A practical approach to sequential nephron blockade in acute decompensated heart failure

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Abstract
Acute decompensated heart failure (ADHF) is a worldwide health problem, with poor prognosis and significant morbidity and mortality. Fluid overload is the primary reason for hospitalization in ADHF. The efficacy of diuretic monotherapy is suboptimal, with a substantial proportion of patients being discharged with residual congestion that portends a poor outcome. Accordingly, the loop diuretic monotherapy from the DOSE trial achieved a successful decongestion in less than 20% of patients. Although the concept of sequential nephron blockade has regained interest following the publication of several randomized clinical trials (RCTs), the optimal approach to combination diuretic therapy is still an area of uncertainty. The selection of an adequate approach remains difficult as comparisons between different trials cannot be made due to different diuretic doses used, timing of sequential blockade, differences in study cohorts or in definitions used to define decongestion. Moreover, a direct comparison of different combination therapies in large trials is lacking. Nonetheless, the approach to the combination diuretic therapy should rather take into account the patient phenotype, the suspected nephron segment responsible for diuretic resistance, and the anticipated electrolyte and acid–base disturbances in order to select diuretic agents with divergent effects. Herein, we review the molecular mechanisms of action of diuretic agents, highlight the most recent trials evaluating combined diuretic therapy in ADHF and identify clinical scenarios, apart from diuretic resistance, for optimal association of diuretics to counteract their anticipated adverse effects.

Keywords
acute decompensated heart failure, diuretics, diuretic resistance, sequential nephron blockade, decongestion, electrolyte abnormalities

Introduction

Acute decompensated heart failure (ADHF) is a worldwide health problem, with poor prognosis and significant morbidity and mortality [1]. Congestion is the main reason for hospital admission for ADHF, while diuretics represent the cornerstone of management of these patients [1,2]. Although current clinical guidelines recommend firstline use of intravenous loop diuretics to mitigate signs and symptoms of fluid overload in ADHF, the percentage of patients free from clinical congestion remains poor at discharge (less than 30%) [3,4]. In addition, the presence of significant residual congestion at day 7 or discharge is independently associated with increased risk of hospital readmission by day 60 and an increased risk of all-cause mortality by day 180 [3]. The reason for these outcomes is the lack of standardized diuretic regimens evaluated in randomized clinical trials (RCTs) which is reflected in the moderate-quality of evidence for the recommendation in the diuretic use among contemporary clinical guidelines [5–7]. Moreover, in the Diuretic Optimization Strategies Evaluation (DOSE) trial, only 18% of patients achieved decongestion at 72 h in the high-dose loop diuretics arm [8]. This underscores the limitations of monotherapy with intravenous loop diuretics to achieve decongestion, outlining the importance of diuretic resistance in ADHF [2,9].

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The pathophysiology of diuretic resistance is multifactorial and involves neurohumoral activation (sympathetic nervous system and renin-angiotensin-aldosterone system), the concept of nephron remodeling, intravascular fluid depletion and a slow plasma refilling rate [10]. Nonetheless, the adaptation to diuretic therapy can be traced to two phenomena: post-diuretic sodium retention and diuretic braking phenomenon [2]. The adaptation of the distal nephron to chronic diuretic therapy has been proposed as the main mechanism underlying the diuretic braking phenomenon. In an animal model, Ellison et al. showed that chronic furosemide infusion in addition to salt ingestion determined an increase in the fractional volume of distal convoluted tubule by 100% [11]. Recently, it was shown that this mechanism translates to human diuretic resistance in heart failure (HF). In a study that enrolled 128 patients with HF that received chronic loop diuretic treatment, it was shown that, after diuretic administration, the fractional excretion of lithium (as a marker of proximal tubule sodium handling) increased significantly more than the fractional excretion of sodium [12]. Accordingly, only a third of the estimated diuretic-induced increase in sodium delivered to distal tubules passed through the distal tubule into the urine without reabsorption [12]. These findings prove that the primary driver for diuretic resistance in HF is distal tubular compensatory sodium reabsorption. Nonetheless, this study also identified a subset of patients that showed a reduced sodium exit from the proximal tubule making it unlikely that a distal nephron blockade will improve diuretic efficacy. In such patients, proximal tubule diuretics [carbonic anhydrase (CA) inhibitors or sodium-glucose cotransporter 2 inhibitors (SGLT2i)] might be more beneficial [12].

Sequential nephron blockade to overcome diuretic resistance in ADHF has gained popularity following the publication of recent trials with CA inhibitors, SGLT2i or thiazide diuretics [4]. Nonetheless, current clinical guidelines generally recommend addition of a second diuretic only after increasing the doses of loop diuretics, albeit with a low-level of evidence [5–7]. The challenges in guiding combined diuretic therapy arise from the heterogeneity of clinical trials in terms of diuretic dosing regimens and primary outcomes (different definitions of decongestion employed, variability in the use of urine output, weight change, change in NT-proBNP, length of hospitalization as primary outcome measures) [4]. Apart from mitigating the diuretic resistance, a successful strategy to employ the sequential nephron blockade should also rely on the possibility to counteract the anticipated adverse effects of diuretic agents in terms of electrolyte and acid-base disturbances (Table 1) [4].

