CFR Cardiac Failure Review

EXPERT OPINION

Therapy

Counteracting the Mechanisms of Heart Failure is the Most Effective Way to Decongest Patients while Improving Outcomes

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Abstract

Diuretic therapy is not associated with improved outcomes in heart failure and may cause significant side effects. Counteracting the core pathophysiological mechanisms of heart failure through neurohormonal blockade while reducing reliance on diuretics is potentially the most effective method of decongestion.

Keywords

Heart failure, guideline-directed medical therapy, congestion

Received: 12 August 2024 **Accepted:** 31 October 2024 **Citation:** *Cardiac Failure Review* 2025;11:e02. **DOI:** https://doi.org/10.15420/cfr.2024.19

Disclosure: JC has received honoraria from Boehringer Ingelheim, Colorado Prevention Center, Grindeks and Novo Nordisk; participates on a Data Safety Monitoring Board for the STRONG-HF study; and was President of the Lithuanian Society of Cardiology (2020-2023). AM has received grants from 4Teen4, Abbott Diagnostics, Roche, Sphyngotec and Windtree Therapeutics; consulting fees from Adrenomed, Corteria, Fire1 and Roche; and honoraria from Bayer, Merck, Novartis and Roche; is co-inventor of a patent owned by S-Form Pharma on combined therapies to treat dyspnoea; and participates on advisory boards for Implicity, the SECRET-HF trial and S-Form Pharma. JB has received consulting fees from Alleviant Medical and White Swell and honoraria from AstraZeneca, Bayer and Boehringer Ingelheim. PP has received consultancy fees from Abbott Vascular, AstraZeneca, Bayer, Boehringer Ingelheim, MSD, Novartis, Novo Nordisk, Pharmacosmos, Radcliffe Group, Relaxera, Servier and Vifor Pharma; honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, MSD, Novartis, Pharmacosmos, Radcliffe Group and Vifor Pharma; and meeting support from Bayer, Boehringer Ingelheim, Novo Nordisk and Vifor Pharma. BD has received grants from 4Teen4 Pharmaceuticals, Corteria Pharmaceuticals, Echosens, Heart Initiative, Roche Diagnostics, Windtree Therapeutics and Xylocor Therapeutics. GC has received grants from 4Teen4 Pharmaceuticals, Corteria Pharmaceuticals, Echosens, Heart Initiative, Roche Diagnostics, Windtree Therapeutics and Xylocor Therapeutics.

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Advances in Understanding Congestion

Congestion is a hallmark of heart failure (HF) syndrome, manifesting both as symptoms (shortness of breath) and signs (oedema). Congestion is caused by the core pathophysiological mechanisms of HF, namely cardiac and vascular alterations leading to both increased cardiac filling pressure and fluid/sodium retention induced mostly by reduction of perfusion. The recent division of congestion into two types, tissue and intravascular congestion, allows for a better understanding of therapeutic challenges.[1,2] Dynamics of congestion in acute HF (AHF) are complicated by the action of diuretics, which decrease plasma volume, shift fluid from venous reservoirs, translocate fluid from tissues into circulation, disrupt the balance of hydrostatic and oncotic pressures in the interstitium and in the lymphatic flow.[1] Tissue and intravascular congestion can be assessed using typical clinical signs, biomarkers and instrumental techniques.[2,3]

Patients with predominant tissue congestion are most difficult to treat in cases of acute, worsening and advanced HF. Different methods of decongestion affect distinct fluid compartments to various degrees. Importantly, although congestion has been shown in multiple studies to be associated with many adverse outcomes in HF and especially AHF, treatment of congestion by more intensive interventions (either a combination of diuretics or mechanical devices) was not shown to improve outcomes in either chronic or acute HF patients.[1–6] This suggests that although congestion is a significant presentation of HF, it may play a lesser role as a driver of disease progression.

What Did We Learn from Clinical Studies Focused on Natriuretics?

