Review Article

Diuretics in Treatment of Heart Failure

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Abstract

Heart failure is the leading cause of hospitalization in patients over 65 years of age, and, in most cases, patients present with signs and symptoms of congestion. Thus, diuretics play a prominent role and are among the most used drugs in heart failure. Although they have been used for decades, the lack of large controlled studies in the literature to support their use more adequately and the eventual development of resistance/tolerance are among the factors that make management of diuretics challenging.

Introduction

Heart failure (HF) affects 1% to 2% of the world population, afflicting more than 23 million people, and its prevalence increases with age. For example, in individuals over 85 years of age, prevalence can reach more than 17%. It is a serious public health problem, given its increasing financial impact. HF is the main cause of hospitalization among patients over 65 years of age, and, in the vast majority of cases, patients present with signs and symptoms resulting from pulmonary and systemic congestion. In this context, diuretics are extremely useful, as they are one of the primary factors in management of congestive syndrome.[1] During the past 3 decades, several drugs have emerged as protagonists in the treatment of HF, generating a real impact in terms of survival, as demonstrated by several multicenter, double-blind, controlled studies. Conversely, there is a lack of data in the literature, based on large controlled studies, to better support the use of diuretics, despite the fact that they have been used for more than half a century in patients with HF.[2]

Furthermore, another challenge is the eventual development of resistance to diuretics. In the context of patients with long-term HF, this occurrence is not uncommon, even though the actual incidence numbers are unknown, with several possible causal factors. These factors can occur alone or together. They range from inadequate dose to dietary issues, nutritional status, electrolyte disturbances, intestinal edema, and even renal dysfunction.[3] Diuretic resistance is an independent factor for mortality, due to both pump failure and sudden death.[4]

Accordingly, understanding how diuretics work, their interactions with the organism and with other diuretics, in addition to the mechanisms and factors that lead to diuretic resistance is of paramount importance so that we can obtain the maximum possible benefits from this longstanding class of drugs.

Keywords

Diuretics; Heart Failure; Heart Diseases.

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Types of diuretics and their use in heart failure

Nephrons are the basic working structure of the kidneys. There are about one million nephrons in each kidney. Each day, about 180 liters of blood passes through the kidneys, where solutes and water are filtered by the glomeruli and reabsorbed or, eventually, eliminated, through the sequence of tubules that make up the structure of the nephron. One of the main solutes in the body is sodium (Na^+). Normally, about 99% of the Na^+ that has been filtered in the glomeruli is reabsorbed in the tubules, at different points and in different proportions, which, therefore, attracts water back to the organism.[5]

For the most part, diuretics are drugs that act to increase solute excretion by the nephrons, mainly of Na^+ salts, such as NaCl, in a process known as natriuresis. In response to the osmotic force of these solutes, there is a reduction in the reabsorption of water in the tubules, resulting in increased water excretion, which we call diuresis. Vasopressin inhibitors are an exception to this rule, as they block free water reabsorption channels in the collecting tubule.[6] The following are the most well known classes of diuretics: carbonic anhydrase inhibitors, osmotic diuretics, loop diuretics, thiazide diuretics, aldosterone receptor antagonists (also known as potassium-sparing diuretics), and vasopressin antagonists. There are also sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which were originally developed for treatment of diabetes, but also have a diuretic effect. With the exception of spironolactone, which belongs to aldosterone antagonists, all diuretics need to be secreted into the tubular lumen in order to have an effect[7] (Figure 1).

Carbonic Anhydrase Inhibitors

Carbonic anhydrase is present in the basolateral and apical membranes of proximal convoluted tubular cells of nephrons, but also in the ciliary process of the eye, the choroid plexus, the intestine, and the pancreas. Its function is to catalyze the hydration of bicarbonate anions (HCO_3). In the proximal convoluted tubule, about two thirds of the Na^+ filtered by the glomeruli and practically all of the HCO_3^- are reabsorbed. Carbonic anhydrase inhibition reduces the availability of hydrogen ions (H^+), which prevents the exchange with luminal Na^+ by the Na^+/H^+ exchanger. Another effect is reduced HCO_3 reabsorption.[8] The prototype of carbonic anhydrase