Herein, we review the molecular mechanisms of action of diuretic agents, highlight the most recent trials evaluating combined diuretic therapy in ADHF and identify clinical scenarios, apart from diuretic resistance, for optimal association of diuretics to counteract their anticipated adverse effects.

General overview of the molecular mechanisms of action of diuretic agents

1. Proximal convoluted tubule – CA inhibitors and SGLT2i

CA inhibitors are among the first developed diuretics in the modern diuretic treatment, replacing mercurial diuretics in the mid-1950s. Carbonic anhydrase was discovered in the early 1930s. Later on, it was observed that patients treated with sulfanilamide, a new antimicrobial agent, developed metabolic acidosis and changes in urine output or composition (alkaline urine). It was shown that it can inhibit carbonic anhydrase, thus increasing urine output. Sulfanilamide was then used in patients with heart failure and edema, which led to a new drug development with diuretic properties: acetazolamide, a CA inhibitor [13–16]. Acetazolamide, as well as loop and thiazide diuretics, reaches tubular lumen by secretion into the proximal tubule through organic anion transporters in the basolateral membrane (OAT1 and OAT3) of the proximal tubular cells [17]. Approximately 70% of the filtered Na^+ is reabsorbed in the proximal tubule through a variety of transporters that couple Na^+ with other substances. The most important transporter with respect to the reabsorbed quantity of sodium is the isoform Na^+/H^+ exchanger located at the luminal membrane, NHE3 [15]. Na^+ is reabsorbed from the lumen with H^+ excretion by NHE3. H^+ is produced intracellularly from H2CO3, which is catalyzed by carbonic anhydrase II (CAII) into $HCO3^-$ and H^+. $HCO3^-$ is reabsorbed back to the bloodstream through the basolateral side of the proximal tubule and H^+ becomes available for the exchange with Na^+. H^+ and $HCO3^-$ form H2CO3 inside the tubular lumen, which then dehydrates to CO2 and H2O by the action of a second carbonic anhydrase, isoform IV (CAIV). Acetazolamide has the capacity to inhibit both CAs, and so with H^+ no longer available for exchange with Na^+, acetazolamide leads to enhanced natriuresis and bicarbonaturia [4]. Since almost 70% of sodium is reabsorbed in the proximal tubule, we would expect CA inhibitors to be strong diuretics, but compensatory distal sodium reabsorption and progressive bicarbonate depletion limits the diuretic efficacy with repeated use over days [4]. Additionally, potassium wasting occurs because of the increased reabsorption of sodium downstream and activation of the renin-angiotensin-aldosterone system [18]. Thus, CA inhibitors are considered to be natriuretic, kaliuretic, and bicarbonaturic [19]. This can lead to hypokalemia and hyperchloremic metabolic acidosis, the most frequent adverse events of CA inhibitors. Other potential side effects can be hypocalcemia (as most filtered calcium is reabsorbed in the proximal tubule [60%–70%]), hypomagnesemia (even if only 10%–25% of magnesium is reabsorbed proximally) and hypocitraturia with alkaline urine, which predisposes the patient to calcium phosphate kidney stones [20]. Long-term administration of acetazolamide should not be considered, because of the high risk of metabolic acidosis. However, it can be the perfect candidate in

Table 1 - Combined diuretic strategies to overcome anticipated adverse events.

Class of medication	Anticipated electrolyte or acid-base disturbances	Add-on diuretic agents to counteract the anticipated primary adverse event
Thiazide diuretics Loop diuretics	Hyponatremia	SGLT2i Vasopressin receptor antagonists
Thiazide diuretics Loop diuretics	Hypokalemia	MRAs
RAASi MRAs ENaC blockers	Hyperkalemia	SGLT2i Loop or thiazide diuretics
Thiazide diuretics Loop diuretics	Metabolic alkalosis	CA inhibitors MRAs
CA inhibitors MRAs	Metabolic acidosis	Thiazide diuretics Loop diuretics
Thiazide diuretics Loop diuretics	Hypomagnesemia	MRAs ENaC blockers
CA inhibitors Loop diuretics	Hypocalcemia	Thiazide diuretics ENaC blockers

Abbreviations: RAASi, renin-angiotensin-aldosterone inhibitors; MRAs, mineralocorticoid receptor antagonists; ENaC, epithelial sodium channel; CA, carbonic anhydrase; SGLT2i, sodium-glucose cotransporter 2 inhibitors

resistant edema with metabolic alkalosis secondary to other classes of diuretics, with strict monitoring for hypokalemia [17]. For many years, acetazolamide was mostly used in glaucoma, intracranial hypertension, or high-altitude disorders, but recent data from ADHF and nephrotic syndrome demonstrates its efficacy in controlling edema in association with other diuretics, especially a loop diuretic [21,22].

