitalization or death (Table 1). Importantly, use of an SGLT2 inhibitor was an exclusion criterion in the ADVOR trial, leaving the unanswered question of whether acetazolamide use improves diuretic efficacy when added to SGLT2 inhibitor therapy given that the therapies have a shared mechanism of action of inhibiting NHE3 transport in the proximal tubule[34,71]. Early data suggest that the combination of acetazolamide and SGLT2 inhibitor therapy might not produce a synergistic diuretic response[72]. Therefore, in patients already receiving SGLT2 inhibitor therapy, the diuretic efficacy of acetazolamide might be attenuated. However, acetazolamide is likely to be more effective than SGLT2 inhibitors in preventing and correcting metabolic alkalosis by inhibiting carbonic anhydrase

throughout the nephron, minimizing chloride loss and suppressing renal ammoniagenesis[73,74].

Thiazide and thiazide-like diuretics

On a population level, natriuresis in response to high-dose loop diuretics seems to be primarily determined by compensatory reabsorption in the distal nephron[61,75]. The specific tubular sodium-transport pathways underpinning this compensatory reabsorption have not been definitively established. The sodium–chloride cotransporter (NCC) has been implicated as the primary contributor, and studies in rodents confirm that chronic exposure to loop diuretics increases the quantity and activity of NCC[76–78]. However, most thiazides interact with multiple sodium-transport pathways, with evidence of effects on carbonic anhydrase, pendrin and the sodium-dependent chloride–bicarbonate exchanger, prohibiting conclusions about the relative importance of any one resorption pathway[76,79].

Regardless of the pathways inhibited, thiazides (and thiazide-like diuretics) have been recommended as the first agent to add during resistance to intravenous loop diuretic therapy[5,7,63]. In combination with loop diuretics, thiazides, on average, increase the diuretic response to a greater degree than either acetazolamide or SGLT2 inhibitors[72,80]. In the CLOROTIC trial[37], the up-front addition of low-dose hydrochlorothiazide to intravenous loop diuretics increased the diuretic response compared with loop diuretic monotherapy. However, hydrochlorothiazide also increased the risk of hypokalaemia and worsening renal function and had a non-significant trend towards increased rates of rehospitalization and death[37] (Table 1). Of note, in observational studies, the early addition of a thiazide diuretic to loop diuretic therapy was associated with worsened outcomes, including an increased rate of death[81]. Therefore, out of all the diuretic adjuvants that can be used in combination with loop diuretics, thiazides are likely to achieve the greatest augmentation in diuresis but frequent monitoring is required because of the greater risk of adverse events.

Mineralocorticoid receptor antagonists

The epithelial sodium channel (ENaC) is a major channel for sodium reabsorption in the principal cells of the connecting tubules and collecting ducts[82]. Aldosterone activates ENaC and increases sodium reabsorption[82]. Transport through ENaC can be reduced by mineralocorticoid receptor antagonists or direct ENaC antagonists (such as amiloride or triamterene). Low-dose treatment with a mineralocorticoid receptor antagonist (spironolactone or eplerenone at target doses of 25–50 mg daily) is GDMT to reduce the risk of morbidity and death in patients with heart failure and probably has a negligible acute diuretic effect[5,7,83]. Even moderate doses (such as 100 mg of spironolactone daily) do not increase the diuretic response in patients with ADHF, but this lack of a response might be due to inadequate dosing[83,84] (Table 1). If spironolactone therapy is intended to augment the diuretic response, a loading dose of 300–400 mg per day and a high daily dose of ~200 mg per day might initially be needed to rapidly achieve therapeutic concentrations of the active metabolites[85].

Vasopressin receptor antagonists

Vasopressin receptor antagonists have not consistently improved outcomes across the multitude of ADHF trials to date and are therefore not recommended for routine use[5,7,22]. Despite a lack of observable benefit in relatively unselected populations of patients with ADHF, vasopressin receptor antagonists are theoretically useful in specific populations. Vasopressin is the prototype regulator of NKCC2 and stimulates increased sodium reabsorption in the loop of Henle. In addition to increasing water clearance, vasopressin receptor antagonists could theoretically improve diuretic and natriuretic response when

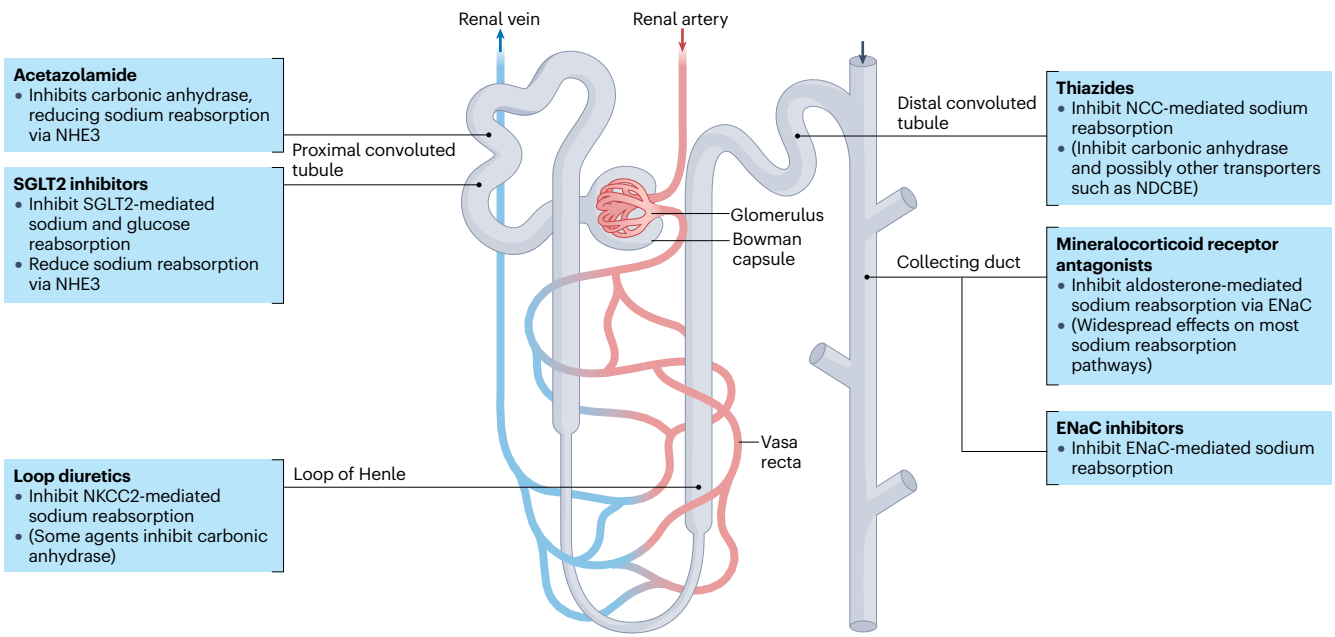

Fig. 1 | Natriuretic therapies and the nephron. The figure shows the primary sites of action of natriuretic therapies in the nephron[67,79,157–159]. Potential secondary mechanisms of action at doses used in the treatment of acute decompensated heart failure are listed in brackets. ENaC, epithelial sodium channel; NCC, sodium–chloride cotransporter; NDCBE, sodium-dependent chloride–bicarbonate exchanger; NHE3, sodium–hydrogen exchanger 3; NKCC2, sodium–potassium–chloride cotransporter; SGLT2, sodium–glucose cotransporter 2.

