Review Article

Treating Diuretic Resistance in Light of New Evidence

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Abstract

Nearly 80% of all patients hospitalized for decompensated heart failure (HF) present hypervolemia with signs and symptoms of congestion,[1,2] for which decongestion is an essential pillar of treatment. Most guidelines recommend the use of loop diuretics as soon as the patient is admitted.[3-5] Despite this, a post-hoc analysis of the DOSE-AHF and CARRESS-HF studies showed that only half of these patients were free of congestion at the moment of high discharge, this being the group with the highest mortality and readmission rates within 60 days.[2]

For the management of congestion, for a long time only the use of loop diuretics was recommended, with little focus placed on the benefits of using additional strategies. Part of the difficulty in achieving euvolemia is due to diuretic resistance. In recent years, however, new drugs have been tested and have proven to be interesting options for treating hypervolemia, especially in patients with refractory congestion and diuretic resistance. This review aims to summarize the strategies studied, the mechanisms involved in diuretic resistance, and the clinical characteristics of these patients, with the aim of assisting in the most appropriate choice of approach to congestion.[6]

Diuretic resistance

When we speak of diuretic resistance, it is important to understand the concept of diuretic efficacy, which represents the relationship between sodium excretion capacity, weight change, and increase in diuresis adjusted by the dose of diuretic in use. Diuretic resistance refers to the inability to achieve decongestion despite the appropriate dose of diuretics and the need to use high doses of diuretics associated with low diuretic efficacy.[7]

Diuretic resistance is multifactorial, involving the activation of the renin-angiotensin-aldosterone system (RAAS), nephron remodeling, previous chronic kidney disease (CKD), and a reduction in intravascular fluid.[6] The exact prevalence is not well-known, but a recent record demonstrated that this condition can affect around 21% of all patients with decompensated heart failure (HF).[6] In general, these individuals present more comorbidities, including renal dysfunction, hyponatremia, and hypotension, and have lower rates of effective decongestion, a greater risk of prolonged hospitalization, re-hospitalization, and an increase of approximately 37% in mortality in 1 year.[6,8]

The main mechanisms involved and the clinical characteristics of these patients are summarized in Table 1.

Keywords

Heart Failure; Diuretic Resistance; Congestion; Hypervolemia; Diuretic Therapy; Decongestion

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Malabsorption and increased abdominal pressure

Oral diuretics (OD) depend on absorption to ensure their bioavailability. Furosemide has a bioavailability that varies from 10% to 100% (average 50%), while bumetanide and torsemide have greater and more consistent oral bioavailability (> 90%), making oral and intravenous doses similar.

In congested patients, intestinal edema can reduce its absorption, causing lower concentrations.[9] Hypervolemic patients, and especially those with right ventricular (RV) dysfunction, who have intestinal edema and reduced splanchnic perfusion, may experience decreased diuretic efficacy with OD medications, showing a better response with intravenous (IV) use. Therefore, this route should be preferred until the oral absorption capacity of the medication is reestablished, when the transition from diuretics to OD is performed and preparation for hospital discharge in the so-called transition of care.

Another frequent congestion phenotype in patients with right-sided HF is ascites, which, when voluminous, causes an increase in intra-abdominal pressure. This increase can cause abdominal compartment syndrome, resulting in worsening kidney function and poor response to diuretics. Recognizing this phenotype is important, as relief paracentesis is important in the management of diuretic resistance, providing a better response to measures.

"Ceiling dose" and shift in the dose-response curve

The diuretic threshold refers to the dose necessary to reach maximum diuretic efficacy and beyond which there is no significant increase in diuresis. In "diuretic-naive" patients, the usual dose of furosemide for this is 80 mg/d. The curve that relates the dose of furosemide necessary for the response in relation to the fraction of urinary sodium excreted in HF is shifted downwards and to the right. The clinical translation of this is the need for higher doses of furosemide to promote a certain response (natriuresis). Furthermore, the maximum response obtained with an increase in furosemide dose is lower than that obtained in healthy individuals.[9]

This phenomenon supports the recommendation to double the dose of loop diuretics in the absence of a satisfactory response, thus seeking to find the individual diuretic threshold.[4]

Table 1 – Resistance mechanisms and presentation C

Mechanisms involved in diuretic resistance		
Mechanism	**Clinical characteristics**	**Approach**
Malabsorption and increased abdominal pressure	Significant edema, especially with RV dysfunction, ascites, and abdominal distension.	Use of intravenous loop diuretics Relief paracentesis (depending on the magnitude of ascites)
Ceiling dose (shift of the dose-response curve)	Need for higher doses of diuretic to achieve satisfactory response. The dose at which there is a response establishes the individual's threshold.	Increasing the dose of loop diuretic
Compensatory post-diuretic Na+ reabsorption	Reduction in diuresis in the interval between doses	Reducing the frequency between doses or continuous infusion
Braking phenomenon Distal nephron remodeling with Na+ reabsorption in the distal convoluted tubule	Reduction in diuretic response to each dose of diuretic Chronic use of diuretics with suboptimal response to isolated loop diuretics despite increasing the dose.	Add thiazides
Neurohormonal activation with Na+ reabsorption in the proximal convoluted tubule (with or without alkalosis)	Chronic use of diuretics with suboptimal response to isolated loop diuretics despite increasing the dose. Increased bicarbonate retention*	Add Acetazolamide or SGLT-2 Inhibitors * If alkalosis, preferably consider acetazolamide.
Intra → extravascular leakage	Hyponatremia and/or hypoalbuminemia with leakage of fluid into the third space (pleural effusion, lower limb edema, ascites) and a worsening of renal function with the use of loop diuretics in the usual dose	Hypertonic solution
Reduced renal perfusion	Signs of increased afterload, low output, or increased intra-abdominal pressure. Renal and/or hepatic dysfunction, increased lactate, drop in Svo2, pallor, cold extremities, reduced pulse pressure, blood pressure variations (hypo or hypertension), voluminous and tense ascites	Consider vasodilators. Inotropes, and paracentesis
Kidney failure	History of previous kidney disease, reduced kidney size, loss of corticomedullary differentiation, albuminuria, elevated slag levels, and/or inability to decongest despite staged strategies	Increasing the dose of loop diuretic Ultrafiltration +/- dialysis