SGLT2i specifically block sodium and glucose reabsorption in the S1 and S2 segments of the proximal convoluted tubule, inducing glycosuria and improvement of glycemic control [23]. These agents have rapidly been incorporated into the standard of care for patients with chronic kidney disease and heart failure (with reduced and preserved ejection fraction), with or without diabetes, as they have been shown to significantly improve renal and cardiovascular outcomes [24–30]. Moreover, the most significant cardiovascular impact of SGLT2i was to reduce the hospitalizations for HF [24,26]. They seem to have many pleiotropic physiological benefits, but the mechanisms of their efficacy are incompletely understood [20,31]. As we have mentioned before, Na^+ reabsorption in the apical membrane of the proximal tubule is coupled with glucose, amongst others. The two cotransporters are SGLT1, located in the apical membrane of the S3 segment and SGLT2, located in the apical membrane of the S1 and S2 segments of the proximal tubule. Na^+ and glucose enter the cell at a 1:1 ratio, with a glucose concentration gradient causing exit of glucose to plasma via GLUT2 in the basolateral membrane. Also, Na^+ is reabsorbed back to the plasma via basolateral Na^+/K^+ pump [23]. Sodium-glucose co-transporter 2 (SGLT2) is the major cotransporter responsible for reabsorption of 80–90% of filtered glucose, whereas only a small amount of Na^+ is reabsorbed through SGLT2 as Na^+ is mostly reabsorbed through NHE3 [31]. SGLT2i reduce glucose reabsorption by 30–50% causing glucosuria with osmotic diuresis. This diuretic effect is presumably responsible for the cardiorenal protective effects. Increased natriuresis was noted with several SGLT2i in both animal and human studies, especially in the first days of treatment [32]. Dapagliflozin also demonstrated increased glucosuria and natriuresis in healthy subjects and a decrease in tissue sodium levels in patients with type 2 diabetes mellitus. These drugs seem to be safer than any other diuretics, with no electrolyte or acid–base disturbances [33]. Taking everything into consideration, SGLT2i are not suitable for monotherapy for their diuretic effect, but they can be an adequate option for diuretic association, especially with loop diuretics, as it can minimize the risk of hyponatremia [34,35].

2. Thick ascending loop of Henle - Loop diuretics

Loop diuretics are the most prescribed diuretics for management of hypervolemia. For signs and symptoms of congestion in HF, prescribing a loop diuretic is a recommendation of class I, level of evidence B [10]. They inhibit 25%–30% of sodium reabsorption through $Na^+/K^+/2Cl^-$ cotransporter (NKCC) in the thick ascending loop of Henle. The intracellular Na^+ is reclaimed to the bloodstream by the Na^+/K^+ ATPase from the basolateral membrane. They also inhibit the same cotransporter at the apical membrane of the macula densa, which causes renin secretion and inhibition of the tubulo-glomerular feedback with impaired concentrating ability of the nephron and significant water excretion. This is the reason why loop diuretics are considered high efficiency diuretics. They are not freely filtered through the glomerulus, because 90% of the diuretic is bound to albumin [36]. Furosemide, torsemide, and bumetanide are examples of loop diuretics. Furosemide is the most accessible and used agent of this class, even though it shows variable bioavailability (between 10%–90%) and has a short half-life compared to the other loop diuretics. It must reach a certain threshold (which varies among patients) to rapidly increase sodium and water excretion. Also increasing doses beyond a “ceiling” does not increase the diuretic efficacy. Regardless of progressive increase in doses of oral furosemide, most frequently patients require intravenous administration. In this manner, the threshold is immediately reached with a prompt diuretic effect. Furosemide has a t1/2 of 2 hours, but its effect lasts for 6 hours, because of the absorption-limited pharmacokinetic feature. This means that furosemide is slowly absorbed from the gastrointestinal tract, thus increasing the duration of furosemide in the plasma. Beyond this period, post-diuretic sodium retention occurs, which is the reason why furosemide should be administered more frequently, at least twice a day; otherwise the sodium retention can reverse the negative sodium balance. About 50% of a dose of furosemide is conjugated to glucuronic acid in the kidneys, thus the plasma half-time is prolonged in patients with renal impairment, while bumetanide and torsemide are largely metabolized by the liver [2,36]. Torsemide also has a longer half-time in patients with heart failure (6 hours) compared to furosemide (2.7 hours), with a reduced post-diuretic Na^+ retention and a prolonged urine Na^+ excretion, making it a better treatment option in patients with renal impairment and heart failure. It can also improve the New York Heart Association functional classification and reduce hospitalization and mortality rates [33].

In patients with heart failure, without renal impairment, the pharmacokinetics of loop diuretics are relatively normal, while there is a pharmacodynamic problem. This occurs secondary to a process called diuretic braking phenomenon [2]. As the extracellular fluid decreases, the natriuretic response to every dose of diuretic also decreases due to several counter-regulatory processes like activation of renin-angiotensin-aldosterone system, activation of the sympathetic nervous system and hypertrophy of distal epithelial cells of the nephron, called nephron remodeling. Thus, the dose-response curve is shifted downwards and to the right, which means there is a secretory defect and a reduced maximal response [2,37]. To overcome this diuretic resistance, we need to increase the frequency of the diuretic doses or associate other classes of diuretics. If renal impairment is associated, then both pharmacokinetics and pharmacodynamics are affected, and we should also increase the dose of diuretic [17].