Table 1 | Major clinical trials of medical therapies in ADHF with primary decongestion outcomes

Trial	Design (number of patients)	Therapies	Initial intravenous furosemide bolus dose[a]	Primary efficacy outcomes	Primary safety outcomes	Key lessons learned	Knowledge gaps
Loop diuretic strategies							
DOSE[32]	Double-blind RCT with two-by-two factorial design for 72 h (308)	Loop diuretics as: (1) bolus versus continuous infusion; (2) 2.5 times (high) versus 1 time (low) the previous oral diuretic dose	Low dose: ~65 mg; high dose: ~164 mg	No significant difference in patient symptoms at 72 h	No significant difference in mean change in SCr at 72 h	Intravenous, high-dose loop diuretics improved objective diuresis measures, with transient mild worsening of renal function	Excluded home diuretic dose >240 mg of furosemide
Diuretic monitoring and titration strategies							
ENACT[113]	Pragmatic, open-label, non-randomized trial for 24 h (401)	2 h UOP-guided (>100 ml/h) or UNa-guided (>50 mmol/l) diuresis versus usual care	Standard of care: 60 mg (40–80 mg); intervention: 120 mg (80–200 mg)	Increased 24-h cumulative natriuresis	No significant difference in renal safety end points	Proof-of-concept UOP-guided or UNa-guided diuresis increases intravenous dose of loop diuretic and cumulative natriuresis	Numerous, given the methodological limitations and duration
PUSH-AHF[36]	Pragmatic, open-label RCT for 48 h (310)	Natriuresis-guided diuresis (UNa >70 mmol/l) versus usual care	Standard of care: 80 mg (40–160 mg); intervention: 80 mg (40–160 mg)	Natriuresis-guided diuresis increased 24-h natriuresis but not 180-day risk of heart failure rehospitalization or death	No significant difference in renal safety end points	Natriuresis-guided strategy increases intravenous dose of loop diuretic and cumulative natriuresis	Can natriuresis-guided therapy until euvolaemia reduce length of hospital stay and improve post-discharge outcomes?
Combination diuretic therapies							
ADVOR[34]	Double-blind RCT for 72 h (519)	Acetazolamide 500 mg per day versus placebo, with background intravenous diuretics	Placebo: 120 mg (80–200 mg); acetazolamide: 120 mg (80–200 mg)	Acetazolamide improved successful decongestion (measured via a congestion score)	No significant difference in renal safety end points	Acetazolamide improved decongestion but only modestly increased diuresis and natriuresis	What is the role of acetazolamide in patients receiving SGLT2 inhibitors, given their similar site of action?
ATHENA-HF[84]	Double-blind RCT for 96 h (360)	Spironolactone 100 mg per day versus placebo (74% of patients) or spironolactone ≤25 mg (26% of patients), with background intravenous diuretics	Usual care: 160 mg (120–320 mg) total daily dose; intervention: 160 mg (100–320 mg)	Higher-dose spironolactone did not improve natriuretic peptide concentration nor diuresis measures	No significant difference in renal safety or hyperkalaemia events	Spironolactone 100 mg per day did not increase decongestion or diuresis	Could higher or loading doses acutely augment diuresis, given the long half-life of active metabolites?
CARRESS-HF[35]	Open-label RCT for 96 h (188)	UOP-guided, stepped, combined diuretic therapy (predominantly with intravenous loop diuretic and metolazone (46% of patients)) versus ultrafiltration (200 ml/h)	Not applicable (intravenous diuretic administered as continuous infusion)	No significant difference in body weight loss at 96 h	Lower mean change in SCr at 96 h with combined diuretic therapy than with ultrafiltration	UOP-guided combined diuretic therapy strategy provided similar decongestion and fewer serious adverse events than ultrafiltration	What are the benefits and risks of combined diuretic therapy until euvolaemia, given that <10% of patients were decongested at 96 h?
CLOROTIC[37]	Double-blind RCT for 72 h (230)	Hydrochlorothiazide 25–100 mg per day (~70% of patients 50 mg per day) versus placebo, with background intravenous diuretics	Placebo: 40 mg (40–60 mg); hydrochlorothiazide: 40 mg (40–60 mg)	Hydrochlorothiazide increased 72-h body weight loss but not patient-reported dyspnoea scores	Hydrochlorothiazide was associated with significantly higher rates of worsening renal function and hypokalaemia	Hydrochlorothiazide improved diuresis and decongestion but increased risk of renal and hypokalaemia events	At what intravenous dose of loop diuretic do the benefits of combined therapy with thiazides outweigh the risks?
DICTATE-AHF[64]	Open-label RCT for 5 days (240)	Dapagliflozin 10 mg per day versus usual care with protocolized intravenous diuretic titration	Usual care: 80 mg (80–120 mg); dapagliflozin: 80 mg (40–160 mg)	Dapagliflozin did not significantly improve body weight loss	No significant difference in renal safety or adverse events	Early SGLT2 inhibitor initiation safely increases diuresis, optimizes guideline-directed medical therapy and expedites hospital discharge	What are the magnitude and duration of the acute benefit of diuretic therapy before renal compensation?

Clinical trials with >100 patients were included. ADHF, acute decompensated heart failure; RCT, randomized clinical trial; SCr, serum creatinine level; SGLT2, sodium–glucose cotransporter 2; UNa, urine sodium concentration; UOP, urine output. [a]Initial intravenous bolus dose of loop diuretic in furosemide equivalents (1 mg of intravenous bumetanide is equivalent to 40 mg of intravenous furosemide). The total daily dose is noted if information on the initial bolus dose was not available.

added to intravenous loop diuretics in patients resistant to diuretics[86]. Furthermore, some of the failures of tolvaptan (a selective vasopressin V_2 receptor antagonist) to improve outcomes have been hypothesized to be related to unopposed vasopressin V_1 receptor stimulation. Therefore, dual antagonists of the vasopressin V_1 and V_2 receptors could be superior to selective V_2 receptor antagonists such as tolvaptan. Further research into vasopressin receptor antagonism is needed.

