How to optimize the use of diuretics in patients with heart failure?

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ABSTRACT

Considering the pathophysiology and clinical presentation of heart failure, using diuretics or drugs with diuretic properties is indispensable for adequate management of heart failure patients. However, in clinical practice, fluid expansion is often undiagnosed, and diuretic therapy is not always adequately titrated. Today, several drug classes with diuretic properties are available in addition to classical thiazides, thiazide-like, and loop diuretics. The purpose of this short review is to discuss different ways to optimize diuretic therapy using currently available drugs. Several approaches are considered, including a combination of diuretics to obtain a sequential nephron blockade, use of a drug combining a blocker of the renin-angiotensin system (RAS) and an inhibitor of the metabolism of natriuretic peptides (ARNI), prescription of potassium binders to maintain and up-titrate RAS blockers and mineralocorticoid antagonists, and finally use of inhibitors of renal reabsorption of glucose through the sodium-glucose cotransporter 2 system. Optimal use of these various drug classes should improve the quality of life and reduce the need for hospital admissions and mortality in heart failure patients.

Key words: loop diuretics, mineralocorticoid receptor antagonists, neprilysin, patiromer, sodium-glucose co-transporter-2 inhibitors, thiazides

INTRODUCTION

Heart failure (HF) is a clinical syndrome with multiple facets; it affects 1%–3% of the adult population worldwide, but with relatively large geographical variations and with prevalence ranging, for example, between 0.45% and up to 6.9% in Europe [1, 2]. In Poland, the prevalence of self-reported HF is estimated to be about 2.4% according to more recent data [3]. The trend in the prevalence of HF is expected to increase in next decades because of the growth and aging of the population, increasing incidence of comorbidities, and, to a certain degree, improved survival of patients with cardiac diseases, such as congestive heart failure or coronary artery diseases. The diagnosis of heart failure is associated with high morbidity and mortality regardless of whether left ventricular ejection function is preserved (HFpEF) or reduced (HFrEF) [4]. In the last decades, the development of new therapeutic strategies for HF management has led to the lowering of HF mortality and hospitalization rates but both remain raised when compared to the general population, and the quality of life of HF patients is generally low.

The main clinical feature of HF is the development of acute or chronic fluid overload resulting from the inability of the heart to maintain adequate cardiac output, particularly adequate renal perfusion [5]. Thus, fluid retention in HF is essentially the consequence of renal hemodynamic and neurohormonal responses (e.g. activation of the renin-angiotensin system [RAS] and sympathetic nervous system, vasopressin, natriuretic peptides, etc.) to reduced renal perfusion. To maintain organ perfusion and homeostasis of the cardiovascular system, kidneys retain sodium and water but at a cost of increased systemic venous pressure. This is often reflected by an increase in blood creatinine, a decrease in urinary sodium

concentration in spot urine, and reduced urine output. These parameters can thus be used as biomarkers of acute or chronic kidney injury due to insufficient renal perfusion, which is particularly useful for diagnosis and management of acute HF when patients are not already on diuretics. Initially, this pathophysiological response is probably effective but with time it becomes deleterious, and it contributes to the development of a vicious circle, repeated episodes of fluid retention aggravating the clinical course of HF. Signs and symptoms of systemic and/or pulmonary congestion such as breathlessness, fatigue, ankle swelling, peripheral edema, or pulmonary rales are the typical clinical expressions of this fluid overload. By itself, congestion appears to be a good marker of an adverse prognosis in HF patients [6]. Thus, decongestion is an important therapeutic target [7]. However, volume expansion remains often underdiagnosed by clinicians, and diuretic therapy is frequently inadequately titrated [6, 8].

Considering the pathophysiology and clinical presentation of HF, it is not surprising that some classes of drugs, such as RAS and diuretics, are the basis of heart failure management. However, whereas strong evidence from randomized controlled trials (RCTs) have demonstrated the clinical benefits of RAS inhibitors in reducing mortality and hospital admissions and improving quality of life in HFrEF patients, the level of evidence regarding diuretic use for the same indications has always remained more controversial in the absence of prospective RCTs evaluating their effects on hard clinical outcomes. Yet, one must acknowledge that most clinical trials demonstrating the ability of new disease-modifying drugs to reduce mortality and hospitalization rates in HFrEF were conducted in patients already on diuretics, including the most recent ones, sodium/glucose cotransporter 2 (SGLT2) inhibitors or non-steroidal mineralocorticoid antagonists (MRA) [4]. Moreover, a meta-analysis has shown that loop and thiazide diuretics reduce the risk of death and HF worsening, compared with placebo in HFrEF patients [9], and the use of diuretics reduces the risk of hospital admissions.