Loop diuretics can cause serious electrolyte and acid-base disturbances, such as hyponatremia, hypokalemia, hyperuricemia, hyperchloremic metabolic alkalosis, and less frequently, hypomagnesemia [36]. They can cause severe hypovolemia and a consequent rise in serum creatinine [38]. Other side effects of loop

diuretics are photosensitivity, dermatitis, acute allergic interstitial nephritis, and ototoxicity (especially when associating other ototoxic drugs like aminoglycosides). The last one is dependent on the dose and rate of infusion of the diuretic. Generally, the dose of furosemide should not exceed 4 mg/min and concomitant administration of aminoglycoside should be avoided [39].

3. Distal convoluted tubule - thiazides and thiazide-like diuretics

From a historical perspective, after the discovery of CA inhibitors it was observed that these drugs were not efficient in monotherapy for decongestion in patients with heart failure. It was thought that for better volume control it was necessary to excrete both Na^+ and Cl^-, unlike the mechanism of action of CA inhibitors. This led to the development of thiazide diuretics [15,16] by chemical modification of the sulfa nucleus of acetazolamide. Chlorothiazide was the first thiazide diuretic, followed by hydrochlorothiazide and bendroflumethiazide, with different pharmacokinetic characteristics. Other modifications of the sulfa nucleus led to thiazide-like diuretics, which have the same effect, but a different chemical compound (chlorthalidone, indapamide, metolazone) [40]. They inhibit about 5%–10% of Na^+ reabsorption through Na^+/Cl^- cotransporter (NCC), at a 1:1 ratio, in the apical membrane of the distal convoluted tubule, both early (DCT1) and distal segment (DCT2) [41]. This intracellular decrease in Na^+ activates the basolateral Na^+/Ca^{2+} exchanger (NCX), to maintain an optimal level of intracellular sodium. This leads to increased reabsorption of calcium from the renal tubule through an apical Ca^{2+} channel according to gradient concentration and then from cytoplasm to plasma through NCX. This is the mechanism responsible for hypocalciuria and kidney stone prevention with administration of thiazides, unlike furosemide, which increases calcium excretion. The distal tubule is also impermeable to water, being responsible for urine dilution [15,42]. Inhibition of NCC leads to a greater Na^+ delivery to collecting duct, where Na^+ is reabsorbed in exchange for K^+ and H^+, leading to hypokalemia and metabolic alkalosis. Hyponatremia and hypokalemia are especially likely to occur in elderly patients. Thiazides can also cause hypomagnesemia, hyperuricemia, hyperglycemia, and severe volume depletion, particularly when used in combination with loop diuretics [40]. Thiazides have a moderate diuretic effect and are mostly used for hypertension, mild congestive heart failure or in combination with loop or other diuretics to overcome diuretic resistance through sequential nephron blockade [43–46]. A major difference from most loop diuretics is the long duration of action of a thiazide diuretic, making once a day administration suitable.

4. Collecting duct - K-sparing diuretics (ENaC blockers and mineralocorticoid receptor antagonists [MRAs]) and vasopressin receptor antagonists

4.1. K-sparing diuretics

K-sparing diuretics differ by their mechanism of action and can be categorized into drugs that directly inhibit the ENaC channel (ENaC blockers: amiloride and triamterene) and drugs that inhibit the same channel indirectly, by blocking the mineralocorticoid receptor (MRAs) with subsequent decrease in the synthesis of ENaC (spironolactone, eplerenone, finerenone). The final effect is the reduction of about 3% of Na^+ reabsorption in the collecting duct. The collecting duct consists of three different types of cells: principal cells, α-intercalated cells, and β-intercalated cells. ENaC channel, also called amiloride-inhibitable sodium channel, is predominantly expressed in the apical membrane of principal cells, but also in connecting tubule (CNT) and the second segment of the distal convoluted tubule (DCT2), overlapping with NCC cotransporter in the last two segments. α-intercalated cells are the major site for proton secretion into the lumen through luminal H+-ATPase; β-intercalated cells secrete bicarbonate through the apical $Cl^-/HCO3^-$ exchanger pendrin [13,41].

ENaC blockers are secreted into the lumen through cationic transporters found in the proximal tubule. They bind to ENaC channel and inhibit Na^+ reabsorption, with a secondary reduction in secretion for both K^+ and H^+. They also reduce Ca^{2+} and Mg^{2+} excretion [47]. Aldosterone has a dual action, nongenomic and genomic. Genomic effects refer to aldosterone binding to the cytosolic mineralocorticoid receptor, which migrates to the nucleus upregulating certain proteins (SGK1, NEDD4-2) with further DNA replication. Spironolactone binds to the mineralocorticoid receptor after entering the principal cell of the collecting duct and inhibits further binding to the nucleus, which impedes DNA replication and protein synthesis for ENaC [18].

