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Stanisław Surma, Andrzej Więcek, Marcin Adamczak

Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia in Katowice

Diuretics — a review of the current state of knowledge

Abstract

Diuretics are drugs that increase diuresis and natriuresis. Diuretics reduce sodium reabsorption in the proximal tubule (SGLT2 inhibitors, carbonic anhydrase inhibitors), the loop of Henle (loop diuretics), the distal tubule (thiazide and thiazide-like diuretics), and the collecting tubule (mineralocorticoid receptor antagonists). The diverse mechanism of action of different diuretics allows them to be used in combination. Different groups of these drugs are used in the therapies of numerous diseases, among others heart failure, nephrological diseases, and hypertension. SGLT2 inhibitors are characterized by antihypertensive, and cardio- and nephroprotective effects, and have no adverse effect on natremia or kalemia. Acetazolamide is used in the treatment of acute heart failure. Loop diuretics have an antihypertensive effect and reduce fluid overload. These drugs uncommonly cause electrolyte disturbances. Thiazide and thiazide-related diuretics have antihypertensive properties. Possible, clinically important complications of the use of these drugs are hyponatremia and hypokalaemia. Mineralocorticoid receptor antagonists exert antihypertensive, nephroprotective, and cardioprotective effects. These drugs increase the risk of hyperkalaemia.

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Key words: diuretics, SGLT-2 inhibitors, loop diuretics, thiazide and thiazide-like diuretics, mineralocorticoid receptor antagonists

INTRODUCTION

This article presents the main classes of diuretics and their applications in the treatment of kidney disease and hypertension.

Diuretics are defined as drugs that increase the excretion of water and sodium in urine (natriuretic effect). The diverse mechanism of action of different diuretics allows them to be used in combination. Individual diuretics affect sodium reabsorption in all sections of the nephron, i.e. the proximal tubule, the loop of Henle, the distal tubule, and the collecting tubule [1]. Figure 1 shows the sites of action of diuretics.

SGLT2 INHIBITORS

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the reabsorption of glucose and sodium in the proximal tubule [2]. In the S1 and S2 segments of the proximal tubule, SGLT2 activity causes the reabsorption of approximately 97% of the glucose filtered in the glomeruli [2]. Reabsorption of glucose by SGLT2 takes place by co-transport with a sodium ion (in a 1:1 ratio), hence SGLT2 inhibitors increase the excretion of glucose and sodium in urine [2–5]. It should be noted that these drugs also reduce sodium reabsorption in the S1 and S2 segments of the proximal tubule by reducing the activity of the sodium-hydrogen exchanger 3 (NHE3) [2–5].

The use of an SGLT2 inhibitor increases natriuresis in a dose-dependent manner [6]. SGLT2 inhibitors have also been shown to increase diuresis [7]. The use of SGLT2 inhibitors leads to weight loss in the initial treatment period mainly due to a decrease in total body water (TBW) volume [8, 9]. Later, weight loss may be due to the effect of SGLT2 inhibitors on adipose tissue metabolism (increased lipolysis, decreased lipid accumulation, decreased visceral adipose tissue mass) [10]. SGLT2 inhibitors reduce water content both inside cells and in the extracellular space. This effect of

Address for correspondence:
Professor Marcin Adamczak, MD, PhD
Department of Nephrology,
Transplantation and Internal Medicine
Medical University of Silesia in Katowice
40-027 Katowice, ul. Francuska 20–24
Tel.: (32) 259-14-01
e-mail: madamczak1@op.pl