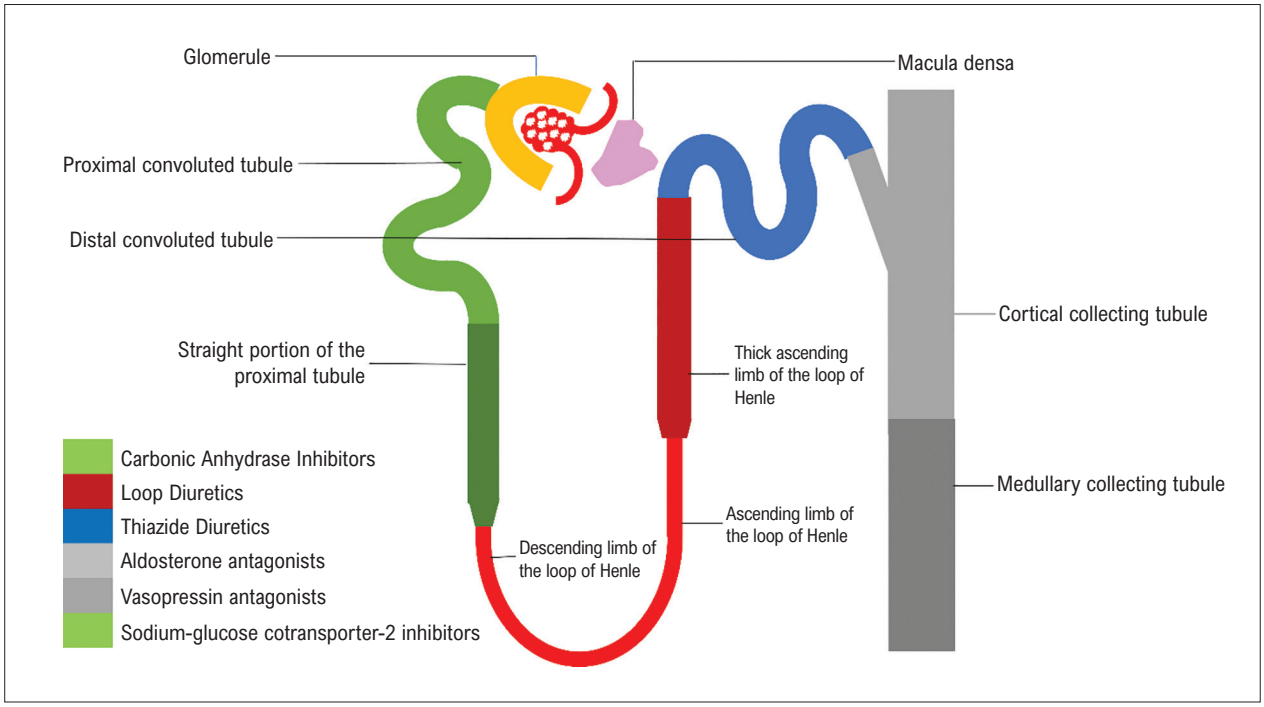

Figure 1 – *Representation of the nephron and its components (by the authors).*

inhibitors is acetazolamide. Currently, its main use is in treatment of glaucoma and metabolic alkalosis; however, before the 1950s, acetazolamide came to be widely used in treatment of HF, but its use was reduced with the advent of loop diuretics.[9] It is imaginable that, since acetazolamide acts in the site where the greatest reabsorption of Na^+ occurs, its diuretic effect would be more intense. However, a good part of this Na^+ that is not absorbed in the proximal tubule is reintegrated into the body in the thick limb of the loop of Henle (Figure 1). Therefore, combined use with loop diuretics would seem promising. However, a small study of 34 patients with acutely decompensated HF, DIURESIS-CHF demonstrated that acetazolamide and furosemide were better than furosemide alone in terms of nautriuresis, but there were no differences in mortality or hospital readmission. The study was interrupted before reaching the target N, which was 80, due to difficulties in randomizing patients.[10] A 2019 meta-analysis demonstrated that use of acetazolamide in patients with HF was able to reduce pH, increase natriuresis, and improve sleep apnea, which is a condition closely related to HF.[11] Two ongoing studies, Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR)[12] and Acetazolamide in Patients with Acute Heart Failure (ACETA)[13] aim to evaluate the use of acetazolamide in combination with furosemide, in terms of efficiency in improving congestion in patients with HF and risk of diuretic resistance.