Amiloride has a t½ of 26 hours, while in patients with CKD, the half-life is significantly increased to up to 100 hours. Triamterene has a hepatic metabolization into its active metabolite. Spironolactone has a bioavailability of >65%, and its metabolites, 7α-thiomethylspironolactone and canrenone, are responsible for their mineralocorticoid receptor antagonism. They have a t½ of 20 hours. Eplerenone has a different molecular structure that provides selectivity for the aldosterone receptor and less so for androgen and progesterone receptors, unlike spironolactone [47]. Finerenone is the first of a new class of nonsteroidal MRAs [20]. The most frequent adverse effect of K-sparing diuretics is hyperkalemia, and special attention should be given to patients concomitantly taking RAAS inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs). They can also cause metabolic acidosis similar to type IV renal tubular acidosis, hyperuricemia, and hypocalciuria [43]. Amiloride can also cause nausea, vomiting, diarrhea, and headache and less frequently can affect the central nervous, gastrointestinal, endocrine, musculoskeletal, dermatological, and hematological systems [48]. Other common adverse effects of spironolactone include antiandrogenic side effects like gynecomastia, erectile dysfunction, dysmenorrhea, and postmenopausal bleeding in women [42].

K-sparing diuretics are weak diuretics. Amiloride is mostly prescribed in a fixed combination with thiazide diuretics as an antihypertensive treatment, but not as a first-line treatment. It is also the drug of choice for patients with full-blown Liddle's syndrome, which is caused by gain-of-function mutations in the gene expressing the ENaC, which manifests with hypertension, hypokalemia, and metabolic alkalosis. This is a perfect combination of diuretics as the risk of hypo/hyperkalemia decreases [40]. Recently, amiloride has been increasingly used for the treatment of edema in nephrotic

syndrome. Patients with nephrotic syndrome have urinary losses of serin proteases that directly activate the ENaC (mostly plasmin), thus supporting the benefit of amiloride in this specific case. Even more so, amiloride has the capacity to reduce plasmin levels as well [49,50]. Spironolactone is generally used for resistant hypertension, primary hyperaldosteronism, or diseases that are associated with secondary hyperaldosteronism like heart failure, cirrhosis, and Bartter and Gitelman syndromes [42].

4.2. Vasopressin receptor antagonists

Vaptans, also called aquaretic agents for their effect of increasing free water excretion, are antagonists of the vasopressin V2 receptor in the collecting duct. Plasma tonicity is regulated by the antidiuretic hormone (ADH), which is synthesized in the hypothalamus as a pre-prohormone, and cleaved into ADH, neurophysin II, and copeptin, with ADH storage in the posterior pituitary gland. Osmoreceptors in the hypothalamus sense a hypertonic environment causing ADH release. ADH then binds to the V2 receptor in the basolateral membrane of the collecting duct, which further translocates aquaporin 2 (AQP2)-containing vesicles to the apical membrane of the collecting duct. AQP2 allows water to flow into the cell and then through AQP3 and 4 into the plasma, thus trying to correct the increased osmolality [51]. ADH binds to two other vasopressin receptors, V1A receptor found in liver, smooth muscle, heart, brain, and platelets, which is responsible for increasing the levels of intracellular calcium and V1B receptor and inducing secretion of corticotropin in the anterior pituitary. Vaptans block activation of V2 receptors by ADH with no AQP2 insertion in the apical membrane with consequent free water diuresis, also called aquaresis.

There are several agents of this class with oral (tolvaptan, satavaptan, lixivaptan) or intravenous administration (conivaptan) [52]. Initially, they were designed to correct hyponatremia of certain conditions (syndrome of inappropriate antidiuretic hormone secretion, cirrhosis, heart failure). Conivaptan is currently the only drug of its class FDA approved for euvolemic hyponatremia in hospitalized patients and it is mainly available in the USA. Tolvaptan was evaluated as an add-on agent in patients with worsening HF. However, the EVEREST trial showed that tolvaptan had no effect on long-term mortality or morbidity [2,53]. There have been arguments that the aquaretic-restricted effect of tolvaptan without any impact on total body sodium content might be responsible for the lack of efficacy in harder endpoints [4]. Nonetheless, in the EVEREST trial, addition of tolvaptan led to a greater weight loss and dyspnea improvement, while the loop diuretic doses were lower at discharge compared to placebo [4]. In HF, however, the decrease in effective arterial blood volume leads to nonosmotic release of ADH and consequent hyponatremia [54]. Thus, vasopressin receptor antagonists may still play a role as adjunct therapies in the acute management of HF especially if hyponatremia is associated [54]. In a post-hoc analysis from the EVEREST trial restricted to patients with hyponatremia, tolvaptan reduced the risk for a combined endpoint of cardiovascular mortality or hospitalization (hazard ratio, 0.60; 95% confidence interval, 0.37–0.98; $P = 0.04$) [54]. Two other trials (TACTICS- HF and SECRET of CHF, the last including only patients with hyponatremia) had similar findings on improvement of weight loss, but not on dyspnea reduction [55,56].

Clinical approach to sequential nephron blockade

The efficacy of diuretic monotherapy is suboptimal with a substantial proportion of patients being discharged with residual congestion that portends a poor outcome [4]. As previously mentioned, the loop diuretic monotherapy from the DOSE trial achieved a successful decongestion in less than 20% of patients [8]. Although the concept of sequential nephron blockade has regained interest following the publication of several RCTs, the optimal approach to combination diuretic therapy is still an area of uncertainty (Table 2) [4]. The selection of an adequate approach remains difficult, because comparisons between different trials cannot be made as a result of different diuretic doses used, timing of sequential blockade, differences in study cohorts, or in definitions used to define decongestion [4]. Moreover, a direct comparison of different combination therapies in large trials is lacking [57].