Salt supplementation

The simplistic paradigm in patients with ADHF is to increase natriuresis (increase sodium output) while restricting salt intake (decrease sodium input), which arithmetically should produce a net negative sodium balance. In this paradigm, sodium input and output are assumed to be independent (reducing sodium intake is assumed not to reduce natriuresis). However, several clinical trials have disproven this simplistic paradigm. A randomized trial of intensive sodium restriction (800 mg per day) versus liberal dietary salt intake (~3–5 g per day) during ADHF reported no significant differences in decongestion outcomes, duration of intravenous diuresis or post-discharge outcomes, despite nearly identical diuretic dosing in the two groups[87]. Deliberate sodium chloride augmentation during intravenous diuresis has been investigated in various randomized trials[88–91]. Oral sodium chloride loading in the OSPREY trial[91] did not significantly change any decongestion efficacy or safety outcomes. Serial dosing of hypertonic saline during intravenous diuresis has been observed to improve diuresis, urinary sodium excretion, weight loss, serum creatinine concentration and serum sodium concentration[88,92]. Collectively, the available evidence indicates that salt administration during ADHF has incompletely understood benefits[93]. A benefit is implicit even in a neutral study because some positive effect of salt administration is implied to offset the arithmetic negative effect of increased sodium intake. In healthy control individuals, a positive relationship exists between sodium intake and sodium excretion by the kidneys that is relatively retained in patients with heart failure[90,94,95]. The kidneys continue to sense salt and increase natriuresis and diuretic response accordingly. Importantly, the kidneys sense salt primarily through chloride, with chloride driving parameters such as renin secretion, tubuloglomerular feedback and the regulation of multiple ion transporters via WNK serine–threonine kinases[96–100]. Hypochloraemia is independently associated with worse diuretic response and less decongestion in trials of patients with ADHF, even after correction for serum sodium concentration[101–103]. The observed benefits of sodium chloride administration might plausibly be mediated through the beneficial effects of chloride in suppressing sodium avidity and decreasing neurohormonal activity. Additional research is needed to understand the population of patients with ADHF who might benefit from salt administration during ADHF and the mechanisms that might underlie the potential benefit[93].

Escalation of diuretic therapy

Integrating all the trials on diuretic medical therapy to produce an evidence-based algorithm for escalation of diuretic therapy with applicability to all patients with ADHF is unfortunately not possible. However, we propose a general approach based on the available trial, observational and physiological data (Fig. 2). This proposed approach to the escalation of diuretic therapy can be used to treat most patients with ADHF and could provide a template for structured standard care in the control groups of clinical trials of novel device or medical strategies in patients with ADHF. The first step to diuretic monitoring is performing a standardized congestion assessment and setting a daily

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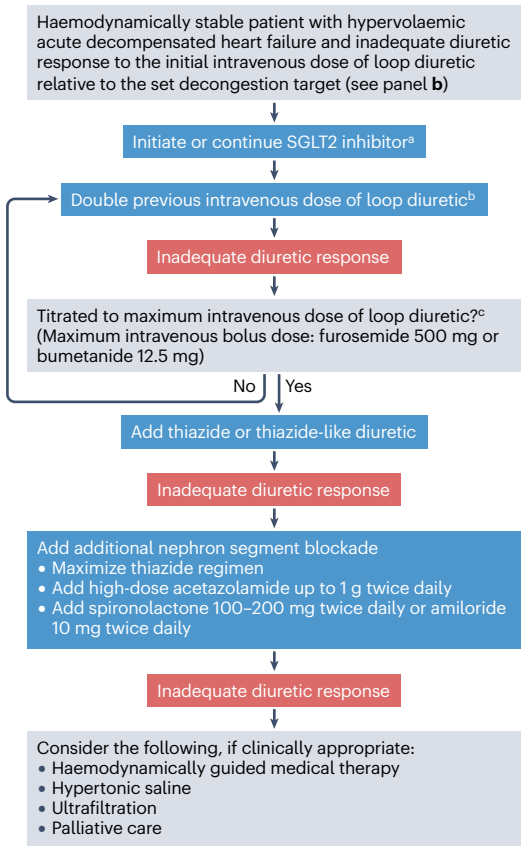

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Volume assessment	Target net negative input–output balance	Target NRPE-calculated natriuresis for 2 g (87 mmol) per day sodium diet[d]
Mild hypervolaemia	Negative 1.0–2.0 l per day	150 mmol sodium per day
Moderate hypervolaemia	Negative 2.0–3.5 l per day	250 mmol sodium per day
Severe hypervolaemia	Negative 3.5–5.0 l per day	350 mmol sodium per day

Fig. 2 | Diuretic therapy escalation algorithm. a, The flowchart shows an algorithm for escalation of diuretic therapy. The maximum daily dose of loop diuretic might be the equivalent to an intravenous furosemide dose of 1,500–2,000 mg per day, based on expert opinion, although some centres have experience with higher daily doses. Intravenous bolus doses >240 mg of loop diuretics should be infused slowly (over a minimum of 1 h) to minimize the risk of ototoxicity. In most patients, an inadequate diuretic response measured 2 h after the diuretic dose could be defined as a urine output <500 ml, a urine sodium concentration <70 mmol/l or cumulative natriuresis <40% of the daily target calculated using the natriuretic response prediction equation (NRPE). **b**, Individualized daily decongestion targets. [a]Up-front administration of acetazolamide before administration of a sodium–glucose cotransporter 2 (SGLT2) inhibitor could be considered if SGLT2 inhibitors are contraindicated or if hypercarbic alkalosis is present. [b]If clinically significant hypokalaemia is present or the patient is at risk of clinically significant hypokalaemia, consider the addition of high-dose mineralocorticoid receptor antagonist therapy to reduce urinary potassium loss. [c]The intravenous bolus dose of loop diuretic that should be achieved before adding a thiazide is unknown but an intravenous dose of 240–500 mg of furosemide is reasonable. [d]Target natriuresis must be adjusted for dietary sodium intake; for each gram of added sodium intake, increase the natriuresis target by 43 mmol.