Loop Diuretics

This is undoubtedly the most used class of diuretics in HF, and it is part of the prescription for more than 90% of patients.[14] The most widely known representatives of this class are furosemide, torsemide, and bumetanide. Loop diuretics act in the thick portion of the ascending loop of Henle, on the Na-K-2Cl pump, where reabsorption of 25% of the filtered Na^+ occurs. Pump inhibition generates less reabsorption of Na^+ and Cl^-, resulting in increased diuresis.[6] They also act on another very similar cotransporter, Na-K-Cl, which is present in the ears, blood vessels, and macula densa. The inhibition of this other cotransporter in the vessels, associated with the well-known increase in prostaglandin synthesis by loop diuretics, generates venodilation, which may partially explain the reduction in pulmonary capillary pressure observed with the use of this class of diuretics.[15] However, the action on the macula densa implies an increase in renin and, consequently, in angiotensin II, which is a potent vasoconstrictor. There is no relationship between the type of diuretic, route of administration, or dosage applied and influence on inhibition of either type of cotransporter. The resulting action on the vessels is thus negligible. Eventual ototoxicity related to loop diuretics has been explained by the inhibition of Na-K-Cl in the ears.[16]

Loop diuretics are organic anions, which circulate bound to proteins. Therefore, instead of being filtered by the glomeruli, loop diuretics are secreted in the proximal tubule.[17] Non-steroidal anti-inflammatory drugs and uremic anions compete for the same structures that facilitate this secretion, which may contribute to resistance to this class of diuretics.[18] When administered orally, furosemide has a bioavailability that varies between 40% and 80%; it is highly influenced by food, which delays its absorption. Additionally, in patients with splanchnic edema, associated with reduced perfusion in this area, absorption, although it occurs fully, is slower, reducing the drug's plasma peak, which also contributes

to drug resistance. In patients with normal renal function, intravenous administration is about twice as potent.[19] In contrast, bumetanide and torsemide are not influenced by food; both have high bioavailability (> 90%), which makes oral and intravenous administration similar. It is known that bumetanide is 40 times more potent than furosemide; however, randomized studies comparing both are lacking.[20] The TORIC trial, which randomized 1377 patients to torsemide versus furosemide or other diuretics, showed greater symptom relief, in addition to good tolerability. Although it was not designed for this purpose, the study also demonstrated a tendency towards lower mortality with torsemide.[21] A meta-analysis of comparative studies of torsemide and furosemide also demonstrated a tendency toward reduced hospital readmissions and all-cause mortality.[22] Nonetheless, studies specifically designed to analyze mortality would be convenient to better evaluate torsemide.[23] The objective of the TRANSFORM-HF trial is to randomize 6000 hospitalized patients with HF and to compare torsemide with furosemide in terms of all-cause mortality.[24]

In HF, in order to achieve improvement in congestion, it is necessary to produce a negative water balance. It is known that, to generate this negative water balance with diuretics, the amount of Na^+ that leaves must be greater than the amount that enters. Increasing the dose of the diuretic and restricting dietary salt help to generate this fluid deficit. It is also known that, after the effect of the diuretic dose wears off, a phase of greater Na^+ retention by the nephrons follows, known as post-diuretic sodium retention.[25] Therefore, reducing the time interval between dosages also contributes to a negative balance. In other words, over the course of 24 hours, the longer the body is under the effect of the diuretic, the greater the likelihood of reaching euvolemia. This gave rise to the rationale behind the largest study on diuretics in the literature, the 2011 DOSE Trial. This randomized and multicenter trial aimed to compare intravenous use of furosemide in two scenarios: intermittent versus continuous infusion, and low versus high doses. The study randomized approximately 600 patients, and it showed significance in secondary outcomes (improved dyspnea and fluid loss) for high doses of diuretics (2.5 times the usual dose used at home) when compared to low doses.[26] There was a greater tendency toward worsened renal function; however, in a later evaluation, this greater elevation in creatinine had no clinical impact.[27] Regarding the comparison between continuous and intermittent use, there was no difference. Nevertheless, the study received some criticism related to the following: patients did not have criteria for diuretic resistance, when the continuous use of furosemide could possibly have some effect; continuous infusion at doses below what was recommended, and no loading dose was administered before initiating continuous infusion to reach the plasmatic equilibrium of drug concentrations.[28] Accordingly, the current guidelines recommend that, in cases of acutely decompensated HF, there should be an increase of at least 2.5 times the usual home dose of the diuretic, at least twice a day, and, in selected cases, such as diuretic resistance, cardiorenal syndrome, or severe right ventricular dysfunction, continuous infusion may be an alternative.[29]