A diuretic response is considered adequate when a urinary sodium sample is 50-70 mmol after 2 hours and diuresis 100-150 ml/h in the first 6 hours.[10,11] The PUSH TRIAL study evaluated an approach to treating decongestion guided by natriuresis. Although there was no difference in clinical outcomes, the guided treatment group had greater natriuresis when compared to the other group.[12]

Compensatory post-diuretic sodium reabsorption

After diuretic administration, excess level of natriuresis and diuresis generate compensatory sodium reabsorption of equal magnitude, resulting in a neutral sodium balance. This is the mechanism by which, despite an adequate initial diuretic response, the individual does not achieve a negative water and sodium balance between diuretic doses. Thus, reducing the time between dosages or administering the loop diuretic in continuous infusion can guarantee exposure of the nephron to a maintained concentration of diuretic, in which the compensatory reabsorption mechanism does not occur.[9]

The DOSE study tested the use of loop diuretics in continuous versus bolus infusion. This study received criticism because the patients did not meet criteria for diuretic resistance, in which this strategy makes more sense. Furthermore, continuous infusion was performed at doses below those commonly recommended and without a loading dose. In selected cases, such as patients with diuretic resistance suspected of compensatory post-diuretic sodium reabsorption or with cardiorenal syndrome and/or severe RV dysfunction, the continuous infusion strategy may be a useful alternative.[13]

"Braking phenomenon" and distal nephron remodeling with compensatory sodium reabsorption

The chronic use of loop diuretics leads to increased sodium avidity in the distal portion of the nephrons. This increase in sodium chloride reabsorption capacity causes a progressive decline in natriuresis with each dose of diuretic, which is called the "braking phenomenon".[13] This is a protective phenomenon, triggered by an acute loss of sodium and water to prevent excessive diuresis and volume depletion. Activation of the RAAS and the sympathetic nervous system can mediate tubular sodium absorption.[9]

Over time, this phenomenon leads to an adaptation mechanism involving cellular hyperplasia and hypertrophy of the distal convoluted tubule, collecting tubules, and collecting ducts.[13] Thus, unreabsorbed sodium in the proximal segments of the nephron and the loop of Henle is avidly reabsorbed in the distal nephron, generating an important mechanism of diuretic resistance.

Clinically, this translates into a loss of diuretic efficacy as with each new dose ("braking phenomenon") or with a chronic use of loop diuretics (distal nephron remodeling). Often, the patient notices that the usual dose no longer generates the same diuresis and that the isolated increase in the loop diuretic does not increase the diuretic response as expected. In these cases, the best alternative is the combination of thiazide diuretics capable of blocking sodium reabsorption at the compensatory site, thereby partially nullifying these resistance mechanisms.

Compensatory sodium reabsorption in the proximal convoluted tubule

Previous studies have already demonstrated that patients with HF frequently have high bicarbonate levels. This retention is stimulated by neurohormonal activation and the use of loop diuretics.[14]

Carbonic anhydrase II catalyzes the formation of HCO3 in proximal tubular cells, generating H+, which is exchanged for Na+ in the proximal nephron through the NHE3 transporter. On the basolateral surface, Na+ transport occurs through the Na+/HCO3 cotransporter (NBC), reabsorbing most of the sodium in the first segment of the proximal tubules.[15] These two transporters are stimulated by angiotensin II, which explains why individuals with HF absorb proportionally more sodium filtered in the proximal nephron than healthy individuals. Therefore, high HCO3 levels in HF can be seen as an indicator of neurohormonal activation due to increased sodium and HCO3 uptake in the proximal tubule.[14]

Loop diuretics also contribute to the increase in HCO3. In addition to having kaliuretic effects (exchange of K+ for H+ in the distal nephron), these inhibit chloride uptake in the macula densa, blocking the NKCC receptor and aggravating neurohormonal (intrarenal) activation, resulting in increased sodium and HCO3 retention in the proximal nephron. As a result, the amount of sodium and chloride present in the thick ascending branch of Henle decreases, in turn generating less substrate for the NKCC receptor, thus reducing the effectiveness of loop diuretics. This is important, as this form of diuretic resistance generally causes the prescription of higher doses of loop diuretics, resulting in a vicious cycle of more neurohormonal activation and compensatory reabsorption of Na+ and HCO3 in the proximal tubule, worsening the condition.

In these cases, the best strategy is to choose an agent capable of acting on the proximal convoluted tubule, such as acetazolamide, rather than thiazides, which would act on the distal convoluted tubule. Recently, acetazolamide proved to be effective in decongestion regardless of the baseline bicarbonate, although the response was amplified in patients with high bicarbonate levels, representing a group of special value for the use of the drug.[5]

Although SGLT-2 inhibitors (iSGLT2) and acetazolamide act on the proximal convoluted tubule, their mode of action and potency differ substantially. It is estimated that around 5% of all proximal sodium uptake is mediated by SGLT2, while 60% is mediated by the apical Na/H exchanger, which is why a greater natriuretic power is expected with acetazolamide than with iSGTL-2.[11,14]

Leakage from intravascular to extravascular

Hyponatremia is a marker of poor prognosis in HF and, by reducing the osmolarity of the intravascular environment, it helps in the leakage of volume into the extravascular space. HF is a disease frequently associated with malnutrition and sarcopenia. Likewise, hypoalbuminemia causes a reduction in intravascular colloid osmotic pressure, causing fluid to leak out of the vessel.

This causes ascites, pleural effusion, and lower limb edema. However, despite signs of congestion, kidney function often worsens after the use of diuretics. This is because diuretic therapy induces relative renal hypovolemia, increasing the level of slag without effective decongestion.

In cases of hyponatremia, hypertonic saline solution (SSH) followed by a bolus of furosemide promotes an increase in intravascular osmolarity, mobilizing fluid intravascularly, allowing a more effective diuretic response with less impact on renal function. Improving nutritional status in sarcopenic and malnourished individuals should also be pursued as a target in the treatment of HF.

Reduced renal perfusion

In patients with decompensated HF, renal perfusion is often compromised, either due to increased afterload or reduced cardiac output, associated with increased central venous pressure, in the so-called cardiorenal syndrome. The patients often have reduced urine output, increased lactate, renal, and/or hepatic dysfunction, decreased central venous saturation, reduced pulse pressure, hypotension, or hypertension, in addition to signs of hypervolemia.

In this scenario, even an early implementation of diuretic therapy may not work, since the kidney is in a state of hypoperfusion, and thus cannot respond adequately to the measures. Therefore, hemodynamic compensation strategies must also be associated, such as vasodilators and/or inotropes, in addition to diuretic measures.