DRUGS WITH DIURETIC PROPERTIES IN THE MANAGEMENT OF HEART FAILURE

Among therapeutic approaches that international guidelines [4, 10] recommend for the management of chronic HF, several involve drug classes with diuretic properties, which contribute to the prevention or treatment of fluid retention and congestion (Table 1). In this review, we will discuss these classes and explain how to optimize their use in patients with chronic HF. Readers are referred to the recent comprehensive publication of Polish experts of the Heart Failure Association of the Polish Cardiac Society for recommendations regarding acute HF management [11].

Classical diuretics: Thiazides and thiazide-like and loop diuretics

Diuretics are indispensable to restore euvolemia in HF patients with symptoms and signs of fluid overload regardless of their left ventricular ejection fraction. In this context, loop diuretics are often the preferred drugs because they produce rapid diuresis enabling relief of symptoms and reducing the need for hospitalization. A recent study did not find significant differences among loop diuretics [12]. Their efficacy is improved when administered with an ACE inhibitor or an ARB, which limits the reactive activation of the RAS. Once signs and symptoms are under control, it is generally recommended to use the lowest dose of loop diuretics or a thiazide or a thiazide-like diuretic when symptoms are very mild. One frequent issue is the development of so-called diuretic resistance to loop diuretics because renal tubular compensatory mechanisms beyond the site of action of loop diuretics limit the natriuretic and diuretic effects of loop diuretics. In addition, when the glomerular filtration rate decreases the concentration of loop diuretic accessing the tubular site of action is reduced. In that case, combining various diuretics can improve the efficacy of loop diuretics and optimize the treatment. Notably, the recent evidence that chlorthalidone lowers blood pressure, albuminuria, and NT-proBNP in patients with advanced chronic kidney disease (CKD) (mean estimated GFR 23 ± 4.2 ml/min/1.73 m^2) and already on diuretics (60% on loop diuretics) might be of interest to manage hypertensive patients with HFpEF [13]. However, a combination of several diuretics acting on different renal tubular sites (sequential nephron blockade) is associated with increased risk of electrolyte disturbances, such as hyponatremia, hypokalemia, hypovolemia, hypotension, and renal impairment, all of which may have a negative impact on morbidity and mortality in HF (for example,

Table 1. Tubular sites of action of drugs with diuretic properties used in heart failure

Type of drug	Main renal site of action	Examples of drug names
Loop diuretics	Thick ascending limb of the loop of Henle	Furosemide, torasemide
Thiazide/thiazide-like diuretics	Distal tubule	Hydrochlorothiazide, chlorthalidone, indapamide
Steroidal MRAs and Non-steroidal MRAs	Collecting-connecting tubules	Spironolactone, eplerenone Finerenone
Natriuretic peptides (neprilysin inhibitors) in association with a RAS blocker (ARNi)	Proximal tubule, distal and collecting tubule	Sacubitril-valsartan
Sodium-glucose cotransporter 2 inhibitors Carbonic anhydrase inhibitors	Proximal tubule	Empagliflozin, dapagliflozin, canagliflozin, sotagliflozin, acetazolamide

Abbreviations: ARNi, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system

by increasing the incidence of ventricular arrhythmias). Interestingly, a recent study has demonstrated the clinical benefits of adding acetazolamide, a diuretic acting on the proximal tubule, in addition to loop diuretics to reduce congestion in patients with acute HF [14] regardless of renal function level [15]. Yet, acetazolamide should not be given alone because its efficacy decreases rapidly due to distal tubular compensation.

Steroidal and non-steroidal mineralocorticoid receptor antagonists

Steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone or eplerenone, have been shown to improve survival, reduce hospital admissions and symptoms in large RCTs involving HFrEF patients [16, 17]. Therefore, they belong to the first-line therapy for this indication. Spironolactone may also be useful in reducing hospitalization rates in HF patients with preserved ejection fraction [18]. Yet, spironolactone is still not approved for the treatment of HF with mild reduction or preserved EF, but trials are ongoing for these indications [19], and its use is supported by the Food and Drug Administration (FDA) in the US based on the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial [20]. The main limitation of MRA use is the development of hyperkalemia, particularly when used with an RAS blocker. This side effect often leads to sub-optimal use of RAS blockers or withdrawal of either one of the drug classes (RAS blocker or MRA).

New potassium binders now make it possible to reduce the risk of hyperkalemia and to maintain HF patients on the highest tolerated dose of MRA and/or RAS blockers [21]. A recent review and meta-analysis of published studies has confirmed that the use of potassium binders increases the rate of medical therapy optimization with RAS blockers and reduces the incidence of hyperkalemia [22]. However, among new binders, zirconium cyclosilicate should be avoided in patients with peripheral edema and/or congestion because it brings a lot of sodium and can aggravate peripheral edema.