decongestion target[4,30]. Daily decongestion targets require individualization but, in Fig. 2, we summarize decongestion targets adapted from clinical trials of patients with ADHF[33,104]. The initial intravenous dose of loop diuretic should be guided by the home oral diuretic regimen (~2.5 times the oral dose or 80 mg furosemide equivalents in diuretic-naive patients)[22]. Monitoring of the diuretic response relative to the decongestion target quickly identifies diuretic resistance. On a population level, diuretic resistance is predominantly an intrinsic problem of poor response of the nephrons to diuretics[58,61]. As a result, most patients can achieve an adequate diuretic response with escalation of diuretic therapy. Non-responders should first have the intravenous loop diuretic therapy maximized, titrating by doubling the previous dose. Simultaneously, all patients without absolute contraindications should start receiving an SGLT2 inhibitor as early as possible, even if long-term therapy is not logistically feasible. When using acetazolamide to augment the loop diuretic effect, it should ideally be used early as tested in the ADVOR trial[73] and because early initiation of acetazolamide might prevent the development of diuretic resistance. Although a strategy of early combination therapy with both loop and thiazide diuretics might increase treatment efficacy, the safety profile of combination therapy seems to be unfavourable, with trial and observational data suggesting a signal for worse post-discharge outcomes compared with the use of high-dose monotherapy with a loop diuretic[32,37,81]. The reduced survival associated with combination therapy with loop and thiazide diuretics during ADHF was not observed in patients receiving higher intravenous doses of a loop diuretic[81]. The peak intravenous dose of a loop diuretic that should be given before adding a thiazide diuretic is unknown, but observational evidence indicates that a dose equivalent to an intravenous bolus dose of 240–500 mg of furosemide can be safely targeted[13,57]. Intravenous doses of loop diuretic should be administered two to three times or more daily. After reaching a maximal dose of the loop diuretic plus SGLT2 inhibitor therapy, a thiazide diuretic should be added. Most thiazide diuretics seem to have equal efficacy at equipotent doses, without evidence for the superiority for one agent, even in patients with a low estimated glomerular filtration rate[78,86]. If an adequate diuretic response is still not achieved, expert opinion and limited data indicate that multi-segment nephron blockade by adding agents such as acetazolamide, a high dose of a mineralocorticoid receptor antagonist and amiloride can increase the diuretic response[105].

Decongestion therapy monitoring strategies

Even the most effective diuretic strategy is dependent on accurate and timely monitoring data for successful titration. The approach to monitoring of the diuretic response has not changed for decades. Both standard-of-care clinical practice and protocols in clinical trials on ADHF rely primarily on body weight, urine output and net input–output calculations to quantify diuretic response[13,22,35,37,63]. Agreement between change in body weight and net input–output is poor, even in the setting of rigorous clinical trials. Generally, the coefficient of determination (r^2) is <25%, indicating that there is >75% disagreement between these metrics, which should agree perfectly[11,106]. Additionally, body weight and net input–output measurements are commonly performed or documented only every 8–24 h, producing substantial delays in therapy titration. Even if precisely and frequently measured, these metrics are focused on water balance. However, sodium accumulation is the primary inciting pathophysiology of extracellular volume expansion[107]. Sodium balance is crucial because individuals with ADHF show wide interpatient variation in the sodium content of the urine[36,54–56]. Low spot urine sodium concentrations after the first intravenous dose of loop diuretic are associated with worse prognoses, including worsening kidney function, worsening heart failure and higher mortality[53,55,108–112]. Furthermore, a positive sodium balance is still associated with more than a twofold increased risk of death, even in patients with a net negative fluid balance[54].

Urinary sodium concentration

Natriuresis-based, quantitative diuretic response metrics overcome many of the practical and physiological limitations of measures based on urine volume and body weight. Measuring cumulative natriuresis is subject to the same practical limitations, but a spot urine sample timed 1–2 h after an intravenous dose of a loop diuretic to measure natriuresis is recommended in patients with ADHF[22,63]. A urine sodium concentration <50 mmol/l is clearly an inadequate diuretic response, but consensus is lacking on a urine sodium concentration that indicates a good diuretic response[22,63]. The multicentre, open-label, non-randomized ENACT-HF trial[113] targeted a urine sodium concentration >50 mmol/l and a urine output >100 ml/h at 2 h after an intravenous dose of loop diuretic in the intervention group compared with usual care. The primary outcome (24-h natriuresis) was significantly greater in the intervention group, which received significantly higher intravenous doses of diuretic. Interpretation of the urine sodium target is difficult because more patients were titrated owing to a low urine output than due to a low urine sodium concentration. The single-centre, open-label, randomized PUSH-AHF trial[36] targeted a urine sodium concentration >70 mmol/l after each intravenous dose of diuretic for the first 48 h of hospitalization for ADHF. Patients in the natriuresis-guided group had significantly greater mean total natriuresis at 24 h and 48 h and received significantly higher intravenous doses of diuretic. The smaller, ongoing DECONGEST trial[114] is targeting a urine sodium concentration ≥80 mmol/l. Importantly, although low urine sodium concentration thresholds, such as 50 mmol/l, are highly specific for a poor diuretic response, a urine sodium concentration >50 mmol/l is common among diuretic non-responders. Of note, ~55% of patients with ADHF have a urine sodium concentration >50 mmol/l before administration of a diuretic[115]. Concentrated urine can have a high sodium concentration despite a low sodium output due to the low volume of the urine. As the threshold of urine sodium concentration value is increased, the number of correctly identified non-responders increases but sensitivity and specificity decrease. Collectively, clinical trials demonstrate that patients with a poor diuretic response can increase natriuresis to target levels with escalation of the intravenous dose of diuretic. However, the urine sodium concentration that should be targeted to achieve a net negative sodium balance in most patients remains unresolved.

Natriuretic response prediction equation

The natriuretic response prediction equation (NRPE) was derived to overcome the limitations of measuring the urine sodium concentration[57,116]. Using urine sodium and urine creatinine concentrations, the NRPE estimates the cumulative urine sodium output from each diuretic dose, allowing diuretic titration to achieve a net negative sodium balance based on the prescribed dietary sodium intake. This calculation is achieved by incorporating the urine creatinine concentration, which addresses the bias that can occur with a low volume of concentrated urine and has improved the performance of urine sodium measurements to predict natriuresis, either in the NRPE or as a ratio[57,117]. The NRPE has been validated against measured 6-h cumulative sodium excretion, demonstrating excellent discrimination across the range of natriuretic responses (area under the curve ≥0.90)[57,116]. The NRPE has

been integrated into a nurse-driven titration protocol (the Yale diuretic pathway) and, in a pre–post design study, resulted in rapid escalation of diuretic therapy, improved fluid and weight loss, and had an overall excellent safety profile[57]. However, whether escalation of diuretic therapy to increase natriuresis in patients with diuretic resistance achieves the clinical benefits associated with a net negative sodium balance in observational cohorts of patients with ADHF is unknown. The ongoing, multicentre, randomized, double-blind ESCALATE trial[104] is testing the hypothesis that NRPE-based diuretic titration until euvolaemia to achieve a net negative sodium balance will improve clinical outcomes compared with structured usual care.

Decongestion device therapies

Various device therapies are being developed to address the problem of incomplete decongestion during ADHF[18] (Table 2). Decongestion devices can be broadly categorized as being indirect or direct devices. Indirect devices have no direct mechanism to remove salt and water. Instead, indirect devices are intended to correct a hypothesized pathophysiology that is driving cardiorenal syndrome and/or diuretic resistance, anticipating that improved cardiorenal parameters will improve the response to background standard-of-care diuretic therapy (Fig. 3a). By contrast, direct devices target salt and water removal directly, although many of these devices also indirectly affect the underlying cardiorenal pathophysiology. Mechanisms such as veno-venous ultrafiltration, peritoneal ultrafiltration, lymph removal, excess perspiration and automated diuretic dosing are targeted by direct devices (Fig. 3b).