Kidney failure

In patients with chronic kidney disease (CKD), the dose required to generate an adequate diuretic response is often higher, due to several factors, including decreased availability of the drug in the nephron, reduced secretion in the proximal tubule, and a decline in sodium filtration due to a reduced glomerular filtration rate (GFR). In practice, the dose of loop diuretics should generally be increased in direct proportion to the decrease in GFR.[10]

Some patients develop a progressive worsening of the renal function and oliguria/anuria in the treatment of decongestion, with the most efficient measure being ultrafiltration associated or not with dialysis.

The nephron and diuretic studies

Several studies have tested different diuretic strategies in the management of acute HF. We divided the main studies according to the site of nephron action addressed (Figure 1 and Table 2).

Proximal convoluted tubule

The proximal convoluted tubule is the segment of the nephron responsible for the reabsorption of 60-65% of filtrate sodium in normal individuals. In HF, through resistance mechanisms, it may be responsible for 75-85% of nephron sodium reabsorption.[9] Due to its potential to promote natriuresis, this segment has been studied in strategies for treating congestion. In this scenario, two therapeutic targets may be interesting: carbonic anhydrase enzyme and SGLT-2 receptors.

Carbonic anhydrase inhibitors

As mentioned above, inhibition of the carbonic anhydrase enzyme reduces the concentration of H+ and HCO3-, and leads to the excretion of Na+ and water. Acetazolamide is a diuretic capable of inhibiting carbonic anhydrase, and its use for decongestion was tested in a study called ADVOR.[5]

The ADVOR study was carried out to evaluate whether acetazolamide associated with a loop diuretic increases the chance of effective decongestion in patients hospitalized for HF. The multicenter study randomized 519 patients with acute decompensated HF to receive intravenous acetazolamide 500 mg/day or placebo, in addition to the loop diuretic. The primary outcome was an improvement in congestion assessed by a composite score of the presence and intensity of peripheral edema, pleural effusion, and ascites after 72 hours, which was achieved in 42.2% of the patients in the acetazolamide group and 30.5% of patients in the placebo group ($p<0.001$). The acetazolamide group had a lower rate of residual congestion and a shorter length of stay, without significantly increasing the incidence of adverse events and with no impact on outcomes of death or re-hospitalization.[5] It is worth noting that patients using iSGLT-2 were excluded. and to date, there are no studies that contemplate the combined blockage of the proximal convoluted tubule (acetazolamide + iSGLT-2). With the introduction of these as disease-modifying drugs in HF, more studies should be carried out to evaluate the effect of the association with other diuretics, such as acetazolamide.

SGLT-2 Inhibitors

Sodium glucose linked transporter type 2 (SGLT-2) is responsible for the reabsorption of sodium and glucose in the proximal tubule of the nephron. Thus, its inhibition can lead to glycosuria and increased diuresis and natriuresis. However, the potential for iSGLT-2 to induce these effects is related to the level of serum glycemia, which is why patients tend to present a low risk of hypoglycemia. iSGLT-2s also reduce sodium reabsorption by inhibiting the sodium-hydrogen cotransporter (NHE3) in the proximal convoluted tubule.[11]

In addition to these mechanisms, iSGLT-2 has also demonstrated robust benefits in the treatment of heart failure with reduced ejection fraction (HFrEF), in terms of reducing hospitalizations and mortality, in important studies such as DAPA-HF (dapaglifozin) and EMPEROR-reduced (empaglifozin). In the setting of refractory congestion, initial studies demonstrated a limited power of these drugs in promoting diuresis and natriuresis;[11] however, more recently new and larger studies have been carried out to evaluate their potential to improve diuretic efficacy. The main studies were: EMPULSE, EMPAG-HF, EMPA RESPONSE-AHF, DAPA RESIST, and DICTATE-AHF.

The EMPULSE study randomized 530 patients into a placebo group versus empaglifozin 10 mg/day in patients with acute HF, regardless of ejection fraction, 24 hours after admission. The primary outcome was a clinical benefit defined by the set of time to death, number, and time to occurrence of a HF event or 5-point variation in the Kansas Quality of Life Questionnaire (KCCQ) at 90 days. The outcome occurred in 53.9% of the empaglifozin group and 39.7% of the placebo group ($p= 0.0054$). Regarding the treatment of congestion, a more significant weight loss was observed in the empaglifozin group (-1.5 kg) when compared to placebo ($p=0.014$).[16]

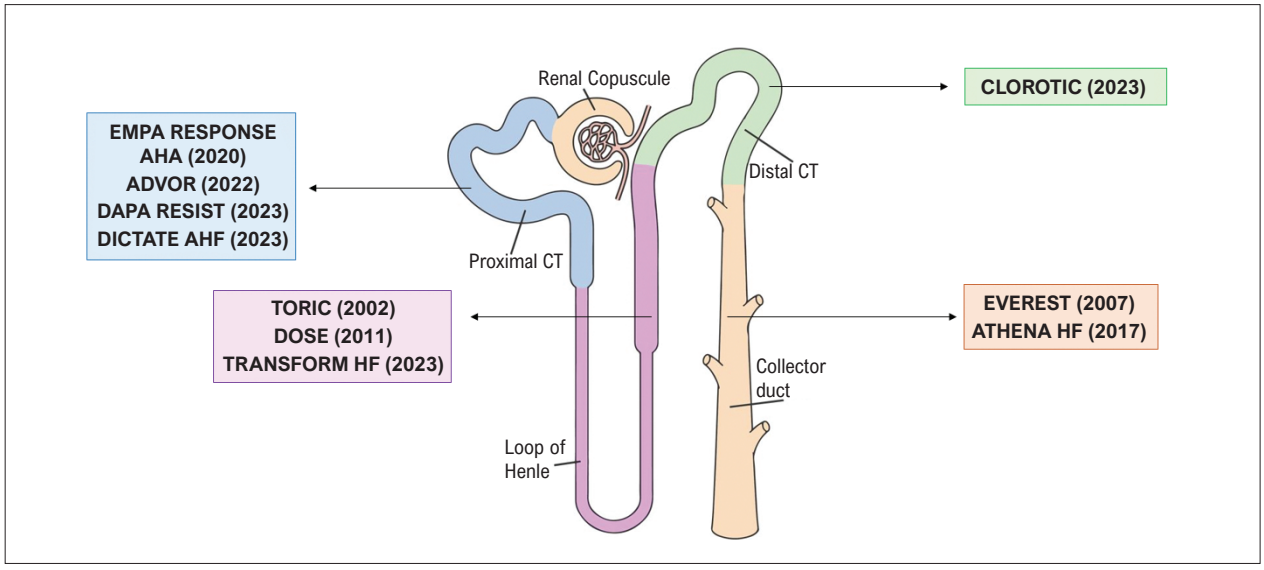

Figure 1 – *Clinical studies according to drugs tested at sites in different segments of the nephron.*