Research efforts to enhance decongestion began about two decades ago with the large PROTECT and EVEREST studies investigating the drugs rolofylline and tolvaptan, respectively.[7,8] Acute dyspnoea improved in both studies, though the effects were small and of doubtful clinical significance. Furthermore, the decongestive effects were accompanied by adverse hemodynamic, electrolyte and renal sequelae. The absence of improvement in all-cause mortality, cardiovascular mortality and HF hospitalisations was disappointing. Recently, two smaller studies were conducted in the AHF population, examining the addition of a second natriuretic agent to loop diuretics. The ADVOR study examined the administration of acetazolamide versus placebo in 519 patients with oedema and elevated natriuretic peptides.[6] By day 4, decongestion,

defined as absence of oedema, pleural effusion and ascites, was more successful in the acetazolamide group; however, there was no difference in symptoms compared to the placebo. In the CLOROTIC study, 230 AHF patients on moderately high doses of furosemide at baseline were randomised to receive hydrochlorothiazide or placebo.[9] In the intervention group, significantly higher weight reduction was achieved, but the effect on dyspnoea at 72 hours was only numerically greater. In both ADVOR and CLOROTIC studies, rates of renal impairment (defined by a rise in creatinine ≥0.3 mg/dl) and hypokalaemia were elevated in the active arms of the studies. Moreover, our meta-analysis of ADVOR and CLOROTIC data showed a worrying signal of increased mortality in AHF patients treated by additional natriuretics: estimated risk of 90-day mortality was found to be 16.6% in the intervention groups versus 13.3% in control groups.[10]

To date, there is no evidence that aquaretics or natriuretics can improve HF patient prognosis despite their key role in sodium and water excretion. In contrast to neurohormonal blockade, diuretics increase renin secretion, cause renin–angiotensin–aldosterone system (RAAS) activation and increase intraglomerular pressures by preventing tubuloglomerular feedback.[11] Furthermore, natriuretics decrease plasma osmolality, which might interfere with fluid translocation from tissues to the intravascular compartment.[1]

IV diuretics should primarily be used when a patient has significant fluid overload, which is typically limited to a few days in uncomplicated cases. In non-responsive patients, a combination of loop diuretics with acetazolamide or thiazide may be more effective in short-term decongestion than loop diuretics alone. Once overt fluid overload is resolved, the patient should be transitioned from loop diuretics to oral diuretic therapy, followed by further optimisation of pharmacotherapy.

Responsiveness and Resistance to Diuretics: Two Clinical Scenarios

Recent studies on enhanced decongestion have enrolled patients without distinguishing between those with a normal response to conventional diuretic doses and those with diuretic resistance. Meanwhile, the majority of patients admitted with AHF are not receiving optimal guideline-directed medical therapy (GDMT), whether in terms of recommended drug classes or, more often, target doses.[12–15] Moreover, when presenting with AHF, patients' usual medication regimens are often interrupted. Most patients respond well to small or moderate doses of IV diuretics that can be converted back to oral loop diuretics within 24–48 hours. These patients are discharged relatively quickly with no or minimal signs of congestion.[4,16] Therefore, it seems rational to reserve enhanced decongestive strategies using additional natriuretic agents for the minority of patients with advanced stages of HF who demonstrate high adherence to GDMT and require diuretic doses at the upper end of the therapeutic doses.

Diuretic resistance can be defined as a failure to increase fluid and sodium output sufficiently to relieve generalised oedema, volume overload or congestion despite escalating diuretic doses.[1] It is important to note that a universally accepted definition of diuretic resistance does not exist. Various authors have used slightly different definitions, making comparison challenging. The idea of compensatory post-diuretic sodium reabsorption in the distal tubule was extrapolated to AHF settings from healthy volunteers, and was considered a major contributor to diuretic resistance in HF.[17] The mechanistic study revealed the opposite effect in hypervolemic AHF patients: increased loop diuretic-induced natriuresis was followed by greater spontaneous sodium excretion during the post-diuretic period.[18] Importantly, basal sodium avidity emerged as the primary determinant of both diuretic-induced and post-diuretic natriuresis in this population. Although this concept requires further confirmation and exploration, it offers critical insights into the relationship between baseline intrinsic sodium avidity and diuretic response, which may play a crucial role in a patient's ability to decongest. Moreover, it suggests that interventions to decrease baseline sodium avidity could directly enhance spontaneous and post-diuretic natriuresis.