Thiazide Diuretics

Thiazide diuretics work by blocking the sodium-chloride cotransporter in the distal convoluted tubule. Although they are less potent than loop diuretics, they may have a synergistic effect by leading to sequential nephron blockade.[30]

Thiazide diuretics bind to proteins, requiring adequate renal flow to be secreted into the tubules.[31] Thus, their effect may be reduced in the presence of severe renal dysfunction. By increasing the arrival of sodium from the collecting ducts, the exchange of sodium with potassium is increased, leading to potassium depletion, which is the most significant side effect.[30]

This class includes chlorthalidone, which is a drug with slower gastrointestinal absorption, with a longer time to start effect and a very long half-life (24 to 72 hours). Hydrochlorothiazide, on the other hand, has a shorter half-life (6 to 12 hours) and a shorter onset of action, and it should be administered close to the loop diuretic to potentiate its effect.[30,31] Although it is not a thiazide diuretic, metolazone acts in a similar manner. It is more potent than hydrochlorothiazide, and it maintains its action even when there is a severe reduction in the glomerular filtration rate.[30] When administered orally its effect is similar to that of an intravenous thiazide diuretic.[32]

Chronic use of loop diuretics leads to increased sodium avidity in the distal portion of the nephrons. This increased ability of the distal nephron to reabsorb sodium chloride eventually leads to a decline in natriuresis, which is known as the braking phenomenon.[33] This phenomenon is associated with nephron remodeling with hypertrophy of the distal convoluted tubule, collecting tubules, and collecting ducts, which has already been demonstrated in animal models.[34] One of the pathways that contribute to nephron remodeling is the activation of the renin-angiotensin-aldosterone system. Another mechanism is the fluid increase in the distal segments of the nephron, which leads to increased transepithelial flow and promotes synthesis of new proteins. There is also the effect of disturbances generated by diuretic use, such as metabolic alkalosis and hypokalemia, which strongly activate the sodium-chloride cotransporter.[33]

Table 1 – Loop diuretics[30]

	Duration	Initial dose	Maximum dose	Side effects
Furosemide	6 h	20 to 40 mg, once or twice daily	600 mg	Hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, ototoxicity
Bumetanide	4 to 6 h	0.5 to 1 mg, once or twice daily	10 mg	
Torsemide	12 to 16 h	10 to 20 mg, once daily	200 mg	

Accordingly, the association of a diuretic with action in the distal nephron can potentially help to reverse this phenomenon. Studies have demonstrated that the association of thiazide diuretics increases diuresis in patients who are already using loop diuretics, contributing to congestion control.[32,35,36] Therefore, even though there are not more robust prospective randomized studies demonstrating improvement in clinical outcomes with the use of thiazide diuretics for treatment of HF, their use, in association with loop diuretics, is recommended in the guidelines for treatment of HF.[37,38]

Aldosterone receptor antagonists

Aldosterone receptor antagonists act by modulating the expression and activation of sodium and potassium channels in the collecting ducts (distal nephron), reducing sodium and water absorption, and increasing potassium secretion.[31] Given that only 3% of the sodium filtered is reabsorbed in the collecting duct, the diuretic effect of this class is not very intense.[30] Nonetheless, they are often used to correct or prevent potassium deficiency generated by use of other classes of diuretics.

Spironolactone is a non-selective aldosterone receptor antagonist, and endocrine side effects (such as gynecomastia) are therefore common, whereas eplerenone, which is more selective for mineralocorticoid receptor, causes these side effects less.[39]

By reducing the deleterious effect of aldosterone on the cardiovascular system, the benefit of this class of diuretic in the treatment of chronic HF has been widely recognized.[4,41] However, its use in the treatment of decompensated HF has not been well established.