The EMPAG-HF study randomized 60 patients with acute decompensated HF within the first 12 hours of hospitalization, who received 25 mg/day of empaglifozin versus the placebo, in addition to standard loop diuretic therapies. The primary outcome was cumulative diuresis over a five-day period. The addition of empaglifozin to the standard therapy resulted in a 25% increase in cumulative urine output over a five-day period (group difference 2.2 L; p=0.003), with no difference in weight change. The daily and cumulative dose of loop diuretics was lower in the empaglifozin group. iSGLT2 increased diuretic efficiency without altering markers of kidney function and injury, reduced the N-terminus of the B-type natriuretic peptide prohormone (NT-proBNP), and proved to be a safe and effective strategy to aid in conventional decongestive treatment.[17]

Also with empaglifozin, the EMPA RESPONSE AHA study randomized 80 patients with acute HF to receive either 10 mg/day of empaglifozin or the placebo for 30 days. The primary outcome consisted of changes in dyspnea assessed by the visual analogue scale, diuresis, variation in NT-proBNP, or length of hospital stay, and showed no difference between the groups. Despite this, in the empaglifozin group, there was an increase in urinary output and a decrease in the combined outcome of worsening HF, re-hospitalization for HF, or death within 60 days, with no increase in adverse effects in relation to placebo.[18]

Dapaglifozin was tested in a multicenter study called DAPA RESIST involving 61 patients and aimed to compare the decongestion effect promoted by dapaglifozin versus metolazone in patients with acute decompensated HF with diuretic resistance. Patients must have insufficient decongestion (defined by loss <1 kg or a water balance <1 liter after 24 hours, despite treatment with furosemide ≥160 mg/day or equivalent) associated with brain natriuretic peptide (BNP) ≥100 pg/ml or NT- proBNP ≥400 pg/ml, persistence of congestion (peripheral edema, ascites, increased central venous pressure, pulmonary congestion in chest radiography or ultrasound), and the prospect of hospitalization for more than 3 days. Subjects were randomized into two groups: 10 mg/day of dapaglifozin and 5 or 10 mg/day of metolazone for up to 3 consecutive days. No difference in the primary outcome (weight change) was found between the groups. The dapaglifozin group showed lower diuretic efficacy (characterized by the need for higher doses of furosemide) and a lower incidence of hyponatremia and hypokalemia.[19]

Recently, the DICTATE-AHF study randomized 240 patients hospitalized for acute decompensated HF with signs of hypervolemia in the first 24 hours of hospitalization to dapaglifozin 10 mg/day or placebo in combination with a loop diuretic. The primary outcome was diuretic efficacy (defined as weight change over cumulative dose of loop diuretic), showing no difference between groups. Despite this, early initiation of dapaglifozin demonstrated an increase in natriuresis and diuresis and a reduction in the necessary amount of loop diuretics and length of hospital stay in relation to placebo.[20]

Loop of Henle

Loop diuretics

The loop of Henle is responsible for the reabsorption of approximately 25% of the sodium. The proximal convoluted tubule reabsorbs around 70% of the filtrate; however, the agents that act on these sites (acetazolamide and iSGLT-2) have failed to demonstrate any major capacity to promote sodium and water loss when used alone, given that a large part of this filtrate is reabsorbed at a later moment in the loop of Henle.[9]

Loop diuretics act by inhibiting the NA-K-Cl pump in the ascending segment of the loop of Henle, resulting in a greater excretion of sodium, chlorine, and potassium. These are transported by proteins, such as albumin, and secreted into the proximal convoluted tubule.[9]

In 2011, one of the most important studies with loop diuretics was carried out, DOSE, which tested the effectiveness of using loop diuretics in 308 patients with decompensated HFrEF in relation to dose (high x low) and infusion regimen (bolus x infusion continuous) in a 1:1:1:1 randomization. A low dose was defined as an intravenous dose equivalent to the patient's oral dose and a high dose as an intravenous dose equivalent to 2.5 times the previous oral dose. The primary outcomes were clinical improvement on a dyspnea scale and an increase in creatinine after 72 hours of treatment. Comparing the "bolus" group with the "continuous infusion" group, no statistical significance was found when considering the efficacy and safety outcomes. The comparison of the "high dose" versus "low dose" groups suggested that, although no difference was demonstrated between the groups, the use of high doses of furosemide was able to promote a greater relief of symptoms, increased diuresis, and a higher loss of weight, at the expense of a greater increase in creatinine when compared to the low dose group.[21]

Torsemide differs from other loop diuretics, such as furosemide, in that it has a longer half-life and duration of action with less variability in oral bioavailability, suggesting a greater diuretic effect. To test the hypothesis of superiority of torsemide in relation to furosemide, the TORIC study was published in 2002, an open cohort, with 1,377 patients, classified by the New York Heart Association (NYHA) II and III, who received 10 mg/day of torsemide orally versus 40 mg/day of furosemide or other oral diuretics, for 12 months, in addition to standard HF therapy. This study showed that torsemide is safe and, although it was not designed to evaluate outcomes, such as mortality, it suggested a lower incidence in patients treated with torsemide. Patients showed functional improvement (NYHA) and a lower incidence of hypokalemia.[22]

In 2022, TRANSFORM-HF was published, with 2,859 patients, designed to determine whether torsemide would result in a reduction in mortality compared to furosemide in patients hospitalized for HF. Although previous studies and meta-analysis suggest advantages of using torsemide over furosemide, this study demonstrated no benefit in relation to mortality or hospitalization due to HF.[23] However, some questions should be considered, such as the non-adherence of participants, crossover between groups, discontinuation of the use of diuretics during follow-up, and the use of new therapies, such as INRA (neprilysin and angiotensin receptor inhibitors) and iSGLT2, as they potentially reduce diuretic needs.