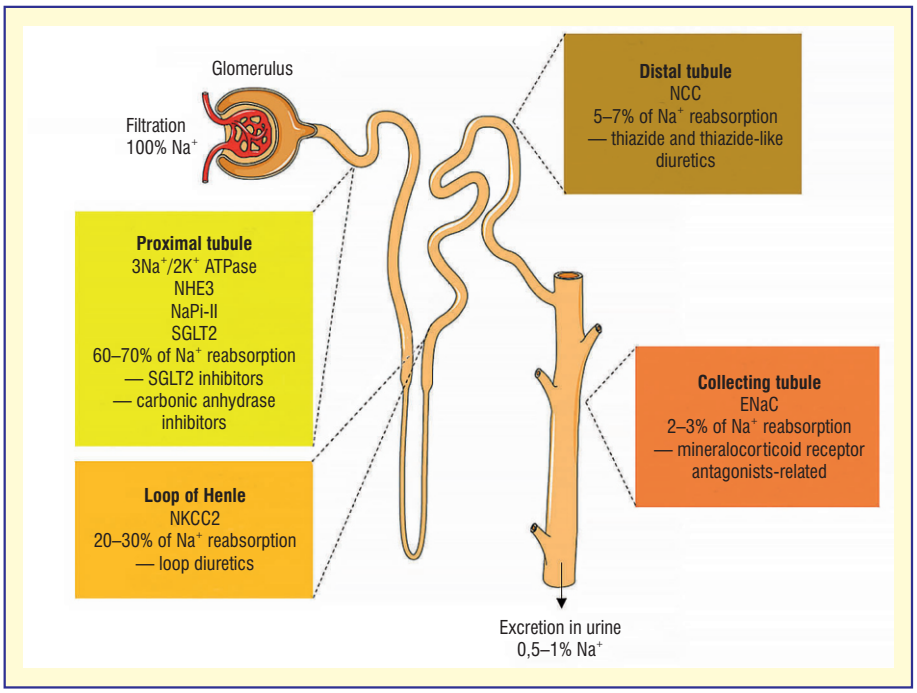

Figure 1. The role of kidneys in sodium balance regulation and the sites of action of individual classes of diuretics. Based on [1]

NHE3 — sodium-hydrogen exchanger 3; NaPi-II — sodium-phosphate cotransporter; SGLT2 — sodium-glucose cotransporter 2; NKCC2 — Na-K-Cl cotransporter 2; NCC — sodium-chloride symporter; ENaC — epithelial sodium channel

SGLT2 inhibitors concerns the extracellular space, although to a lesser extent than loop diuretics, which explains why their use does not lead to an increase in plasma renin activity (PRA) or an increased activation of the sympathetic nervous system (SNS) [11]. PRA and SNS are increased when using other diuretics (e.g. loop and thiazide diuretics) [5].

The use of SGLT2 inhibitors also reduces the sodium content in the subcutaneous tissue. In a randomized clinical trial, Karg et al. used magnetic resonance imaging to demonstrate a significant reduction in subcutaneous sodium content in patients with type 2 diabetes who were treated with dapagliflozin when compared to placebo [12]. The reduction of sodium content in the body caused by SGLT2 inhibitors mainly involves the intracellular space and non-osmotic sodium stores in the connective tissue, and probably in the vascular endothelial glycocalyx [1]. Vascular endothelial glycocalyx is a 0.5-μm-thick gel layer composed of negatively charged glycosaminoglycans. It is an endothelial mechanoreceptor that ensures proper reactions with formed blood elements and regulates endothelial permeability [13, 14]. Reducing the concentration of sodium in the extracellular space has a positive effect on the glycocalyx, i.e. it increases its height and reduces its stiffness [15, 16] and stimulates the endothelial nitric oxide synthase (eNOS), which increases nitric oxide (NO) production that has a vasodilating effect [14, 16]. In a study with 54 patients with type 2 diabetes, Sugiyama et al. demonstrated that adding dapagliflozin to the basal antidiabetic treatment resulted in improved vascular endothelial function after 6 months, as measured by the response of the brachial artery wall to hyperemia (flow-mediated dilation, FMD) [17]. In a study with 80 patients with type 2 diabetes, the same authors showed that using dapagliflozin plus metformin (as opposed to metformin monotherapy) for 16 weeks contributed to an increase in FMD [18].

SGLT2 inhibitors have a moderate antihypertensive effect. A meta-analysis by Ren et al., which included 9 randomized clinical trials and 2450 patients with hypertension or prehypertension, showed that SGLT2 inhibitors reduced systolic blood pressure by 5 mmHg and diastolic blood pressure by 1.7 mmHg. During a 24-hour ABPM, SGLT2 inhibitors reduced systolic blood pressure during the day (Mean difference (MD) = –4.57; 95% CI: –5.43 to –3.71) and at night (MD = –2.80; 95% confidence interval (CI): –3.76 to –1.84) [19].

SGLT2 inhibitors reduce the risk of cardiovascular and kidney disease [20]. This has been confirmed by a meta-analysis of 13 randomized clinical trials involving over 90,000 patients. SGLT2 inhibitors have been shown to reduce the risk of progression of chronic kidney disease (CKD) in patients both with and without concomitant diabetes (relative risk (RR) = 0.63; 95% CI: 0.58–0.69, respectively). It was also found that, regardless of the presence of diabetes, SGLT2 inhibitors reduced the risk of death from complications of cardiovascular disease and the risk of heart failure (HF) exacerbation (RR = 0.77; 95% CI: 0.74–0.81), as well as the risk of all-cause mortality (RR = 0.89; 95% CI: 0.85–0.94) [21].