Indirect devices

Indirect devices seek to improve the diuretic response and, consequently, decongestion by mechanisms such as reducing renal venous pressure, selectively increasing renal arterial pressure, improving lymphatic recirculation or providing negative pressure to the renal collecting system (Table 2). Whether any of these mechanisms are relevant in human heart failure is much debated, and the myriad of different mechanisms targeted reinforces the lack of consensus. On a population level, diuretic resistance is probably not mediated by any one haemodynamic derangement, which explains why studies evaluating haemodynamic parameters and diuretic response have found minimal associations[118–124]. On a population level, the final common pathway of diuretic resistance in mechanistic studies is an adaptive state of increased sodium avidity in the kidney tubules and is not a problem of cardiac haemodynamics[13,56,58,62,75,124].

In addition to mechanistic observations, randomized clinical trials of medical therapies that improve the same haemodynamic parameters as those targeted by the many indirect devices have universally shown no significant improvement in decongestion. Vasodilators such as nesiritide, serelaxin and ularitide substantially reduce venous pressure but do not meaningfully improve decongestion or diuretic response[118,120,121,125,126]. In a rigorous mechanistic study, the vasodilator cimlanod substantially improved cardiac output but diuretic response and kidney function worsened significantly[127]. Positive inotropes improve cardiac output but are not associated with meaningfully improved decongestion or diuretic response[118,119]. However, medical therapies targeting haemodynamic parameters have other 'off-target' systemic effects (for example, nesiritide lowers venous pressure but also arterial pressure) that might theoretically attenuate the beneficial effects.

'Selective' indirect devices are hypothesized to avoid these off-target effects, but this assumption might be overly simplistic because manipulating one aspect of the cardiovascular system without altering it systemically is very difficult. Devices that lower renal venous pressure also reduce cardiac preload and therefore might lower cardiac output and blood pressure. Devices that raise renal arterial pressure also reduce proximal aortic pressures, thereby unloading arterial baroreceptors, which might worsen kidney sympathetic nerve activity. Devices that improve lymphatic circulation could reduce kidney interstitial pressure, augment preload and consequently cardiac output, but at the expense of worsened central and therefore renal venous pressure. As such, the net effects of these devices might extend beyond the specific candidate mechanism targeted and might not be more selective than their systemically administered pharmacological equivalents.

Indirect arterial devices. Indirect arterial devices locally increase pressure around the renal arteries with the aim of increasing glomerular filtration rate and diuretic response (Table 2). Decreases in mean arterial pressure have been consistently associated with increases in serum creatinine concentration during therapy for ADHF[128–131]. After multivariate adjustment, the relative decrease in blood pressure was still significantly associated with worsening renal function, unlike right atrial pressure and cardiac index[130]. Contrary to the association between change in blood pressure and glomerular filtration rate, no association exists between a reduction in blood pressure and diuretic response[131]. Diuretic response paradoxically improved with a GDMT-induced reduction in blood pressure in an observational series, which might be due to greater neurohormonal antagonism effects offsetting decreases in blood pressure[131]. Although the increase in renal arterial pressure from indirect arterial devices will stimulate kidney baroreceptors, it will also unload the heart and great vessels by decreasing both afterload and filling pressures. Therefore, the net effect on kidney neurohormonal activation could be either improvement or worsening. Indirect arterial devices require careful haemodynamic and neurohormonal mechanistic studies to understand these interconnected complexities between organ systems.

Improving kidney perfusion should be beneficial in patients with ADHF. However, whether these devices can lead to a sustained improvement in kidney perfusion in patients with ADHF has not been proven and basic physiological principles suggest that they might not. First, the kidneys do not behave as a passive vascular circuit, whereby increased pressure passively increases kidney blood flow. As an example of the adaptations to increased kidney perfusion, the mean systolic blood pressure in a patient with ADHF on admission to the hospital is ~140 mmHg but, despite this hypertension, these individuals present with volume overload and often with diuretic resistance and a low estimated glomerular filtration rate[18]. Although a hypertensive ADHF profile is unlikely to be the target population for decongestion devices, this ADHF phenotype provides insight into the compensatory adaptations of the human body. After an initial increase in kidney perfusion with increased blood pressure, the multitude of autoregulatory systems in the kidneys (myogenic autoregulation, glomerulotubular balance and tubuloglomerular feedback) stabilize glomerular filtration, intra-renal solute gradients and sodium excretion, rapidly regulating kidney perfusion back to baseline. Although we know that complete adaptation to these devices is likely to occur in the long term (hypertension is not a disease of volume depletion), the exact kinetics of this adaptation could be debated. No mechanistic studies have investigated renal haemodynamics (true glomerular filtration rate and renal blood flow) in the setting of ADHF. We hypothesize that renal adaptation

Table 2 | Decongestion device therapies in acute decompensated heart failure

Therapy	Mechanism	Therapeutic goal	Access	Device placement	Power source	Systemic anticoagulation?	Diuretics for fluid removal?	Market stage
Indirect arterial devices								
Aortix (Procyrion)	Percutaneous MCS with impeller rotation accelerating blood from the aortic arch to the descending aorta (3.5 l/min) to create a trans-aorta pressure gradient	Decrease afterload and increase renal perfusion	18 F sheath in the femoral artery	Suprarenal descending thoracic aorta	External	Yes	Yes	Investigational
Cancion System (Orqis Medical)	External MCS with a magnetically levitated centrifugal pump that recirculates blood from the iliac artery to the thoracic aorta with continuous, non-pulsatile flow up to 1.5 l/min	Decrease afterload and increase renal perfusion	Inflow: 12 F in the left femoral artery	Inflow: left iliac artery	External	Yes	Yes	Abandoned
			Outflow: 12 F in the right femoral artery	Outflow: descending thoracic aorta at the tracheal carina				
ModulHeart (Puzzle Medical)	Percutaneous MCS with three serial axial flow pumps inserted separately and assembled in the aorta to provide 4 l/min flow	Decrease afterload and increase renal perfusion	22 F sheath in the femoral artery	Suprarenal descending thoracic aorta	External	Yes	Yes	Investigational
Reitan catheter pump (CardioBridge)	Percutaneous MCS with foldable pump head expanded after insertion to accelerate blood via axial flow to the descending aorta to create a trans-aorta pressure gradient (10 mmHg)	Decrease afterload and increase renal perfusion	10 F sheath in the femoral artery	Suprarenal descending thoracic aorta	External	Yes	Yes	Investigational
Second Heart Assist pump (Second Heart Assist)	Percutaneous MCS with self-expanding stent-based impeller pump to provide 4–6 l/min flow and create a trans-aorta pressure gradient (>10 mmHg)	Decrease afterload and increase renal perfusion	14 F sheath in the femoral artery	Suprarenal descending thoracic aorta	External	Yes	Yes	Investigational
Indirect venous devices								
PreCARDIA (PreCARDIA)	Intermittent SVC occlusion with intravascular balloon (cycle 5-min inflation, 0.5-min deflation) reducing venous inflow by ~30% during occlusion	Reduced central venous pressure and renal vein pressure	14 F sheath in the right internal jugular vein	SVC above SVC–right atrium junction	External	Yes	Yes	Investigational
Doraya (Revamp Medical)	Passive renal flow regulation that impedes venous flow (pressure gradient ~6 mmHg) in IVC before renal veins	Reduced renal vein pressure	12 F sheath in the femoral vein	IVC below renal veins	NA (passive)	Yes	Yes	Investigational
Nephronyx Perfuser System (Nephronxy)	Stent-based passive perfuser with an intake nozzle below renal veins that accelerates and entrains venous flow, while a diffuser stabilizes venous pressure reduction	Reduced renal vein pressure	Femoral vein	IVC adjacent to renal veins	NA (passive)	Yes	Yes	Investigational
Transcatheter Renal Venous Decongestion System (Magenta Medical)	Axial flow pump with self-expanding cages above and below renal veins isolates IVC segment with renal veins to decompress renal veins	Reduced renal vein pressure independent of central vein pressure	8F sheath in the femoral vein	IVC adjacent to renal veins	External	Yes	Yes	Investigational