In recent years, several new nonsteroidal MRAs have been developed for the treatment of hypertension and management of patients with type 2 diabetes and CKD [23]. Among them, finerenone has recently become available on the market. Two large RCTs, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) [24] and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) [25], pooled in the FIDELITY analysis [26], demonstrated cardio-renal benefits of finerenone in these patient groups, reducing significantly the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure and lowering the risk of CKD progression. In these trials, heart failure at baseline was an exclusion criterion (yet 7% of enrolled patients had HF) and 96% of participants had hypertension. In this context, finerenone reduced new-onset HF and improved HF outcomes irrespective of a history of HF and the eGFR and urinary albumin/creatinine ratio [27, 28]. Serum potassium was slightly higher on finerenone (0.14–0.16 mmol/l), but the incidence of hyperkalemia was comparable in both treatment groups (finerenone and placebo) during the trial. It is noteworthy that changes in serum potassium were strictly controlled during the studies; hence the situation might differ in a real-life setting. The diuretic effect of finerenone is supposed to be weak and irrelevant to the explanation of the observed clinical benefits. Nonetheless, data in healthy subjects showed that the natriuretic potency of 10 mg finerenone in an acute clinical experiment is equivalent to that of 50 mg eplerenone, which is definitively not negligible [23].

In summary, finerenone could now be considered an effective approach in patients with HFpEF associated with type 2 diabetes and CKD. Today, additional studies are ongoing to define the place of finerenone alone [19] or in combination with SGLT2 inhibitors [29], which will be discussed below.

Blockers of the renin-angiotensin system and neprilysin inhibitors

Blockade of the renin-angiotensin system using either angiotensin-converting enzyme inhibitors (ACEi) or angiotensin 2 receptor blockers (ARBs) is recommended as the first-line treatment in HF patients. In addition to their hemodynamic effects, both ACEi and ARBs have been shown to increase urinary sodium excretion by two different mechanisms, i.e. through a reduction of the renal tubular effects of angiotensin 2 and a decrease in plasma aldosterone levels [30]. These natriuretic properties contribute to the overall benefits of RAS blockers in hypertension and HF, but they are often insufficient to prevent or manage acute or chronic fluid retention in HF. This is the reason why RAS blockers are generally used with a thiazide diuretic to optimize their efficacy in hypertension as well as in HF.

When the heart is failing, natriuretic peptides (ANP, BNP) are secreted by the atria and ventricles to maintain cardiovascular homeostasis. Natriuretic peptides have multiple effects on the cardiovascular and renal systems causing diuresis and natriuresis, inducing systemic vasodilatation, and inhibiting renin. In the kidney, natriuretic peptides act at different sites. At the glomerulus level, ANP increases glomerular capillary pressure and improves GFR. At the tubular level, natriuretic peptides, such as ANP, inhibit sodium and water reabsorption throughout the nephron, acting on the proximal tubule but also the thick ascending limb of the loop of Henle and the collecting duct [31]. Natriuretic peptides are degraded by a neutral endopeptidase (NEP). Augmentation of the natriuretic peptide system using NEP inhibitors has been explored as an additional therapeutic strategy for the treatment of hypertension or HF, but it appears that NEP inhibitors

proved useful only when combined with an inhibitor of the RAS [32–34]. It is in this context that the first ARNI (dual-acting angiotensin-receptor-neprilysin inhibitor) was developed for hypertension and heart failure [35]. LCZ696 contains an equimolar amount of ARB valsartan and sacubitril, a prodrug of a neprilysin inhibitor [32]. In a large RCT conducted in HFrEF patients, among whom 80% were on a diuretic and approximately 55% received an MRA, valsartan/sacubitril was found to be superior to an ACE inhibitor in reducing cardiovascular mortality, HF hospitalization, and HF symptoms [35, 36]. In patients with HF and ejection fraction > 45%, sacubitril-valsartan did not result in a significantly lower rate of total hospitalization for heart failure and death from cardiovascular causes, but the borderline effect was accepted by the FDA [37].

Today, the use of ARNI is, therefore, recommended to optimize the use of RAS blockers in HF. One of the main reasons why ARNI are superior to an ACEi or an ARB alone, even when these are used with a diuretic, is that neprilysin inhibition provides a kind of physiological "sequential nephron blockade", which is reinforced by co-administration of classical diuretics (loop diuretics or thiazides) or an MRA. In this respect, post-hoc analysis of the trial: the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin-converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF), has shown that the use of sacubitril-valsartan is associated with a significant reduction in the administration of loop diuretics [38]. Another advantage relies on the fact that a physiological nephron blockade by natriuretic peptides does not induce the classical side effects of diuretics such as hyperuricemia or hyperkalemia. The main side effects of ARNI in the PARADIGM trial [36] were hypotension and orthostatic hypotension (approximately 16%), cough (approximately 11%), kidney dysfunction (3.3%), hyperkalemia (4.3% with K >6.0 mmol/l), and angioedema (0.2%).