In patients with CKD without diabetes, the most important randomized and placebo-controlled studies using SGLT2 inhibitors are DAPA-CKD (dapagliflozin 10 mg/day) [22] and EMPA-KIDNEY (empagliflozin 10 mg/day) [23].

The DAPA-CKD study included 4304 patients with CKD treated for at least 4 weeks with renin-angiotensin system agents at the highest tolerated dose (68% with type 2 diabetes; mean estimated glomerular filtration rate (eGFR) 43 ± 12 mL/min/1.73 m^2) who were followed for 2.4 years (median follow-up). After randomization, patients were treated with dapagliflozin or a placebo. Patients continued treatment with the highest, well-tolerated doses of drugs that reduce the activity of the renin-angiotensin system. In this study, dapagliflozin reduced the risk of developing a renal function endpoint that included a permanent reduction in eGFR by at least 50%, end-stage renal disease (ESRD), or death due to kidney disease by 44% (hazard ratio (HR) = 0.56; 95% CI: 0.45–0.68). Dapagliflozin also reduced the risk of death from cardiovascular complications or exacerbation of HF (HR = 0.71; 95% CI: 0.55–0.92), and all-cause mortality (HR = 0.69; 95% CI: 0.53–0.88). After two weeks of dapagliflozin treatment, there was a clinically insignificant (associated with its mechanism of action, i.e. reduced hyperfiltration) reduction in eGFR of 3.97 ± 0.15 mL/min/1.73 m^2 compared with 0.82 ± 0.15 mL/min/1.73 m^2 in the placebo group [22]. However, long-term use of dapagliflozin was associated with a significantly slower loss of eGFR compared to placebo (–1.67 ± 0.11 mL/min/1.73 m^2/year *vs*. –3,59 ± 0,11 mL/min/1.73 m^2/year) [24]. Dapagliflozin decreased albuminuria compared to placebo, with an average urine albumin-to-creatinine ratio (UACR) reduction of 29.3%; 95% CI: 25.2–33.1 [25]. Dapagliflozin was well tolerated by patients [22].

It should be emphasized that the Kaplan-Meier survival curves in the DAPA-CKD study separated after 4-8 months of dapagliflozin treatment in CKD patients both with and without concomitant type 2 diabetes (HR = 0.57; 95% CI: 0.45–0.73 and HR = 0.51; 95% CI: 0.34–0.75, respectively) [26].

The second study was the EMPA-KIDNEY study which included 6609 patients with CKD treated for at least 4 weeks with renin-angiotensin system agents at the highest, well-tolerated dose (46% with type 2 diabetes; mean eGFR 37 ± 14 mL/min/1.73 m^2). Study participants received either empagliflozin or placebo for years (median follow-up) together with the highest, well-tolerated doses of renin-angiotensin system agents. The EMPA-KIDNEY study showed that empagliflozin reduced the risk of CKD progression and death due to cardiovascular complications (HR = 0.72; 95% CI: 0.64–0.82). Empagliflozin also reduced the risk of hospitalization (HR = 0.86; 95% CI: 0.78–0.95) and was well tolerated [23].

The reduction of eGFR by approximately 3–4 mL/min/1.73 m^2 observed in the DAPA-CKD and EMPA-KIDNEY studies during the initial period of SGLT2 inhibitor use [22, 23] is associated with a reversible hemodynamic mechanism of action of these drugs, i.e. a decrease in glomerular capillary pressure resulting from the contraction of afferent vessels and dilation of efferent vessels. These drugs inhibit the reabsorption of sodium in the proximal tubule, which leads to increased delivery of sodium and chlorides to the macula densa. This results in the contraction of afferent vessels due to the activation of the so-called tubuloglomerular feedback, which then leads to an increased release of adenosine [2, 27]. Kidokoro et al. conducted an experimental study with diabetic mice (Ins$^{+/Akita}$), where administration of empagliflozin caused a contraction of the glomerular afferent blood vessels and a reduction in the single nephron glomerular filtration rate (SNGFR) [28]. In another study with 40 patients with type 1 diabetes, Cherney et al. showed that the use of empagliflozin for 8 weeks reduces hyperfiltration by affecting the tubuloglomerular feedback mechanisms [29]. Moreover, in a randomized clinical trial of 44 patients with type 2 diabe-