Distal convuluted tubule

Thiazide diuretics

Thiazide diuretics inhibit sodium re-uptake in the distal convoluted tubule by blocking the NaCl co-transporter. In healthy individuals, this segment is responsible for only 5% of sodium reabsorption. However, in individuals with a chronic use of loop diuretics, compensatory mechanisms can lead to hypertrophy of the tubular cells of the distal nephron, generating an increase in sodium reabsorption and a secondary decline in natriuresis.[9] Thiazides bind to proteins, requiring an adequate renal flow so that they can be secreted into the tubules and their effect may be reduced in the presence of severe renal dysfunction. These can cause significant hypokalemia, given that, for every sodium ion lost, 2-3 potassium ions are excreted. Metolazone, chlorthalidone, and hydrochlorothiazide represent this class of medications. Chlorthalidone has slower gastrointestinal absorption, with a long half-life (24 to 72 hours) compared to hydrochlorothiazide (6 to 12 hours). Metolazone is more potent than hydrochlorothiazide and maintains its action even when there is a severe decrease in the glomerular filtration rate.[13]

In 2023, the CLOROTIC trial was published with the aim of evaluating the addition of hydrochlorothiazide to furosemide as a strategy for treating congestion. The study randomized 230 patients, in functional class (FC) III and IV, with a full spectrum of ejection fraction and high levels of natriuretic peptides. The primary outcome was weight change and improvement in patient-reported dyspnea within 72 hours. The thiazide group showed greater weight loss (-1.5 kg, $p = 0.002$) and increased diuresis and natriuresis when compared to the placebo, with no difference in patient perception regarding improvement in dyspnea, hospitalization rate, or mortality. In the safety outcome, there was a higher rate of increase in creatinine in the thiazide group (46.5% x 17.2%; $p<0.001$), but no difference was found in hypokalemia and hyponatremia. In a post-hoc analysis using potassium levels ≤ 3.5 and ≤ 3.0 mmoL/L, hypokalemia was more frequent with thiazides.[23] The similar prevalence of hypotension between groups is important, as this is a frequent concern in the management of patients with acute HF. CLOROTIC also showed no differences in the length of stay.[24]

Collecting duct

Mineralocorticoid receptor antagonists

Spironolactone, eplerenone, and finerenone are mineralocorticoid receptor antagonists (MRAs). They work by blocking the action of aldosterone, a hormone that stimulates sodium reabsorption and potassium excretion in the distal nephron. For many years, it was believed that medications that inhibit the RAAS, such as angiotensin-converting enzyme inhibitors (ACEIs), would be sufficient to suppress the production of aldosterone. Therefore, it would not be necessary to combine these medications with an MRA, which would increase the risk of hyperkalemia. However, recent data have shown that aldosterone inhibition by ACE inhibitors is only transient. The first study then emerged to test the effect of spironolactone, an MRA, on morbidity and mortality in patients with severe HF. RALES (1999) randomized 822 patients, NYHA III-IV, left ventricular ejection fraction (LVEF) < 35%, to 25 mg/day of spironolactone versus the placebo, with a primary outcome of death from all causes. This study was interrupted early due to evidence of superiority of spironolactone.[25] Therefore, for the first time, a diuretic reduced the risk of morbidity and mortality in patients with severe HF, becoming a class I recommendation as a disease-modifying agent, most likely due to cardioprotective and non-diuretic mechanisms.

However, with a focus on treating congestion, the ATHENA-HF study was conducted to test the incremental efficacy of high doses of MRA, in addition to standard loop diuretic therapy, in the treatment of acute HF. Therapy with a dose of 100 mg of spironolactone daily proved to be no better than a dose of 25 mg in reducing NT-proBNP, increasing diuresis after 96 hours, reducing weight, and improving symptoms or congestion scores. High doses of MRA were safe, not triggering hyperkalemia or a worsening of renal function.[26] In addition to the benefit in clinical outcomes, MRAs are useful to compensate for hypokalemia, resulting from the use of loop diuretics and thiazides, maintaining an electrolyte balance.

Vasopressin antagonists

Vasopressin V2 receptor antagonists (aquaretics) act by blocking these receptors and inhibiting water absorption by the distal nephron. They are effective in treating hyponatremia and can also be used to reduce volume overload in patients with HF. Nevertheless, the EVEREST study showed no decrease in morbidity and mortality in acute HF due to tolvaptan.[27] This class of drugs is not routinely used to treat congestion in patients with HF.

Others

Hypertonic saline solution

The use of SSH in acute HF seems counterintuitive, since these patients show a greater sodium retention due to the activation of the neurohumoral system, considering that the fundamental objective of congestion management is to promote natriuresis. However, patients with refractory congestion often present sodium and water leakage into the extravascular space due to the magnitude of hypervolemia and hypoalbuminemia and/or hyponatremia. In this context, the use of loop diuretics in high doses can lead to a worsening renal function due to a state of relative renal hypovolemia. The rationale for the hypertonic solution is that it would promote an increase in intravascular osmolarity, mobilizing excess fluid from the extravascular to the intravascular. Hence, the association of a bolus loop diuretic would increase the power of natriuresis and diuresis without a large variation in pressure and, therefore, with less impact on glomerular hemodynamics.

A randomized, double-blind clinical study carried out by Issa evaluated the effect of SSH in preventing kidney failure in patients with acute HF. Patients were allocated to receive 100 ml of SSH (7.5% NaCl) or placebo, followed by a loop diuretic, two to three times a day. The primary outcome was an increase in serum creatinine ≥ 0.3 mg/dl. The results showed that SSH was effective in preventing kidney failure.

In the SSH group, only 2 (10%) patients showed an increase in serum creatinine, while in the placebo group, 6 (50%) showed this change (p=0.01).[28] Other studies have also demonstrated the power of this solution in promoting an increase in diuresis/natriuresis and weight loss. A meta-analysis with 5 randomized clinical trials and 1,032 patients treated with SSH plus IV furosemide versus 1,032 patients treated with IV furosemide alone demonstrated a decrease in all-cause mortality in the SSH group (p = 0.0003), in addition to a reduction in hospitalizations (p = 0.001).[29] There was also evidence of a better renal safety profile and increased weight loss. A retrospective analysis of a cohort of 40 patients, with a mean Na of 131 mmol/l and LVEF of 35%, showed that SSH with high doses of furosemide IV generated increased diuresis and weight loss (p = 0.01 and <0.001, respectively), as well as an improvement in renal function without causing electrolyte abnormalities.[30]

Ultrafiltration

Based on the hypothesis that ultrafiltration (UF) provides benefits, such as greater control over decongestion and reduced neuroendocrine activation, studies have evaluated the real benefit and safety of this technique in patients with HF. The two largest studies, UNLOAD and CARRESS HF, present conflicting results.