In a randomized study of 360 patients hospitalized with congestion, the use of a higher dose of spironolactone (100 mg per day) was not superior to placebo or a low dose of the drug (12.5 or 25 mg per day), which was maintained in the event that the patient was already using it. There was no improvement in the primary outcome (NT-proBNP variation) or secondary outcomes (clinical congestion score, dyspnea, urine output, or weight change). Likewise, there was no difference in safety outcomes (serum potassium and glomerular filtration rate), showing that the use of a higher dose of spironolactone in this context appears to be safe.[42]

In patients with heart failure with reduced ejection fraction (HFrEF) who are hospitalized for decompensation, early initiation of a low dose of aldosterone receptor antagonist (spironolactone 25 mg per day) or its maintenance in patients who are already using it may assist in reducing hypokalemia induced by diuretic treatment, in addition to increasing the chance that the patient will be discharged with optimal disease-modifying therapy, and it should be encouraged.[31]

Sodium-glucose cotransporter-2 inhibitors

SGLT-2 inhibitors inhibit sodium and glucose reabsorption in the proximal convoluted tubule, resulting in glucosuria, natriuresis, and increased urinary volume.[43]

Large multicenter studies that investigated the long-term effect of this class of medication in patients with HFrEF demonstrated a significant benefit in reducing morbidity and mortality.[44,45]

The DAPA-HF study, which compared the effect of dapagliflozin versus placebo, associated with optimal therapy, in 4744 patients with HFrEF, demonstrated a significant reduction in the primary endpoint of cardiovascular death or worsening of HF (26% reduction). When the outcomes were evaluated individually, a reduction was observed both in cardiovascular death (18% reduction) and in worsening of HF (30% reduction). Reduced death due to any cause, improved HF symptoms, and improved quality of life were also identified with use of the medication.[44]

Similarly, in the EMPEROR-Reduced study, which evaluated the use of empagliflozin compared to placebo in 3730 patients with HFrEF, a reduction was observed in the primary outcome of cardiovascular death or hospitalization due to HF (25% reduction) with the use of the drug. Moreover, the authors observed reduced decline in glomerular filtration rate in the group that used the drug, as well as a lower risk of serious kidney outcomes (chronic dialysis, kidney transplantation, more than 40% reduction in glomerular filtration rate).[45]

However, this benefit does not seem to be due exclusively to the increase in diuresis or to better glycemic control. The most accepted mechanisms are improved left ventricular wall tension secondary to decreased preload and afterload, improved cardiomyocyte metabolism and bioenergetics, myocardial sodium-hydrogen pump inhibition (which leads to higher concentration of calcium in the mitochondria), reduced cardiac necrosis and fibrosis, and alterations in the production of cytokines in the epicardial fat tissue.[46]

To date, the use of the drug to control congestion in patients with decompensated HF has not been well established.

In a sub-analysis of the DAPA-HF study, the diuretic dose used did not change significantly during follow-up in patients randomized to dapagliflozin when compared to the placebo group.[43]

Table 2 – Thiazide and thiazide-like diuretics[30]

	Duration	Initial dose	Maximum dose	Side effects
Hydrochlorothiazide	12 h	25 to 50 mg, once or twice daily	50 mg	Hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, hyperuricemia
Chlorthalidone	24 to 72 h	12.5 to 25 mg, once daily	100 mg	
Indapamide	36 h	2.5 mg, once daily	20 mg	
Metolazone	8 to 14 h	2.5 mg, once daily	20 mg	

On the other hand, the SOLOIST-WHF study, which evaluated the effect of sotagliflozin in patients with type 2 diabetes who had recently been hospitalized for worsening HF, showed a benefit for the drug when it was started close to decompensation. In this study, randomized patients started the medication before discharge (48.8%) or shortly after (median of 2 days after discharge). There was a reduction in the primary outcome of cardiovascular death and hospitalizations or urgent consultations for HF.[47]

Further studies are needed to define the role of this class of medication (which has some diuretic effect) in decompensated patients with pulmonary congestion and diuretic resistance.

Vasopressin antagonists

Although sodium retention is the greatest determinant of congestion in HF, hyponatremia, which indicates water accumulation, is common and confers worse prognosis.[29] Inappropriate elevation of vasopressin in HF plays a role in water retention, contributing to congestive symptoms and electrolyte disturbances.[48] Blockade of vasopressin receptors that are present in the collecting ducts inhibits the action of the antidiuretic hormone and increases the excretion of free water (aquaresis).[29]

In the EVEREST study, which evaluated the effect of tolvaptan (oral vasopressin-2 receptor antagonist) in patients with HFrEF who were hospitalized for decompensation, no improvement was observed in overall mortality, cardiovascular mortality, or hospitalization for HF, although improvement of dyspnea, greater weight loss, and reduced edema were identified during the first days, in addition to improved sodium levels in patients with hyponatremia.[48]

Subsequently, smaller studies evaluating early use of tolvaptan in acutely decompensated patients with diuretic resistance, renal dysfunction, or hyponatremia showed no improvement in dyspnea, notwithstanding greater weight loss.[49,50]

Although there is a rationale for using vasopressin antagonists in congested patients with hyponatremia, to date, in view of the results of the studies carried out, there is no recommendation for their use in the treatment of HF.