tes (RED study), van Bommel et al. showed that the use of dapagliflozin leads to a decrease in intraglomerular pressure and a decrease in vessel wall resistance in the efferent vessels. This effect of empagliflozin was associated with increased urinary prostaglandin E_2 (PGE_2) concentrations [30]. Increased prostaglandins may lead to dilation of efferent glomerular vessels [31, 32]. It should be emphasized that the decrease in eGFR at the start of treatment with SGLT2 inhibitors is due to the nephroprotective effect of these drugs and may mean effective long-term nephroprotection. In the DAPA-CKD study, patients receiving dapagliflozin who experienced an initial reduction in eGFR > 10% had a long-term lower decrease in eGFR (–1.58 mL/min/1.73 m^2/year) compared to patients whose initial eGFR reduction was less pronounced (–2.44 ml/min/1.73 m^2/year) [33].

SGLT2 inhibitors do not cause electrolyte imbalances, which is an important advantage over other diuretics [34]. A meta-analysis by Leibensperger et al. showed no significant effect of SGLT2 inhibitors on serum sodium and potassium levels (weight mean difference (WMD) = 0.00; 95% CI: –0.03 to 0.33 and WMD = 0.00, 95% CI: –0.02 to 0.02, respectively) [35]. Yavin et al. conducted a meta-analysis of 14 randomized clinical trials, where no effect of SGLT2 inhibitor (dapagliflozin) on kalemia was found (incidence rate ratio (IRR) = 0.90; 95% CI: 0.74–1.10) [36]. Neuen et al. conducted a meta-analysis of nearly 50,000 patients, the majority of whom (80––100%) used renin-angiotensin system agents, which showed that SGLT2 inhibitors reduced the risk of hyperkalemia (HR = 0.84; 95% CI: 0.76–0.93) [37]. In the CREDENCE study of 4401 patients with type 2 diabetes and CKD, Neuen et al. demonstrated that canagliflozin reduced the risk of hyperkalemia in patients treated with renin-angiotensin system agents (RR = 0.77; 95% CI: 0.61–0.98) [38]. In the EMPEROR-Preserved study of 5988 patients with heart failure with preserved ejection fraction (HFpEF), Ferreira et al. showed that empagliflozin reduced the risk of hyperkalemia in patients treated with mineralocorticoid receptor antagonists (RR = 0.74; 95% CI: 0.56–0.96) [39].

In summary, SGLT2 inhibitors are characterized by antihypertensive and nephroprotective effects and do not affect sodium and potassium concentrations.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase inhibitors include acetazolamide. Acetazolamide causes a decrease in the secretion of hydrogen ions into the proximal tubule and thus the reabsorption of sodium in this part of the nephron (ion exchange through the sodium-hydrogen exchanger 3, NHE3) (Fig. 1) [40]. Acetazolamide is used to treat glaucoma, altitude sickness, and, more recently, acute congestive heart failure [41]. In a randomized clinical trial (ADVOR) involving 519 patients with acute congestive heart failure, Mullens et al. used acetazolamide in dose 500 mg/day and a loop diuretic for 3 days, compared to a loop diuretic monotherapy. The authors showed that the use of acetazolamide led to increased natriuresis and reduced fluid retention [42].

Acetazolamide treatment is short-term — about 3 days. Despite this, acetazolamide treatment may cause adverse effects. In a meta-analysis of 42 studies, Schmickl et al. showed that the use of acetazolamide increased the risk of paresthesia, dysgeusia, polyuria, and fatigue [43].

To summarize, acetazolamide is a diuretic that has found an application in the treatment of acute congestive heart failure.

LOOP DIURETICS

Loop diuretics reduce the activity of the sodium-potassium-chloride 2 cotransporter (Na-K-Cl cotransporter 2, NKCC2) in the thick ascending limb of the loop of Henle (Fig. 1), increasing the excretion of sodium, potassium, and chloride in urine [44]. According to the European Society of Cardiology (ESC) guidelines from 2021, loop diuretics are recommended for patients with HFrEF and signs and/or symptoms of fluid retention. The aim of this treatment is to reduce the symptoms of HF, improve physical performance, and reduce the risk of hospitalization for HF (recommendation class: I; level of evidence: C) [45]. The 2023 ESC and European Society of Hypertension (ESH) guidelines, and the 2019 Polish Society of Hypertension (PTNT) guidelines, indicate that loop diuretics can be used as antihypertensive drugs when eGFR is reduced < 30 mL/min/1.73 m^2 [46, 47]. In addition, current ESH guidelines allow the use of these drugs in antihypertensive treatment when eGFR is 30–45 mL/min/1.73 m^2 [46].