Inhibitors of sodium-glucose co-transporter 2 (SGLT2i)

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2i) have been developed to lower blood glucose without stimulating insulin in patients with type 2 diabetes through a novel mechanism of action, i.e. the inhibition of renal glucose reabsorption in the proximal tubule. Subsequently, it was found that drug-induced glucosuria induces a loss of water and sodium via osmotic diuresis resulting in a negative salt and water balance [39]. The clinical expression of the reduction in plasma volume is a drop in blood pressure and GFR. SGLT2 inhibitors also induce a weight loss of between 2 and 4 kg after 6–12 months of treatment, which is related in part to the early volume contraction and thereafter to caloric wasting.

The cardiovascular and renal benefits of SGLT2 inhibition have been demonstrated in several large RCTs in patients with type 2 diabetes, patients with CKD or heart failure, and patients with high risk of atherosclerotic cardiovascular disease. These trials have been reviewed and analyzed in a large meta-analysis of all placebo-controlled studies [40]. The main findings of these RCTs are that SGLT2 inhibitors, when compared with placebo, reduce the risk of kidney disease progression by about 30%, risk of acute kidney injury by 23%, risk of cardiovascular death or hospitalization for heart failure by 23%, and risk of cardiovascular death by 14%, regardless of the presence or absence of type 2 diabetes. In heart failure, cardiac benefits were observed in HFrEF patients as well as in those with preserved EF [41]. In a post-hoc analysis of the trial: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR--Preserved), the use of empagliflozin was associated with a significantly decreased likelihood of diuretic dose escalation and an increased likelihood of de-escalation [42]. A similar observation was made with dapagliflozin with a significant reduction of new loop diuretic initiations, dose increases, and mean loop diuretic dose over time, compared to placebo [43, 44].

The observation that SGLT2 inhibitors are also beneficial in patients with very reduced kidney function, in whom glucosuria is weak, suggests that SGLT2 inhibition provides cardio-renal protective effects that may go beyond glucosuria [45], involving perhaps direct cardiac effects through inhibition of inflammatory processes, reduction of oxidative stress, improvement of myocardial metabolism, or decrease in cardiac sympathetic nerve activity [46].

Taken together, these data provide evidence that the diuretic effects of SGLT2i play a role in improving clinical outcomes in HF patients. Therefore, SGLT2 inhibitors are recommended in the most recent guidelines for the management of heart failure [4, 10]. Additional studies are still ongoing to assess further the potential role of SGLT2 in kidney and cardiac diseases, for example, in acute heart failure or in combination with other new compounds such as finerenone in diabetic kidney disease [29]. Indeed, preliminary results from the FIDELITY dataset (based on a small number of patients) have suggested that the association of SGLT2 inhibitors and finerenone might be superior to the SGLT2 inhibitor alone.

CONCLUSION

Drugs with diuretic properties are important for accurate management of patients with heart failure. Today, several drug classes recommended for heart failure treatment have such properties. These include classical diuretics (loop diuretics, thiazide, and thiazide-like diuretics), mineralocorticoid receptor antagonists (steroidal and non-steroidal), dual-acting angiotensin-receptor-neprilysin inhibitors, and SGLT2 inhibitors. As summarized in Table 2, there are several ways of optimizing diuretic therapy in heart failure either by combining these drug classes or preventing the occurrence of side effects, such as hyperkalemia, which can lead to suboptimal use or withdrawal of recommended

Table 2. Summary of ways to optimize diuretic therapy in heart failure

Type of drug	Optimization	Most important risks
Loop diuretics	Associate another diuretic: thiazide or thiazide-like	Increased risk of hyponatremia, hypokalemia, hypovolemia
Steroidal MRAs and Non-steroidal MRAs	Use a potassium binder to reduce the risk of hyperkalemia enabling up-titration or maintenance of MRAs	Adverse effects of potassium binders: constipation, nausea, hypomagnesemia, diarrhea, abdominal discomfort (patiromer). Edema and hypokalemia (zirconium cyclosilicate). Increased number of drugs
RAS blocker + conventional diuretic	Replaced by sacubitril-valsartan (ARNi) Use of a potassium binder to blunt hyperkalemia	Increased risk of hypotension, cough, angioedema
Sodium-glucose cotransporter 2 inhibitors	In addition to a loop diuretic, ARNi, MRA	Genito-urinary infections Diabetic ketoacidosis Hypotension

Abbreviations: see Table 1

therapies. However, with recent therapeutic developments, this process is not finished, and future clinical trials will provide additional information on how to optimize these treatments to improve further the quality of life and survival of HF patients.

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