Nonetheless, the approach to the combination diuretic therapy should rather take into account the patient phenotype, the suspected nephron segment responsible for diuretic resistance and the anticipated electrolyte and acid-base disturbances in order to select diuretic agents with divergent effects (Table 1).

1. Clinical Scenario 1 – Proximal nephron blockade and hyponatremia

The landmark trials that have proved significant cardiovascular benefits of SGLT2i in patients with HF regardless of the ejection fraction (EF) or diabetes status have placed these agents in the standard of care of HF [24,27]. SGLT2i have a weak diuretic effect in monotherapy as less than 10% of the sodium handled by the proximal tubule is reabsorbed by the sodium-glucose cotransporter 2 [58]. Nonetheless, SGLT2i lead to significant natriuresis when combined with loop diuretics [59], while animal data points toward an additional effect of SGLT2i on NHE3 as well [60].

SGLT2i have been evaluated in several trials as an add-on therapy in ADHF [61]. The EMPA-RESPONSE-AHF trial randomized 80 patients to either empagliflozin 10 mg or placebo for 30 days [62]. Despite not showing a significant difference between the study arms in any of the primary endpoints (dyspnea, diuretic response, length of hospitalization, change in NT- proBNP), empagliflozin significantly increased the urinary output and reduced the risk of a composite endpoint of worsening or rehospitalization for HF or death at 60 days [62]. The EMPAG-HF randomized 60 patients with ADHF within 12h of admission to empagliflozin 25 mg daily or placebo in addition to standard decongestive therapies [63]. Daily addition of empagliflozin resulted in a 25% increase in cumulative urine output over 5 days (median 10.8 L versus 8.7 L in placebo, group difference estimation of 2.2 L [95% CI, 0.84 to 3.6]; $p = 0.003$). Furthermore, empagliflozin increased diuretic efficiency compared with placebo (14.1 mL urine per milligram furosemide equivalent [95% CI, 0.6–27.7]; p =

Table 2 - Trials evaluating sequential nephron blockade.

Site of additional blockade	Trial	Background diuretics	Additional comparator agent versus placebo	Primary endpoint	Results	Additional findings
Proximal nephron blockade	EMPA-RESPONSE-AHF [62]	Loop diuretics	Empagliflozin (10 mg)	- Change in dyspnea - Diuretic response - Change in NT-proBNP - Length of stay	- No difference in any of the primary endpoint events	- Lower incidence of a combined endpoint of in-hospital worsening of HF, rehospitalization for HF and mortality at 60 days. - Greater urinary output with empagliflozin
	EMPAG-HF [63]	Loop diuretics	Empagliflozin (25 mg)	- Cumulative urinary output over 5 days	- 25% increase in cumulative urine output over 5 days	- Empagliflozin increased diuretic efficiency compared with placebo, with more pronounced decrease in NT-proBNP
	EMPULSE [64]	Loop diuretics	Empagliflozin (10 mg)	- Weight loss - Weight loss adjusted per mean daily loop diuretic dose - Change in NT-proBNP - Hemoconcentration - Clinical congestion score	- Empagliflozin demonstrated significantly greater reductions in all studied markers of decongestion at all time-points	- Greater weight loss at Day 15 was associated with significantly higher probability for clinical benefit at Day 90 (composite endpoint of all-cause death, heart failure events, and a 5- point or greater difference in Kansas City Cardiomyopathy Questionnaire total symptom score change from baseline to 90 days)
	DIURESIS-CHF [71]	Loop diuretics	Acetazolamide	- Natriuresis after 24 h	- Natriuresis after 24 h was similar in the combinational treatment vs. loop diuretic only arm	- Loop diuretic efficiency, defined as natriuresis corrected for loop diuretic dose, was higher in the group receiving acetazolamide
	ADVOR [22]	Loop diuretics	Acetazolamide	- Successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy	- Patients with acetazolamide add-on achieved more frequently successful decongestion both within 3 days after randomization (42.2% vs. 30.5%) and at discharge (78.8% vs. 62.5%).	- Acetazolamide led to a greater urinary output and natriuresis - Acetazolamide did not decrease the risk of death or rehospitalization for HF
Distal nephron blockade	CLOROTIC [79]	Loop diuretics	Hydrochlorothiazide	- Change in dyspnea - Change in body weight	- Patients assigned to HCTZ were more likely to lose weight at 72 h than those assigned to placebo, but there were no significant differences in patient-reported dyspnea	- Patients allocated to HCTZ showed greater 24-h diuresis and weight loss for each 40 mg of furosemide - There were no differences in mortality or rehospitalizations
	ATHENA-HF [83]	Standard therapy that may include low-dose spironolactone (12.5 or 25 mg)	Spironolactone 100 mg	- Change in NT-proBNP levels from baseline to 96 hours	- No significant difference in the log NT-proBNP reduction between the 2 groups	- No significant change in clinical congestion score, dyspnea assessment, urinary output, weight change, mortality or rehospitalization for HF.
	EVEREST [84]	Standard therapy	Tolvaptan	- All-cause mortality - Cardiovascular death or hospitalization for HF	- Tolvaptan had no effect on long-term mortality or heart failure–related morbidity	- Tolvaptan improved day 1 patient-assessed dyspnea, day 1 body weight, day 7 edema.