Approach to diuretic resistance

Diuretic resistance can be defined as the failure to reverse a congestive condition with an appropriate dose of diuretic and fluid and saline restriction. It is extremely common in patients with HF, but its real prevalence is unknown, largely due to the non-homogeneity of clinical studies (different diagnostic criteria, different populations, different doses of diuretics, etc).[3] However, it is known that diuretic resistance is an independent factor for mortality, due to both pump failure and sudden death.[4] Therefore, it must be promptly recognized. It has a multifactorial etiology, but inadequate diuretic doses are among the most frequent. It is known that, in HF, an adaptive phenomenon of "tolerance" to diuretics occurs over time, so that, in order to reach the same level of natriuresis as in healthy individuals, patients with HF require higher doses[3]. Table 3 lists some factors that may be involved in diuretic resistance. The search for possible causal factors is the first step in treating it.

Sequential nephron blockade

Up to 75% of cases of diuretic resistance in patients with acutely decompensated HF can be attributed to hyperactivation of Na-Cl transporters along the distal nephron, as a result of adaptive nephron remodeling.[51] Although this has not been properly tested in clinical studies, a plausible strategy in this scenario is sequential nephron blockade, with the introduction of a second, or even a third diuretic, which would prevent this adaptive hyperreabsorption of Na^+ in the distal convoluted tubules or collecting tubules, thus generating greater diuresis.[52]

Hypertonic saline solution

Another alternative for managing patients with diuretic resistance is the use of hypertonic saline solution (HSS) associated with high-dose intravenous furosemide. Studies evaluating this therapy in patients with acutely decompensated HF have shown improvement in short- and long-term outcomes. The rationale for using HSS is its osmotic effect, which would lead to mobilization of extravascular fluid, maintaining adequate intravascular content in spite of the increase in diuresis and natriuresis caused by the high diuretic dose.[53] Furthermore, it would act in correction of hyponatremia and hypochloremia, which may be correlated with diuretic resistance and mortality.[54]

In a study with 1771 patients with HFrEF who were hospitalized for decompensation, Paterna et al demonstrated that the group of patients who received HSS associated with a high dose of furosemide, compared to the group who received only the diuretic, showed increased urine output and serum sodium level, reduced hospitalization time, lower readmission rate, and lower mortality during follow-up.[55]

In a meta-analysis that included 11 randomized studies (total of 2987 patients), the authors observed that the use of HSS was associated with increased urine output, weight loss, increased urinary sodium excretion, correction of serum

Table 3 – Factors associated with diuretic resistance[29]

Inadequate diuretic dose	Neurohumoral activation
Poor adherence to water and saline restriction	Renal insufficiency
Visceral edema	Use of non-steroidal anti-inflammatory drugs
Poor splanchnic perfusion	Impaired drug secretion in the tubules
Poor renal perfusion	Malnutrition and hypoproteinemia
Nephron remodeling	

sodium, reduced serum creatinine, reduced length of hospital stay, and reduced rates of HF readmission and mortality. The benefits in the clinical outcomes identified, especially in mortality, seem to be disproportionate to the increase in urine output and weight loss. It is hypothesized that sodium loading could reduce adrenergic and renin-angiotensin system activation as well as their deleterious effects on the cardiovascular system.[53]

Given that the studies on this topic have some methodological problems, and the majority of them included a small number of patients, in addition to having used different HSS concentrations and forms of administration, more quality studies are needed to define the indications and the best way to use this intervention. Nevertheless, in patients hospitalized for decompensated HF with signs of hypervolemia and resistance to diuretic therapy, the use of HSS should be considered.[37]

Ultrafiltration

Ultrafiltration (UF) is similar to hemodialysis, but only fluid is removed from the body.[56] The first major study on this modality applied to HF was the UNLOAD Trial, in 2007. It showed greater weight loss and fewer hospitalizations with UF when compared to standard diuretic therapy, although there was no difference in serum creatinine or length of hospital stay.[57] It is worth underscoring that the study was strongly criticized due to the low dose of diuretics used and the lack of clarity regarding the calculation of the sample size. On the other hand, the CARRESS-HF study, in 2012, which compared UF with aggressive diuretic therapy in patients with HF and worsened renal function, showed no difference in relation to weight loss or improvement in symptoms, with significant worsening of creatinine in the UF group. Furthermore, UF was associated with a higher rate of adverse events.[58] This study was also strongly criticized for the following reasons: high crossover rate, UF conducted in patients who still had high urinary output, and exclusion of patients with more severe kidney disease (who might be the patients who would benefit most). Accordingly, the guidelines currently recommend the use of UF only as a rescue therapy, in cases where all of the previously mentioned measures have failed[59] (Figure 2).