Table 2 (continued) | Decongestion device therapies in acute decompensated heart failure

Therapy	Mechanism	Therapeutic goal	Access	Device placement	Power source	Systemic anticoagulation?	Diuretics for fluid removal?	Market stage
Other indirect devices								
eLym System (WhiteSwell)	Venous catheter isolates the venous section between the left subclavian and innominate vein with two balloons, while a catheter-based pump decompresses venous pressure at the thoracic duct zone to increase lymphatic drainage into the venous system	Reduce venous pressure in the thoracic duct to increase lymphatic system drainage	Catheter in the left internal jugular vein	Thoracic duct outflow at the junction of the left subclavian and jugular veins	External	Yes	Yes	Investigational
JuxtaFlow Uretal decompression (3ive Labs)	Urinary catheter placed in the renal pelvis exerts negative pressure (−30 mmHg) via an external pump to reduce renal hydrostatic pressure	Reduce intra-nephron pressure to increase filtration and solute reabsorption	Urethra by urologist	Renal pelvis of kidney	External	No	Yes	Investigational
Direct devices								
Ultrafiltration	Direct removal of ultrafiltrate (up to 500 ml/h) from the plasma via an extracorporeal pump moving blood across a semipermeable membrane with a transmembrane pressure gradient, then returning blood to the circulation	Continuous removal of isotonic intravascular ultrafiltrate in hospitalized patients	Peripheral venous catheter	Jugular or basilic vein	External	Yes	No	Approved
Reprieve System (Reprieve Cardiovascular)	Automated decongestion management system with continuously titrated intravenous loop diuretics and replacement intravenous fluid to accurately achieve and maintain the programmed net negative fluid or sodium balance	Accurately achieve decongestion targets without over-diuresis or under-diuresis or worsening renal function	Urinary catheter for urine measurement; peripheral intravenous line for fluid administration		NA	No	Yes	Investigational
Peritoneal sodium removal (Sequana Medical)	Direct sodium removal via the peritoneal cavity by instillation of sodium-free peritoneal solution and drainage of high-sodium exudate after dwell time	Intermittent direct sodium removal in excess of fluid in hospitalized or ambulatory patients	Peritoneal catheter	Intraperitoneal catheter	NA	No	No	Investigational
Lymphatic fluid removal (NXT Biomedical)	Direct removal of lymphatic fluid via venous percutaneous access to the lymphatic thoracic duct	Short-term, percutaneous lymphatic drainage and removal in hospitalized patients	Venous access to lymphatic thoracic duct	4 F catheter in the thoracic canal duct	NA	No	No	Investigational
AquaPass (AquaPass Medical)	Wearable suit connected to a low-humidity, warm-air unit that pumps air into the suit to achieve a skin temperature of 36–38°C measured via a temperature sensor, activating the eccrine sweat glands to perspire (~150 ml/h)	Serial, intermittent (1–8 h treatments) decongestion via controlled perspiration	Non-invasive	Non-invasive	External	No	No	Investigational

F, French; IVC, inferior vena cava; MCS, mechanical circulatory support; NA, not applicable; SVC, superior vena cava.

to the increased blood pressure will occur within minutes to hours, leading to minimal efficacy. However, if the kinetics of adaptation are substantially slower than physiology would predict, a substantial issue will occur with a rebound effect of worsening glomerular filtration rate and natriuresis after device withdrawal. Careful study of the effects of these devices is necessary.

Indirect venous devices. Indirect venous devices aim to mitigate the negative effect of elevated renal venous pressure, hypothesizing that improved glomerular filtration and diuretic response will follow (Table 2). In experimental models, isolated congestion of the kidney can worsen glomerular filtration rate and sodium handling[132–134]. Increased venous pressure is often assumed to worsen kidney function directly through a simple hydraulic effect of decreasing kidney perfusion pressure[132]. However, congestion has complex effects on kidney autoregulation, with a paradoxical increase in kidney vascular resistance[135]. Furthermore, inadequately understood physiology in animal models, including factors such as hydration and neurohormonal status, can result in very different kidney responses with a similar degree of congestion[132].

Despite this robust literature in animal models, haemodynamic measures of venous congestion have not been shown to have a relationship with diuretic resistance and have only a weak and inconsistent relationship with glomerular filtration rate in contemporary cohorts of patients with ADHF[123,124,130,136]. The disconnect between animal experiments and observations in humans might stem from differences between selective kidney congestion in experimental models compared with systemic congestion in patients with ADHF. Importantly, congestion of the heart and great vessels results in favourable effects on kidney function and natriuresis, such as the release of natriuretic peptides and the suppression of kidney sympathetic nerve activity. This situation probably explains why, on a population level, only a weak positive relationship exists between higher central venous pressure and better diuretic response[124]. Most indirect venous devices in development use passive partial obstruction of venous flow to the central circulation (occlusion of the inferior or superior vena cava), thereby reducing venous return and, subsequently, cardiac filling pressures. Therefore, the positive effect of kidney venous decongestion might be offset by reducing the positive effects of congestion of the heart and great vessels, depending on the status of cardiac loading. Given these complexities, randomized, sham-controlled trials of indirect devices targeting kidney venous pressure are needed.

Other indirect devices. Another approach of indirect devices is to improve lymphatic flow by selectively reducing venous pressure near the thoracic duct outlet with the aim of increasing decongestion[137] (Table 2). Lymphatic drainage is the primary route of interstitial fluid (oedema) removal, and patients with heart failure have increased lymphatic flow[138]. Devices targeting the lymphatic system have two candidate mechanisms of action: increasing salt and/or water delivery to the intravascular space (which paradoxically is the opposite of the proposed mechanism of action of indirect venous devices) and decreasing kidney interstitial pressure by facilitating kidney lymphatic drainage. Accelerating lymphatic drainage could increase renal venous pressure, which could theoretically increase renal interstitial pressure and negate the improved kidney lymphatic drainage.