Loop diuretics are seen as having a special role in reducing overhydration in patients with CKD. Overhydration exacerbates the progression of CKD (reduced renal perfusion, increased sodium retention, increased glomerular capillary pressure, exacerbation of heart failure) and increases the risk of death in patients with ESRD [48, 49].

Esmeray et al. conducted a study where 100 patients with stage 3–5 CKD were divided into two groups: 52 patients without clinical signs of overhydration treated with diuretics to maintain proper volemia, and 48 patients with signs of overhydration put under observation only (i.e. treatment with antihypertensive drugs that are not diuretics); the effect of diuretic treatment on the progression of CKD was assessed. It was shown that patients who did not receive diuretics had a higher risk of CKD progression (odds ratio (OR) = 1.76; 95% CI: 1.20–2.57) [50].

The use of loop diuretics in hypertensive patients allows the reduction of systolic and diastolic blood pressure by 8 mmHg and 4 mmHg, respectively, as demonstrated in a meta-analysis of 9 randomized clinical trials conducted by Musini et al. [51].

Electrolyte imbalances in patients who use loop diuretics (e.g. furosemide) are relatively rare. Zamboli et al., in a study of 113 patients with CKD using furosemide, showed an occurrence of hyponatremia in 4.4% [52]. In turn, in a study involving 11213 patients from the general population, Mannheimer et al. demonstrated that the use of furosemide reduced the risk of hospitalization associated with hyponatremia (OR = 0.61; 95% CI: 0.57–0.66) [53]. Adamczak et al. conducted an analysis of the PolSenior study and showed that in 4654 people, with an average age of 76.5 ± 11 years, hypokalemia occurred in 1.3% of patients using loop diuretics [54].

In conclusion, loop diuretics are characterized by antihypertensive effects and reduce body overhydration. Electrolyte imbalances are relatively rare with these drugs.

Some patients may develop resistance to loop diuretics. The most common causes of resistance include: 1) incorrect diagnosis (e.g. presence of venous or lymphedema); 2) patient noncompliance with sodium restriction; 3) insufficient penetration of the drug into the kidneys (dose too low or administered not often enough, impaired drug absorption caused by intestinal edema in the course of hypoalbuminemia, among others); 4) decreased drug excretion (impaired renal tubular uptake due to uremic toxins, metabolic acidosis, reduced renal blood flow or reduced effective arterial blood volume, or decreased functional renal mass); 5) insufficient drug interaction in the kidneys (in patients with reduced eGFR, activated renin-angiotensin system, distal tubular hypertrophy, or using non-steroidal anti-inflammatory drugs) [55].

In patients with significant proteinuria (e.g. nephrotic syndrome), there is an increased amount of proteases such as plasmin in the urine. A study by Schork et al., which included 117 patients with CKD, showed that plasminuria was associated with overhydration [56]. Plasmin and other proteases stimulate the activity of the epithelial sodium channel (ENaC), which leads to increased sodium reabsorption in the collecting tubule. Resistance to loop diuretics can be overcome in these patients by using an epithelial sodium channel (ENaC) inhibitor — amiloride or triamterene [57, 58]. However, these drugs are not available in Poland. Another mechanism that may reduce the effectiveness of treatment with loop diuretics is the increase in the expression of pendrin in the collecting tubules, which enhances sodium reabsorption in this segment of the nephron [58, 59].

In the management of patients with resistance to loop diuretics, the following should be considered: increasing the dose or the frequency of administration of the drug, or adding another diuretic that acts on a segment of the nephron other than the loop of Henle [60].

THIAZIDE AND THIAZIDE-LIKE DIURETICS

Thiazide and thiazide-like diuretics reduce the activity of the sodium-chloride symporter (NCC) in the luminal membrane of the cells in the initial section of the distal tubule, increasing the renal excretion of sodium and chloride (Fig. 1) [61, 62].