Conclusion

In spite of the great advances in the last years, there are still many "blind spots" to knowledge regarding HF management, especially related to the use of diuretics, where there is still a lot of empiricism. Knowledge about the pharmacokinetic and pharmacodynamic properties of these drugs helps to improve the management of hypervolemia; nevertheless, larger and better clinical studies are needed.

Author Contributions

Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Seguro LFBC e Xavier Júnior JL.

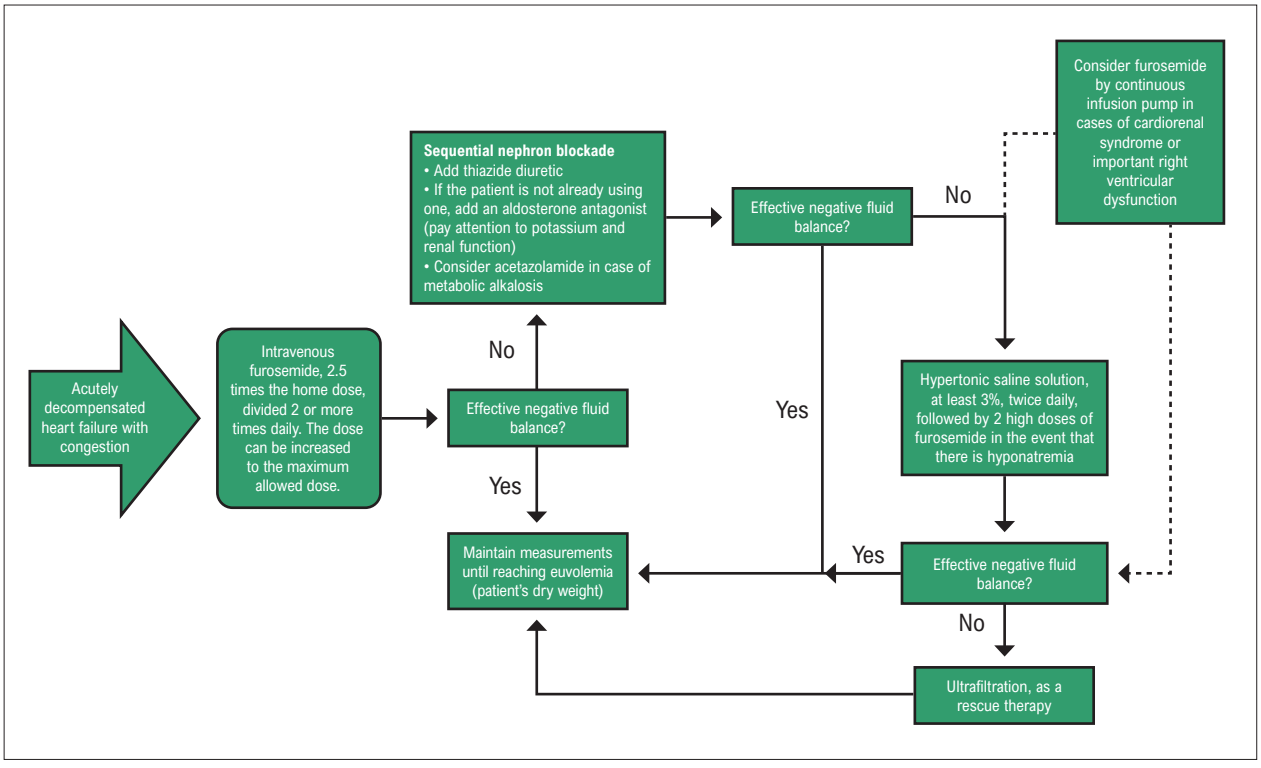

Figure 2 – *Flowchart for handling diuretic resistance in heart failure.*[29-31]

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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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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