It is also important to acknowledge that chronic exposure to loop diuretics promotes histological, molecular and functional adaptations in the tubular part of the nephron, leading to significantly reduced diuretic responsiveness.[19,20]

High doses of loop diuretics were associated with significantly worse outcomes.[21,22] However, based on available data, a direct causal link between diuretic dosage and patient outcome cannot be established. Patients with advanced disease may require higher diuretic doses, reflecting association with rather than causation of mortality. Currently, a basal and relatively fixed sodium-avid state (the kidney's tendency to retain sodium) seems to be the main driver of diuretic response and a key determinant of decongestive capacity in AHF patients.[23,24] Direct sodium removal therapy, which uses the peritoneal cavity to remove sodium via diffusion, may potentially serve as an alternative decongestion therapy.[25] Early identification of impaired diuretic response using urine sodium concentration 2 hours after loop diuretic administration may guide future trials targeting patients with high basal sodium avidity.[24] Two recent large-scale studies, PUSH-AHF and ENACT-HF, demonstrated clinical advantages of urine Na-driven decongestion protocols over standard care, including greater natriuresis and shorter hospital stays.[26] The ongoing ESCALATE trial aims to determine whether urine chemistry decongestion algorithms outperform standard care in clinical settings.[27]

Rapid Up-Titration of Guideline-directed Medical Therapy for Effective Decongestion

The concept of neurohumoral, adrenergic and inflammatory activation as a key pathogenetic axis of HF was put forward more than two decades ago and has led to improved medical treatment.[28–30] Distinguishing between chronic and acute HF enabled clinical trials to target these populations with different aims and interventions. The STRONG-HF study confirms the role of excessive activation of the RAAS and the sympathetic nervous system as the main mechanisms of AHF, which can be ameliorated by rapid and aggressive optimisation of neurohormonal blockade.[31–33] Several metrics of congestion, including a clinical congestion score, were significantly improved in the STRONG-HF study and led to smaller daily doses of loop diuretics at day 90 in the high-intensity care (HIC) group.[34] The benefits of the HIC strategy were apparent in all three components of the congestion score: effective decongestion in the HIC group at day 90 was evidenced by increased weight loss and NT-proBNP change in the high-intensity arm; a significantly higher proportion of HIC patients with no signs of congestion prior to randomisation remained congestion-free at 90 days compared to the standard care group; and patients receiving a higher average percentage of target GDMT doses had improved congestion scores. Study data demonstrate that decongestion achieved through optimal GDMT is linked to better clinical outcomes: compared to unsuccessful decongestion, successful decongestion was associated with a lower risk of 180-day HF readmission or death, 180-day all-cause death and 180-day HF readmission. These data suggest that congestion may be an epiphenomenon of HF severity, likely driven by neurohormonal, sympathetic and inflammatory activation, affecting both vascular and cardiac function and leading to kidney maladaptation as well as sodium

and fluid retention. Rapid initiation and up-titration of neurohumoral blockers to counteract the neurohormonal drive should result in prompt and sustained alleviation of congestion (*Figure 1*). Neurohumoral activation also leads to hypochloraemia associated with diuretic resistance, attenuation of the Gauer-Henry reflex leading to excess renal sympathetic activity despite elevated cardiac filling pressures and accumulation of osmotically active sodium in interstitial glycosaminoglycan buffers.[35–37] All four pillars of current GDMT have been shown to reduce renal sodium avidity.[38–40]