The UNLOAD trial in 2006 evaluated 200 patients with acute HF with signs of congestion. Patients were randomized to receive UF or intravenous diuretics. The primary outcome assessed weight loss and dyspnea 48 hours after randomization. The trial showed that UF was safe and effective in reducing weight and dyspnea after 90 days, and the UF group presented lower rates of readmission and a worsening of HF.[31]

The CARRESS HF study randomized 2,033 patients, comparing UF with a fixed removal of 200 ml/h to goal-based pharmacological therapy for decongestion in patients with congested HF and a worsening renal function. The trial failed to demonstrate the superiority of UF over the use of diuretics and was associated with a higher rate of adverse events.[32] Ultrafiltration is not without risks and can present complications, including infection, hemorrhage, electrolyte disturbances, anemia, and thrombocytopenia.

Currently, ultrafiltration is used as a rescue therapy to relieve congestion in refractory cases or with a significant worsening of renal function during decongestion, when dialysis is necessary. The PURE HF study should bring more answers regarding UF, as it serves to evaluate whether or not peripheral veno-venous ultrafiltration complementary to low-dose diuretics is effective in reducing outcomes, such as mortality and hospitalization for HF, within 90 days after randomization when compared to isolated intravenous diuretics.

Practical approach

Considering all of the above, we suggest a flowchart of a practical approach to diuretic management (Figure 2) according to the recommended drugs and doses (Table 3). However, it is essential to individualize this approach according to the patient's clinical presentation and the mechanisms suspected of being involved in the diuretic resistance in each case (Table 2).

Currently, most of the controversies revolve around which would be the best drug to be associated with the loop diuretic: iSGLT-2, acetazolamide, or thiazide. Figures 3 and 4 provide some considerations to be contemplated in this choice.[11,33,34] However, it is worth highlighting that a) there are no studies with the simultaneous association of two or three of these

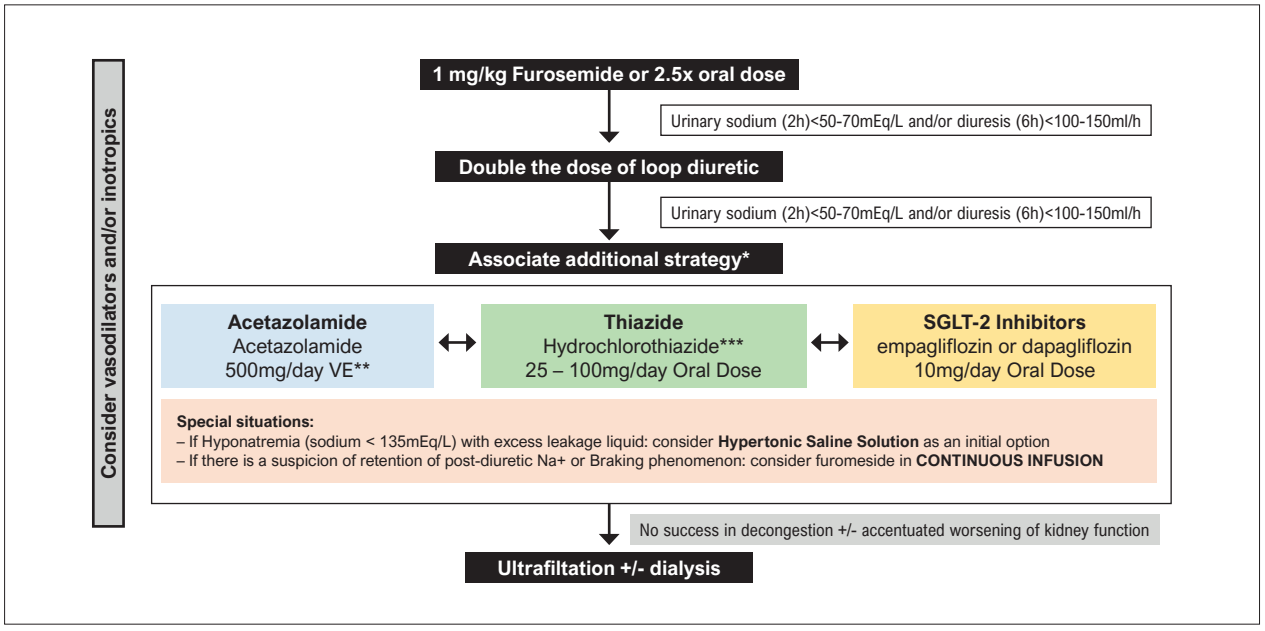

Figure 2 – *Congestion management flowchart. * There are no studies of the association of these strategies to date. ** In Brazil, on the oral dose is available. *** TGF>50ml/min: 25mg, 20-50ml/min: 50mg, <20ml/min: 100mg.*