The JuxtaFlow Renal Assist Device (Roivios) is a urinary catheter that applies negative pressure to the kidney pelvis, which is theoretically transferred upstream via the nephrons to decrease kidney interstitial pressures and ultimately improve kidney function and natriuresis. Similar to the hypothesis that kidney congestion impedes the diuretic response, negative kidney pressure aims to lower pressure in the encapsulated kidney to improve the diuretic response.

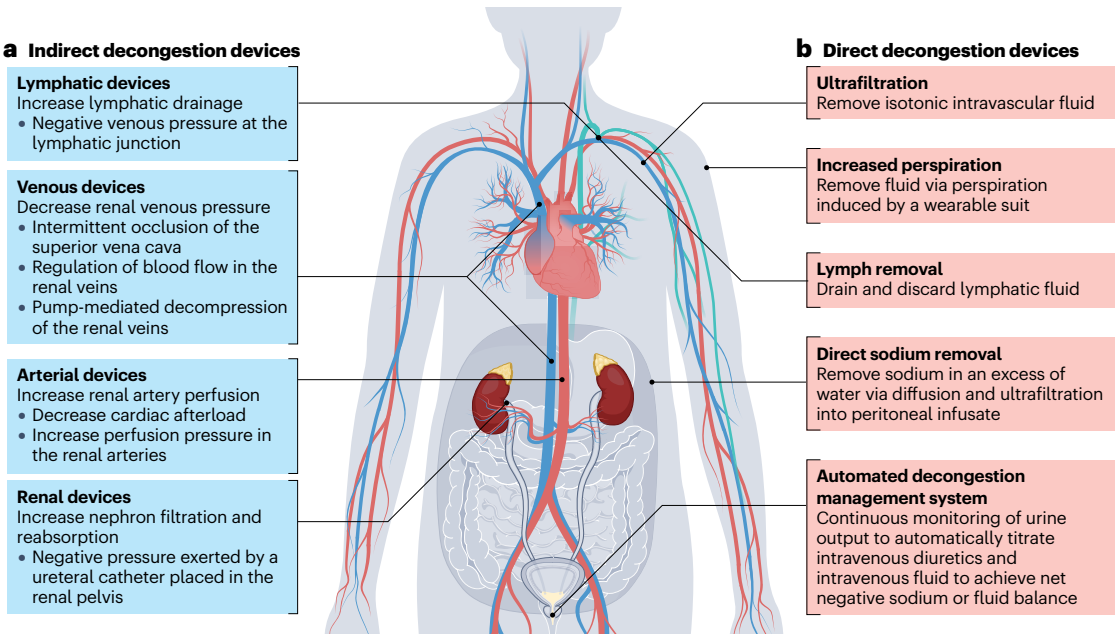

Fig. 3 | Indirect and direct decongestion devices. a, Indirect decongestion devices use various mechanisms of action to correct a hypothesized pathophysiology driving cardiorenal syndrome or diuretic resistance, relying on diuretic therapy for sodium and water removal. **b**, Direct decongestion devices directly remove sodium and water by various methods.

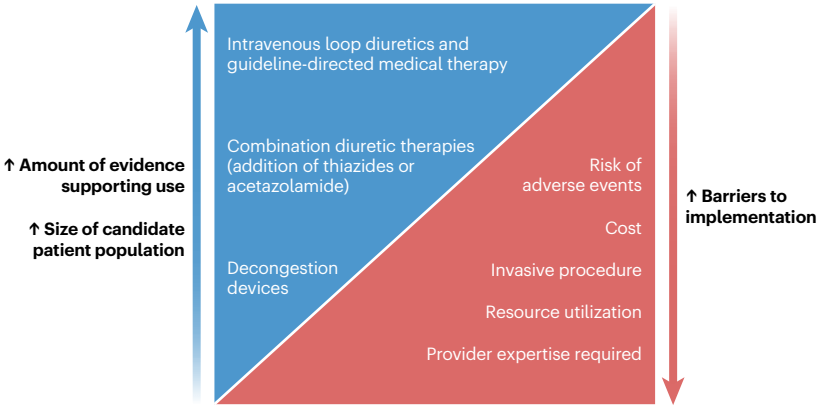

Fig. 4 | Practical considerations for decongestion devices in acute decompensated heart failure. Medical therapies are used for most patients with acute decompensated heart failure owing to the extensive experience, low cost and ease of implementation. Invasive decongestion devices are likely to be reserved for a smaller pool of candidate patients who are refractory to medical therapies because these devices are associated with higher risks of adverse events, high costs and high complexity of use. Devices and strategies that optimize the use of existing medical therapies can have an immediate benefit on decongestion, with limited incremental risk.

Direct devices

Direct devices are designed to remove fluid and/or sodium directly from the body rather than target cardiorenal pathophysiology (Table 2 and Fig. 3b). Veno-venous ultrafiltration involves removing isotonic plasma fluid directly from the vascular compartment. Most haemodialysis machines can perform isolated ultrafiltration, and a proprietary machine exists that can provide ultrafiltration rates up to 500 ml/h, with minimal extracorporeal volume[139]. As a direct decongestion device, ultrafiltration has proven efficacy in removing large quantities of sodium and water from patients. Three large trials have investigated the comparative efficacy and safety of ultrafiltration compared with diuretic therapy. In the UNLOAD trial[140], ultrafiltration improved 48-h body weight loss and reduced 90-day rehospitalization rates. However, these results were not replicated in the CARRESS-HF trial[35], in which aggressive medical decongestion therapy was implemented in the control group, and body weight loss was similar but serum creatinine concentration slightly increased with ultrafiltration. Of note, important methodological issues (such as the limited duration of therapy with a low rate of complete decongestion in both treatment groups, a fixed rate of ultrafiltration and high crossover rates) in the ultrafiltration treatment group probably influenced the results[141]. The AVOID-HF trial[142] had a similar protocolized control group to that of the CARRESS-HF trial. The AVOID-HF trial was terminated early, prohibiting definitive conclusions, but a trend towards reduced rates of rehospitalization with ultrafiltration was observed[142]. All three trials reported a non-negligible but non-prohibitive rate of catheter-related and circuit-related adverse events with ultrafiltration. Ultrafiltration is recommended by international guidelines when optimized diuretic therapies do not achieve adequate decongestion[4,5,7]. In summary, ultrafiltration is largely used only as salvage therapy despite a clear and powerful efficacy to directly remove salt and water as well as data from two pivotal clinical trials suggesting a reduction in rehospitalization. Given that ultrafiltration is less invasive than most of the newer decongestion devices that are under investigation, this experience illustrates the high threshold for the adoption of decongestion devices into the routine management of patients with ADHF. Investigators should be mindful of this lesson when future trials are designed.