Continued Table 2 - Trials evaluating sequential nephron blockade.

Site of additional blockade	Trial	Background diuretics	Additional comparator agent versus placebo	Primary endpoint	Results	Additional findings
Distal nephron blockade	TACTICS-HF [55]	Loop diuretics	Tolvaptan	- Proportion of patients with at least moderate improvement in dyspnea by 7-point Likert scale at both 8 and 24 h, without death or need for rescue therapy within 24 h (defined as responders)	-The proportion defined as responders at 24 h (primary study endpoint) was 16% for tolvaptan and 20% for placebo (p = 0.32).	- Tolvaptan addition resulted in greater weight loss and net fluid loss compared with placebo
	SECRET of CHF [56]	Loop diuretics	Tolvaptan	- 7-point change in self-assessed dyspnea at 8 and 16 h	- No difference in the primary endpoint of day 1 dyspnea reduction	- Tolvaptan led to a significantly greater weight loss and dyspnea reduction at day 3.

Abbreviations: HF, heart failure; HCTZ, hydrochlorothiazide

0.041) and led to a more pronounced decrease of NT-proBNP [63]. Moreover, the cumulative dose of loop diuretics was lower in the empagliflozin group compared to placebo [63]. Lastly, the EMPULSE trial randomized patients with ADHF after stabilization (24h) to empagliflozin 10 mg daily or placebo for 90 days [64]. Empagliflozin was associated with a benefit on all markers of decongestion, while a greater weight loss at day 15 was associated with a clinical benefit at 90 days (composite of all-cause death, heart failure events, 5-point or greater difference in a total symptom score change from baseline to 90 days) [64]. Moreover, in all trials empagliflozin was safe and well tolerated with no adverse effects on renal function.

While SGLT2i showed a benefit in both the management of ADHF and long-term management of HF, the preference for these agents as add-on therapy might also be derived from the positive influence on several electrolyte abnormalities [61]. In a propensity-matched analysis, both loop and thiazide diuretics were associated with hyponatremia [65]. In addition, dilutional hyponatremia is frequently encountered in ADHF. Due to their osmotic diuretic properties, SGLT2i have been shown, in two RCTs of patients with the syndrome of inappropriate antidiuresis, to significantly increase serum sodium levels [66,67]. In terms of potassium homeostasis, a post-hoc analysis of the CREDENCE trial showed that among patients treated with RAAS inhibitors, canagliflozin reduced the risk of hyperkalemia without increasing the risk of hypokalemia (see also Clinical Scenario 3) [68].

2. Clinical Scenario 2 – Proximal nephron blockade and metabolic alkalosis

Hypochloremic metabolic alkalosis frequently develops following loop and thiazide diuretic treatment [61]. It is frequently encountered in patients with HF, as a consequence of neurohumoral activation, and is a contributor to diuretic resistance in such circumstances [69]. In a post-hoc analysis of 678 patients from the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials that had a baseline serum bicarbonate assessment, 46.6% of patients had metabolic alkalosis and serum bicarbonate level further increased following decongestive therapies [69]. Contrary to initial beliefs, a change in serum bicarbonate was not associated with significant decongestion, and elevated bicarbonate level at baseline was identified as an independent predictor of later rehospitalizations for HF [69,70]. These observations have led to the reconsideration of CA inhibitors in ADHF [4].

The DIURESIS-CHF trial randomized 34 patients with ADHF to bumetanide and either acetazolamide (250–500 mg daily) or placebo [71]. The primary endpoint (natriuresis after 24 h) was similar in the two treatment arms [71]. However, the loop diuretic efficacy (defined as natriuresis corrected for loop diuretic dose) was significantly higher with acetazolamide add-on [71]. This pilot study led to the larger Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial that randomized 519 patients with ADHF to receive i.v. acetazolamide (500 mg daily) or placebo in addition to loop diuretics [22]. Patients with an acetazolamide add-on achieved more frequently successful decongestion both within 3 days after randomization (42.2% vs. 30.5%, risk ratio, 1.46; 95% confidence interval [CI], 1.17 to 1.82; $p < 0.001$) and at discharge (78.8% vs. 62.5%, risk ratio, 1.27; 95% CI, 1.13 to 1.43). Acetazolamide led to a greater urinary output and natriuresis, without an increased risk of adverse events [22]. Nonetheless, some criticism arose from the definition of decongestion in the ADVOR trial that may have led to a higher incidence of the primary endpoint occurrence compared to previous studies, especially in light of the fact that the difference in urinary output was only approximately 0.5 L and that the clinical findings did not lead to a reduction in deaths or rehospitalizations for HF [4,61]. Nonetheless, acetazolamide remains an adequate add-on option in patients with metabolic alkalosis and significant residual congestion.