Thiazide and thiazide-like diuretics are one of the five basic classes of antihypertensive drugs [47]. In a meta-analysis of 60 randomized clinical trials, conducted by Musini et al., thiazide monotherapy was shown to reduce systolic and diastolic blood pressure by 9 mmHg and 4 mmHg, respectively, in hypertensive patients [63]. Liang et al. conducted a meta-analysis of 12 randomized clinical trials and demonstrated that thiazide-like diuretics have a stronger antihypertensive effect compared to thiazide diuretics (systolic

blood pressure: MD = −5.59 mmHg; 95% CI: −5.69 to −5.49, and diastolic blood pressure: MD = −1.98 mmHg; 95% CI: −3.29 to −0.66) [64].

In patients with CKD, hypertension is often treatment-resistant, therefore in 80–90% of these patients monotherapy is insufficient, and the use of ≥ 2 antihypertensive drugs is necessary to achieve the therapeutic goal [65]. In a randomized clinical trial, Agarwal et al. administered chlorthalidone (12.5–50 mg/day) or placebo for 12 weeks in 160 patients with CKD (eGFR in the range 15–30 mL/min/1.73 m^2) who were unsuccessfully treated for hypertension. The addition of chlorthalidone was associated with a reduction of 11 mmHg (95% CI: –13.9 to –8.1) in a 24-hour systolic blood pressure measurement and a 50% (95% CI: 37–60) reduction in albumin/creatinine ratio [66]. The results of this study were reflected in the 2023 ESH recommendations, indicating the advisability of using chlorthalidone in the treatment of hypertension in patients with eGFR in the range of 15–30 mL/min/1.73 m^2 [46]. A meta-analysis by Teles et al. evaluated the efficacy of thiazide and thiazide-like diuretics other than chlorthalidone in antihypertensive therapy in patients with CKD (eGFR ranging from 13.0 ± 5.9 to 26.8 ± 8.8 mL/min/1.73 m^2), and showed that these drugs significantly reduced mean blood pressure in these patients (MD = –6.18 mmHg; 95% CI: –7.77 to –4.59) [67].

Until recently, it was thought that the use of thiazide or thiazide-like diuretics may accelerate the progression of autosomal dominant polycystic kidney disease (ADPKD). The results of a recent observational study indicate that these fears are unfounded. Kramers et al., in a 4-year study involving 533 patients with ADPKD and an eGFR in the range of 30–60 mL/min/1.73 m^2, evaluated the effect of thiazide or thiazide-like diuretics on the progression of ADPKD. In this study, 76% of patients received antihypertensive therapy based on renin-angiotensin system inhibitors, while 23% of patients received a thiazide or thiazide-like diuretic (91% of those treated with a thiazide or thiazide-like diuretic used a renin-angiotensin system inhibitor). The use of a thiazide or thiazide-like diuretic was shown not to accelerate the progression of ADPKD (HR = 0.80; 95% CI: 0.50–1.29), assessed as: ≥ 40% reduction in eGFR, need to initiate renal replacement therapy, or death [68]. The results of this study indicate that the use of a thiazide or thiazide-like diuretic in patients with ADPKD is safe.

It should be emphasized that the use of thiazide or thiazide-like diuretics is associated with a significant risk of electrolyte imbalances — including hyponatremia and hypokalemia.

A study by Clayton et al., which included 950 patients treated in GP clinics in the UK during 1990-2002 and who used thiazide or thiazide-like diuretics, showed that hyponatremia occurred in 14% of patients and the incidence of hyponatremia increased with patient age [69].

One of the possible patients of this complication is thiazide-induced hyponatremia (TIH), which is a specific type of hyponatremia [62]. Under physiological conditions, PGE_2 is secreted into the collecting tubule lumen and does not increase water resorption because it is efficiently transported by the prostaglandin transporter (PGT) to the renal interstitium [1, 34, 62, 70]. In patients with the SLCO2A1 gene mutation, after administration of a thiazide or thiazide-like diuretic, PGE_2 is not transported by PGT and instead stimulates EP4 prostaglandin receptors, causing increased displacement of aquaporin-2 into the luminal membrane of tubular cells, which results in increased water resorption. As a result of this, plasma becomes diluted [1, 34, 62, 70].