The Reprieve System (Reprieve Cardiovascular) is a bedside fluid management system that monitors diuretic response in real time and automatically titrates a continuous intravenous infusion of loop diuretic and saline to achieve target levels of decongestion[143]. The Reprieve System uses a dose-finding phase that consists of a log-linear ramped increase in diuretic dosing until the desired urine output is achieved, which then triggers the transition to a continuous infusion to maintain the therapeutic concentration of diuretic identified. In the first hour, intravenous doses of diuretics are either titrated to an effective dose or patients are identified as being poor responders to high doses of loop diuretics. In theory, the Reprieve System allows rapid diuretic titration to an aggressive diuretic response target, while reducing the risk of over-diuresis, worsening renal function and diuretic resistance by administering saline as needed[143]. Clinical trials[144,145] are ongoing to test whether the Reprieve System can improve cardiorenal and decongestion outcomes, and a pivotal trial is being planned.

Direct sodium removal, analogous to standard peritoneal dialysis, is a heart failure-specific therapy that uses the peritoneal cavity for salt and water removal. Direct sodium removal therapy removes large quantities of sodium (in an excess of water) using sodium-free peritoneal solutions administered via a peritoneal catheter into the peritoneal cavity[146,147]. Unlike in-hospital decongestion devices that are used for a short period in hospitalized patients, direct sodium removal can be performed in either a hospital or an outpatient setting, with patients with ADHF continuing direct sodium removal therapy after discharge from hospital. Direct sodium removal allows the complete withdrawal of chronic diuretic therapy for extended periods. In early, unblinded, non-controlled studies, direct sodium removal induced nearly complete resolution of diuretic resistance and improved multiple cardiorenal parameters, observations that persisted for several months after cessation of direct sodium removal therapy[147]. These preliminary findings are encouraging but require replication in randomized, controlled trials.

Finally, lymphatic drainage and induced perspiration have been investigated as direct fluid-removal and salt-removal strategies. Direct lymph removal follows the same hypotheses as improved lymphatic drainage but instead discards the lymphatic fluid rather than returning it to the central circulation[148]. A potential limitation to lymph removal is the loss of proteins, antibodies and lymphocytes contained in the lymph. Lymph removal has been used as an immunosuppressive therapy in kidney transplantation, suggesting that the loss of antibodies and lymphocytes might be clinically relevant[149]. The AquaPass System (AquaPass) is a non-invasive method for direct removal of fluid and sodium. A wearable suit connected to a warm-air unit maintains a skin temperature of 36–38 °C, activating the eccrine sweat glands[150]. In feasibility studies, a sweat rate of >150 ml/h was achieved in most

patients during treatments up to 8 h, with a median hourly weight loss of 215 g/h (ref. 150). Sweat sodium concentrations were not measured.

Considerations for decongestion devices

Medical therapies are inexpensive, widely available with numerous combinations to tailor therapeutic strategies to individual patients, have decades of experience, require no unique procedural expertise, and can be safely prescribed in the environments in which ADHF is most commonly treated. Decongestion devices will need to demonstrate substantial incremental clinical value that outweighs the increased complexities, risks of adverse events from invasive procedures, costs and resource utilization compared with optimized medical decongestion therapies[35,45,142] (Fig. 4).

Indirect devices require testing in randomized clinical trials to determine their place in therapy for augmenting the diuretic response in patients with ADHF. To date, data are mostly limited to animal models, first-in-human experiences and early feasibility single-group trials[38–42,137,151–153]. Randomized clinical trials will need to be designed with protocols to optimize the medical decongestion therapies in the control groups, including standardized decongestion targets, rapid assessment of diuretic response and evidence-based titration algorithms involving the full armamentarium of medical decongestion therapies.

Similarly, direct devices also require testing in randomized clinical trials to determine their place in the treatment of ADHF. Direct devices should quantify the volume, sodium content and other solute concentrations of the fluid directly removed. Additionally, randomized trials of direct devices should consider formally and serially measuring the native diuretic response to assess the effect of non-renal sodium removal on sodium handling by the kidneys[147].

Several implementation barriers must be considered in the development and investigation of decongestion devices (Table 2). Limiting decongestion devices to patients with refractory congestion to offset the invasive risks would substantially reduce the number of candidates. Projections from patients with residual decongestion at discharge from hospital in registries or after only 72 h in clinical trials of ADHF will overestimate the candidate pool[154,155]. Most devices in development require environments with higher levels of care (such as monitoring in an intensive care unit), where bed availability and costs also limit the number of patients who can receive therapy. The placement and operation of decongestion devices require training and expertise, limiting the ease of implementation. Concomitant systemic anticoagulation is required for most intravascular decongestion devices, which increases the risk of bleeding events, particularly when transitioning from or to oral anticoagulants[35,45]. Lastly, the cost and reimbursement for device therapies need to be considered. Devices increase costs compared with inexpensive medical therapies unless substantial reductions in length of hospital stay or readmissions are achieved. The payer perspective and the types of reimbursement programmes are important to consider, given the discordant costs to hospitals versus payers between different models of reimbursement[156].

Conclusions

The major driver of inadequate decongestion at the ADHF population level is increased kidney sodium avidity, which can be addressed by fully optimizing available medical decongestion therapies (diuretics) in most patients. Optimizing medical therapies and/or strategies that facilitate the use of existing medical therapies can have an immediate effect on decongestion, with limited risk or cost. Most devices, either clinically available or in development, are invasive and do not have data to support their superiority over medical therapies. Therefore, clinical trials of decongestion devices must show substantial clinical benefit over optimized medical therapies to offset their associated risks and costs of use.

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Author contributions
The authors contributed substantially to all aspects of the article.

Competing interests
Z.L.C. reports grants from AstraZeneca and personal fees from Abiomed, Kestra Medical Technologies, Lexicon Pharmaceuticals, Reprieve Cardiovascular and Vectorious. K.D. reports speaker and consultancy fees to his employer from Abbott, AstraZeneca, Boehringer Ingelheim, Echosense, FIRE1 and Novartis. J.M.T. reports grants and/or personal fees from 3ive Labs, Abbott, AstraZeneca, Bayer, BD, Bristol Myers Squibb, Cardionomic, Corteria, Edwards Lifesciences, FIRE1, Lexicon Pharmaceuticals, Lilly, MagentaMed, Merck, Novartis, Otsuka, Precardia, Regeneron, Relypsa, Reprieve, Sanofi, Sequana Medical, Windtree Therapeutics and W.L. Gore. J.M.T. has a patent relating to the treatment of diuretic resistance issued to Yale University and Corvidia Therapeutics, a patent relating to methods for measuring renalase issued to Yale University, and a patent relating to the treatment of diuretic resistance pending with Reprieve.

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