Table 2 – Summary of the main studies with diuretics in HF

		Intervention time	Follow-up time	Intervention	Number of patients	Population characteristics	Previous loop diuretic dose (intervention group)	Average feve (intervention group)	Primary outcomes	Results
PROXIMAL CONVOLUTED TUBULE	EMPA RESPONSE AHA (2020)	4 days	30 days	Empaglifozin 10mg/day vs Placebo	79	AHF independent of LVEF, BNP ≥ 350 or NT-proBNP≥1400 using loop diuretics	100mg	36% (48% recurrent HF)	Improvement of dyspnea, diuretic response, length of hospital stay, and change in BNP	Primary outcome was not obtained, but empaglifozin did redeuce the combined outcome of worsening HF, readmission due to HF or death within 60 days
	EMPAG HF (2022)	5 days	---	Empaglifozin 25mg/day vs Placebo	60	AHF, independent of LVEF, using loop diuretics, BNP >100 pg/mL or NT-proBNP >300 pg/mL randomized in the first 12 hours of hospitalization	63% used loop diuretics	45% (60% recurrent HF)	Increased diuresis	Empaglifozin increased diuresis by 25% in 5 days compared to placebo (p=0.003). Also, less need for furosemide, greater diuretic efficacy and greater drop in NT-proBNP. No difference in weight loss.
	EMPULSE (2022)	90 days	90 days	Empaglifozin 10mg/day vs Placebo	530	AHF independent of LVEF, furosemide > 40mg IV or equivalent and signs of congestion	204 mg	32% (31% recurrent HF)	All-cause mortality, number and timing of HF events, and increase in KCCQ score	The primary outcome was 53.9% in the empagliflozin group and 39.7% in the placebo group (p= 0.0054). There was an improvement in the diuretic response and a greater drop in NT-proBNP.
	ADVOR (2022)	3 days	90 days	Acetazolamide 500mg/day vs Placebo	519	AHF independent of LVEF, furosemide>40mg, signs of hypervolemia, NT-proBNP>1000 or BNP>250	259mg	43%	Decongestion assessed by a congestion score	Primary outcome achieved in 42.2% of the acetazolamide group and 30.5% of the placebo group (p<0.001). Shorter hospital stay (-1.1 day) and greater diuresis. No difference in death or re-hospitalization.
	DAPA RESIST (2023)	3 days	90 days	Dapaglifozin 10mg/day vs metazolone 5 or 10mg/day	61	AHF independent of LVEF, furosemide >160mg, NT-proBNP ≥ 400 or BNP ≥ 100	260mg (dapaglifozina) 229mg (metazolone)	45%	Diuretic effect, evaluating weight change	No difference in the primary outcome, but greater need for furosemide and lower diuretic efficacy in the dapaglifozin group.
	DICTATE AHF (2023)	5 days	30 days	Dapagliflozin 10mg/day vs Placebo	240	AHF, independent of LVEF, using loop diuretics	80mg (EV)	48% with EF<40%	Diuretic effect, evaluating weight change	No difference in the primary outcome. Dapagliflozin group: greater diuresis, reduced length of stay, and lower dose of loop diuretic

LOOP OF HENLE	TORIC (2002)	12 months	12 months	Torasemide 10mg/day vs Furosemide 40 mg/day or other diuretics	2.303	Chronic HF, NYHA II-III	---	---	Safety, tolerability, and efficacy of torasemide	Torasemide was safe and well tolerated. It suggests a reduction in mortality ($p < 0.05$), although not designed for this. There was an improvement in CF NYHA ($p = 0.00017$).
	DOSE (2011)	3 days	60 days	Furosemide bolus vs. infusion continues and doses high vs. Casualties (1:1:1:1)	308	Chronic HF regardless of LVEF	134mg x 127mg 131mg x 131mg	35% x 35% 36% x 33%	Global assessment of symptoms and creatinine variation in the first 72 hours	No difference was found between the strategies. The high dose group: greater symptom relief, diuresis, and weight loss, but greater increase in creatinine.
	TRANSFORM HF (2023)	12 months	12 months for hospitalization e 30 months to death	Torsemide vs. Furosemide (dose at the discretion of the examiner)	2.859	ICA, LVEF independent of LVEF, NYHA II-III, average NT PRO BNP of 3,013	754 (torsemida) 778 (furosemide)	~70% with EF<40% (~30% recurrent HF)	All-cause mortality	The primary outcome was not achieved ($p = 0.76$).
DISTAL CONVULUTED TUBULE	CLOROTIC (2023)	5 days	90 days	Hydrochlorothiazide 25-100 mg/day vs. placebo	230	Chronic HF regardless of LVEF, hospitalization for AHF, use of diuretics 30 days before hospitalization	80mg	55% (68% EF>50%)	Change in body weight and dyspnea in the first 72 hours	No difference in dyspnea between the groups ($p=0.497$). The HCTZ group: greater weight loss ($p < 0.001$), greater diuresis, less need for furosemide and greater tendency for kidney failure (46.5 vs. 17.2%; $P<0.001$) and hypokalemia.
COLLECTOR DUCT	EVEREST (2007)	Período mínimo 60 days	~9,9 months	Tolvaptan 30 mg/day e. placebo	4.133	Chronic HF, LVEF < 40%, NYHA III-IV	---	27.50%	Mortality from all causes and composite of cardiovascular death and hospitalization due to HF	Negative primary outcome ($p = 0.55$). Improvement in secondary outcomes of dyspnea, body weight, and edema. When hyponatremia, Na levels increased significantly.
	ATHENA HF (2017)	96 hours	96 hours	Spironolactone 100 mg/day vs. placebo or spironolactone 25 mg/day	360	ICA, independent of LVEF, NT proBNP > 1000 or BNP > 250	122mg	35%	Change in NT proBNP levels in the first 96 hours	No difference in the change in NT-proBNP ($p = 0.57$) and in secondary outcomes (dyspnea score, congestion score, urine output, weight change, need for loop diuretics).

AHF: acute heart failure; LVEF: left ventricular ejection fraction; HF: heart failure; IV: intravenous; Na: sodium; HCTZ: Hydrochlorothiazide; NYHA: New York Heart Association; CF: Functional class; KCCQ: Kansas City Cardiomyopathy Questionnaire; BNP: atrial natriuretic peptide; --- Data not described in the study.

Table 3 – Diuretics used in the treatment of HF and their side effects

Drugs	Doses	Side Effects
Acetazolamida	500mg IV* (No definition of oral dose)	Changes in blood glucose, hyponatremia, hypokalemia, and metabolic acidosis
Dapagliflozina	10mg 1x/day O	Genitourinary infection; can cause skin rashes.
Empagliflozina	10mg 1x/day O	Genitourinary infection; may cause allergic skin reactions.
Furosemide	40mg - 240mg/day O 20mg - 240mg/day IV	Hypocalcemia, hypokalemia, hypomagnesemia, hyperuricemia, alkalosis, kidney failure, and ototoxicity.
Torsemida*	5 - 200mg/day O	Hyponatremia, hypokalemia, hyperuricemia, metabolic alkalosis, and ototoxicity.
Hydrochlorothiazide	25-100mg/day O	Hyperuricemia, hypokalemia, hyponatremia, hypomagnesemia, hyperglycemia, and hypochloremic alkalosis.
Metolazona*	2,5 - 5mg O/day	Hyperuricemia, hypokalemia, hyponatremia
Espironolactona	25 - 50mg O/day	Hyperkalemia, painful gynecomastia, renal dysfunction