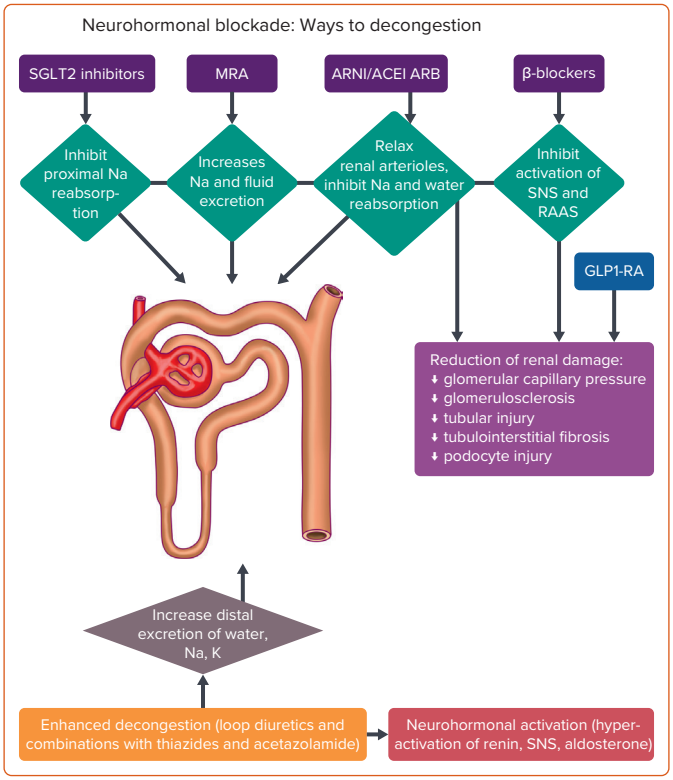
Sodium-glucose Cotransporter 2 Inhibitors in Heart Failure

The STRONG-HF trial was conducted before the introduction of sodium-glucose cotransporter 2 inhibitors into clinical practice; due to the action point in the proximal renal tubule, it has been suggested that these agents can further amplify decongestion.[41] As anticipated, improved decongestion was observed in the EMPAULSE study with the early addition of sodium glucose cotransporter 2 inhibitors during AHF admission.[38]

The STEP-HFpEF trial recently demonstrated multiple benefits of semaglutide in patients with obesity-related HF with preserved ejection fraction, including improved exercise capacity and quality of life.[42,43] Secondary analyses showed improvement in C-reactive protein and natriuretic peptide levels.[44] From baseline to 52 weeks, loop diuretic requirements decreased in the semaglutide group yet increased in the placebo group ($p<0.0001$).[45] These results suggest that in patients with obesity-related HF with preserved ejection fraction, addressing key pathophysiological drivers of HF reduces the need for diuretic therapy. Similarly, in the CORTAHF study, the use of steroids in AHF improved decongestion indices, highlighting the role of anti-inflammatory treatments in HF management.[46]

In summary, there are two common scenarios in AHF regarding decongestion therapy response. In the first and most frequent scenario, patients respond to standard diuretic doses and GDMT initiation or escalation. The second scenario is diuretic resistance, in which advanced decongestion strategies such as sequential nephron blockade, aquaretics or ultrafiltration may be helpful. Focusing exclusively on diuretics (combining drugs and adjusting doses based on natriuresis) effectively reduces weight, oedema and dyspnoea, but does not improve clinical outcomes. Therefore, the vast majority of admitted HF patients benefit from initiation and rapid optimisation of quadruple GDMT as the best strategy for sustained decongestion and improved clinical outcomes.[47]

Figure 1: Ways of Decongestion by Neurohormonal Blockers and Natriuretics



Demonstrates the ways of decongestion by neurohormonal blockers and natriuretics, their effects on sympathetic nervous and RAAS and nephroprotective potential. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; GLP1-RA = glucagon-like peptide-1 receptor agonist; MRA = mineralocorticoid receptor antagonist; RAAS = renin–angiotensin–aldosterone system; SGLT2 = sodium–glucose cotransporter 2; SNS = sympathetic nervous system.

The most effective way to reduce congestion is to counteract its core pathophysiological mechanisms, such as RAAS activation, adrenergic activation and inflammation, including that induced by obesity. Once this has been achieved, congestion will be improved, and the need for diuretic therapy will diminish. GDMT should be viewed as an active decongestive treatment rather than a mere complement to diuretics in AHF. Since diuretics are not associated with improved outcomes and can cause significant side effects, focusing on core pathophysiological mechanisms of HF while reducing diuretic use represents a promising direction for modern HF therapy.[4,48] ❑

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