3. Clinical Scenario 3 – Distal nephron blockade and hyperkalemia

RAAS blockade represents the cornerstone for the management of patients with HF, but the widespread implementation of adequate

regimens of ACEIs, ARBs, and MRAs is significantly limited in real-world clinical practice by the occurrence of hyperkalemia or worsening of renal function (WRF), especially in those with preexisting chronic kidney disease [72]. The landmark RALES trial demonstrated that the addition of 25 mg of spironolactone in patients with HF and reduced EF led to a 30% reduction in mortality [73]. A subsequent population-based analysis showed that following the publication of the RALES trial, the prescription for spironolactone increased by approximately four-fold [74]. Moreover, even the use of the newer selective nonsteroidal MRA finerenone still leads to a higher risk of hyperkalemia [75]. Nevertheless, this translated into a significantly increased risk of hospitalizations and mortality associated with hyperkalemia [76]. This frequently leads to suboptimal dosing or discontinuation of RAAS blockade, which alters the cardiovascular outcomes [76]. An observational study from the United Kingdom that included RAAS inhibitors prescribed for patients with new-onset CKD or HF showed that those with hyperkalemia had a higher risk of RAAS inhibitors down-titration that led to a seven-fold increase in mortality [76]. In analysis of the ESC-HFA-EORP Heart Failure Long-Term Registry, it was shown that the discontinuation of RAAS inhibitors rather than hyperkalemia was associated with mortality, leading to the hypothesis that hyperkalemia is a marker for RAAS inhibitor discontinuation, but not a risk factor for worse cardiovascular outcomes [77].

Thiazide diuretics might improve the hyperkalemia associated with RAAS blockade in patients with HF in addition to the potential benefit of improving the diuretic efficacy of loop diuretics. A pooled analysis of patients that received a stepwise pharmacological approach from the CARRESS-HF, DOSE-AHF, and ROSE-AHF trials showed that a combination of loop and thiazide diuretics led to more weight loss compared to loop diuretic monotherapy [78]. The CLOROTIC trial randomized 230 patients with ADHF to hydrochlorothiazide (HCTZ) or placebo for 5 days, in addition to loop diuretics. Patients randomized to HCTZ lost more weight at 72 h [−2.3 vs. −1.5 kg; adjusted estimated difference (95% CI) −1.14 (−1.84 to −0.42); P=0.002], but this did not translate into an improvement in patient-reported dyspnea, rehospitalization, or mortality [79]. Nonetheless, the combination therapy led to significantly higher rates of hypokalemia (either potassium level of ≤ 3.5 mmol/L or ≤ 3 mmol/L) [79]. In addition, HCTZ use was associated with a higher risk of WRF. Despite the initial belief that WRF portends a worse outcome, contemporary data points towards an effective decongestion, as WRF in patients with a good diuretic response was not associated with poor outcomes [80]. Moreover, the mean eGFR in this study was approximately 40 ml/min, while about 20% of patients had a baseline eGFR of less than 30 ml/min [79]. While previous concerns that thiazide diuretics are less effective in patients with low eGFR, recent data provides the evidence of their important antihypertensive effects in patients with advanced CKD (eGFR less than 30 ml/min) [81,82]. Given that distal tubular compensatory sodium reabsorption is the mechanism for diuretic resistance in a substantial proportion of patients with HF, the kaliuretic properties of loop-thiazide diuretic combination might be also the appropriate choice to mitigate the hyperkalemia associated with contemporary management of HF.

4. Clinical Scenario 4 – Collecting duct blockade and hypokalemia

Both loop and thiazide diuretics can lead to the development of hypokalemia [65]. Moreover, in the CLOROTIC trial, their combination led to significantly higher rates of hypokalemia (either potassium level of ≤ 3.5 mmol/L or ≤ 3 mmol/L) [79]. Despite the fact that higher doses of spironolactone (100 mg) did not lead to an improvement in markers of decongestion or NT-proBNP in the ATHENA-HF trial, MRAs use might be beneficial in counteracting hypokalemia and metabolic alkalosis associated with loop and thiazide diuretics, especially given their benefit for mortality shown in the RALES trial [73,83].

Conclusion

In conclusion, the use of diuretic therapy remains fundamental to the successful management of heart failure. Without a definitive proven strategy from observational/randomized trials, the approach to the sequential nephron blockade should rather take into account the patient phenotype, the suspected nephron segment responsible for diuretic resistance, and the anticipated electrolyte and acid–base disturbances in order to select diuretic agents with divergent effects.

Abbreviations

ACEIs, angiotensin-converting-enzyme inhibitors
ADH, antidiuretic hormone
ADHF, acute decompensated heart failure
ARBs, angiotensin receptor blockers
AQP, aquaporin
CA, carbonic anhydrase
CKD, chronic kidney disease
CNT, connecting tubule
DCT, distal convoluted tubule
EF, ejection fraction
ENaC, epithelial sodium channel
HCTZ, hydrochlorothiazide
HF, heart failure
MRAs, mineralocorticoid receptor antagonists
NHE3, sodium-hydrogen exchanger 3
RAAS, renin-angiotensin-aldosterone system
RCTs, randomized controlled trials
SGLT2i, sodium-glucose cotransporter 2 inhibitors
WRF, worsening renal function

Disclosures

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