*IV: intravenous; O: orally; * Not available in Brazil.*

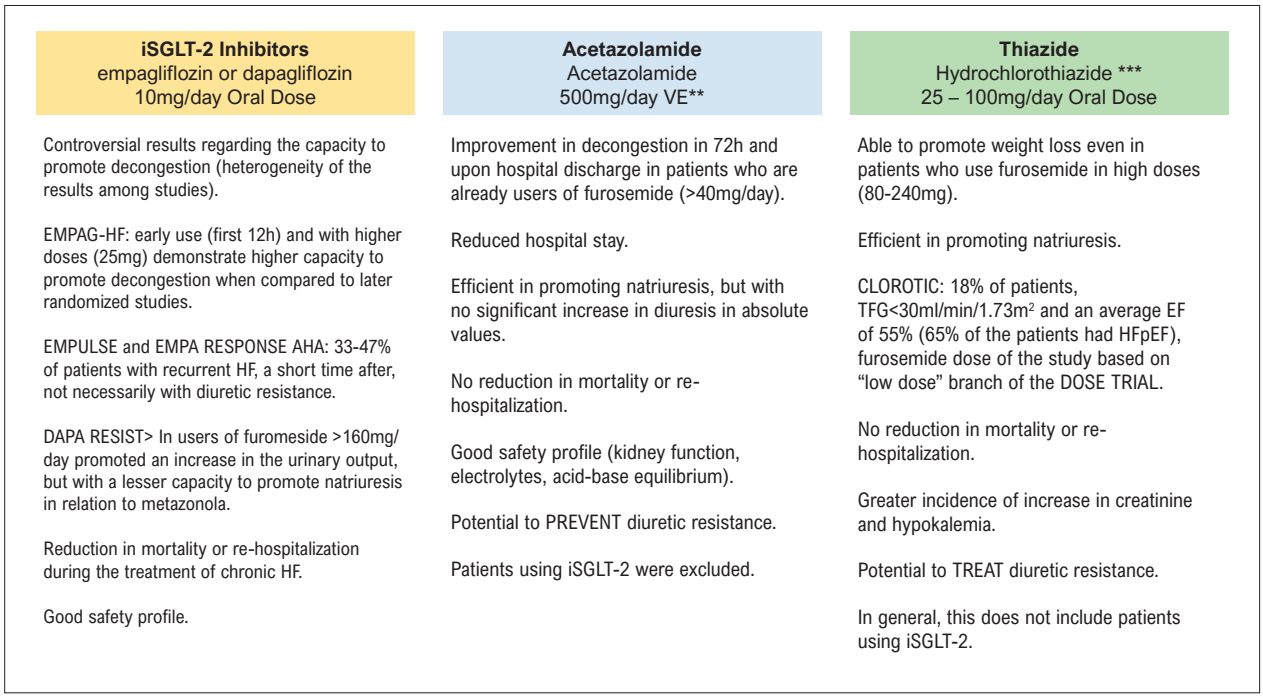

Figure 3 – *Considerations regarding sequential nephron blockade options.*

drugs; b) with the introduction of iSGLT-2 in the maintenance treatment of chronic HF, the admission of patients already using these medications will be more frequent; therefore, when faced with diuretic resistance, the choice will focus on the addition of acetazolamide versus thiazide; c) more studies are needed to test the safety and effectiveness of these combinations.

Management of acute HF, especially refractory congestion, is essential. Ensuring euvolemia at the time of discharge means, in addition to symptomatic improvement, prognostic improvement must also occur. However, this is a challenging topic in the treatment of HF. Many years after the discovery of diuretics, there is still no consensus on what strategy is the best in clinical practice. Fortunately, this topic has gained prominence more recently, and many studies have been dedicated to answering these open questions.

Author Contributions

Conception and design of the research: Bonatto MG; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Bonatto MG, Coiradas A, Monferdini L, Freitas AKE.

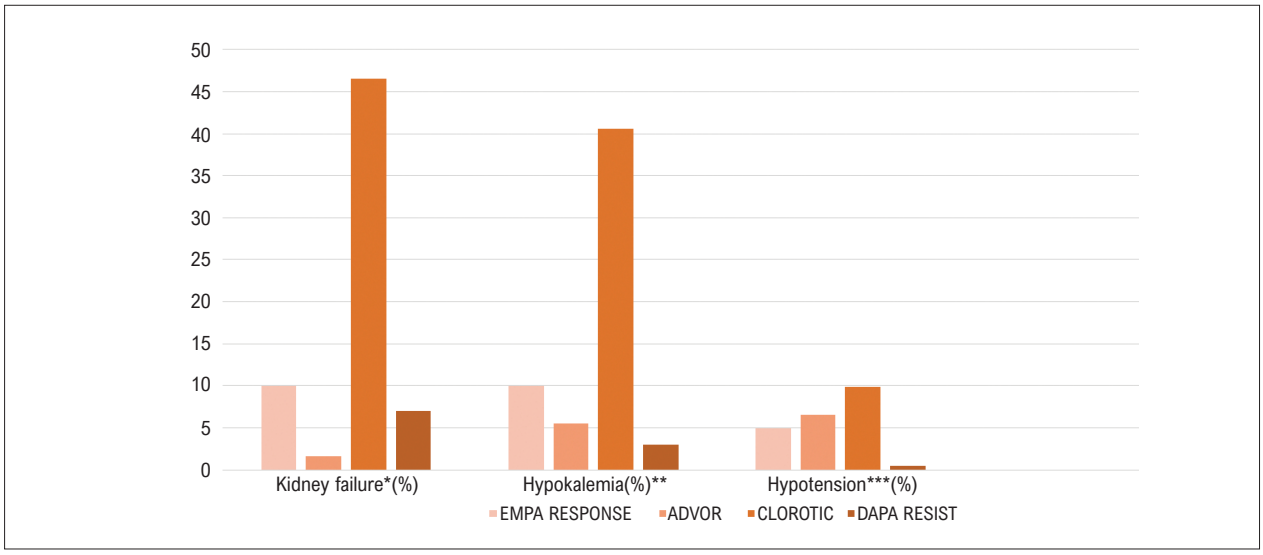

Figure 4 – *Incidence of the main side effects in different diuretic combination options. *Kidney failure: reduction in TFGe> 50% - except in the EMPA RESPONSE study, in which it was not specified; **Moderate to severe hypokalemia (k ≤ 3mmol/L); ***In the DAPA RESIST study, there was not hypotension in the dapagliflozin group.*

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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