Barber et al. conducted a meta-analysis of 43 studies, which included 3269 patients with TIH, and showed that the factors increasing the risk of TIH were old age and low body weight [71]. Moreover, TIH was found to occur most often (50–90%) during the first 3 weeks of using thiazide or thiazide-like diuretics [71]. However, TIH can occur at any time of using these drugs and recurs after taking them again [1, 34, 62]. In patients susceptible to TIH, natremia decreases within a few hours of administration of a thiazide or thiazide-like diuretic, and TIH may occur within the first 48 hours of treatment [72]. It should be emphasized that any thiazide or thiazide-related diuretic may cause TIH (cases of TIH have been reported during treatment with hydrochlorothiazide, bendofluazide, indapamide, and chlorthalidone). TIH most commonly occurs with high doses of a diuretic, but 10% of TIH was caused by hydrochlorothiazide at a dose of only 12.5 mg [34]. TIH is usually profound hyponatraemia (116 mmol/L; 95% CI: 113.4–119.5 mmol/L) [71]. The most common clinical manifestations of TIH include nausea, vomiting, confusion, headache, abnormal and

profound somnolence, convulsions, and coma [71].

Prevention of TIH includes: monitoring of symptoms of hyponatremia; educating the patient on the possible symptoms of hyponatremia; frequent [Na^+] testing in patients treated with thiazide or thiazide-like diuretics (at least after 2–3 weeks of treatment and at least annually thereafter) [1, 34, 62]. If TIH occurs, besides acute hyponatremia treatment, it is recommended to stop using these drugs, not to use them in the future (if a diuretic is necessary, a loop diuretic may be used), and to avoid excessive water intake (i.e. > 2.5 L/day) [1, 34, 62].

Hypokalemia is another clinically relevant electrolyte imbalance that can occur during treatment with thiazide or thiazide-like diuretics. As mentioned previously, these drugs reduce the activity of NCC in the cell luminal membrane in the initial section of the distal tubule. As a result, there is an increase in the concentration of sodium ions in the tubular fluid that reaches the collecting tubule, which increases the excretion of potassium ions in urine [73]. Adamczak et al. conducted an analysis of the PolSenior study and showed that in 4654 people, with an average age of 76.5 ± 11 years, hypokalemia occurred in 3.3% of patients using thiazide diuretics and in 2.6% of patients using thiazide-like diuretics [54]. A Roush et al. meta-analysis of 14 randomized clinical trials, which included 883 patients with hypertension, the effect of hydrochlorothiazide and indapamide on the incidence of hypokalemia was compared. The study showed no significant difference in the incidence of hypokalemia between these agents [74].

Thiazide diuretics may, in specific situations, increase the risk of skin cancers. This applies primarily to the use of hydrochlorothiazide, which, due to its chemical structure, is a photosensitizer [75]. A meta-analysis of 30 studies showed that the use of thiazide diuretics significantly increases the risk of malignant melanoma (OR = 1.10; 95% CI: 1.04–1.15), basal cell carcinoma (OR = 1.05; 95% CI: 1.02–1.09) and squamous cell carcinoma (OR = 1.35; 95% CI: 1.22–1.48) [76]. Another meta-analysis confirmed that the use of hydrochlorothiazide was associated with an increased risk of: skin cancers other than melanoma (OR = 1.16; 95% CI: 1.08–1.24), squamous cell carcinoma (OR = 1.32; 95% CI: 1.06–1.65) and malignant melanoma (OR = 1.11; 95% CI: 1.02–1.20). Unlike hydrochlorothiazide, the use of indapamide (a thiazide-like diuretic) did not increase the risk of skin cancer [77]. The analysis of adverse effects of hydrochlorothiazide treatment in 511115 patients documented that that the risk of squamous cell carcinoma and melanoma increases with longer use (over 10 years) and with higher cumulative doses of this drug [78]. Therefore, patients treated with hydrochlorothiazide for a long time should undergo periodic dermatological consultations with the recommendation to avoid intense exposure to sunlight.

In summary, thiazide and thiazide-like diuretics have antihypertensive effects. Clinically significant and frequent complications of the use of these drugs include hyponatremia and hypokalemia. The use of hydrochlorothiazide may also increase the risk of skin cancers.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

The use of mineralocorticoid receptor antagonists leads to a decrease in the activity of the ENaC in the collecting tubule cells (Fig. 1) [1, 73]. Other mechanisms of action of these drugs include: reduction of oxidative stress, antifibrotic effect, anti-inflammatory effect, and reduction of glomerular hypertrophy [75].

Mineralocorticoid receptor antagonists have been used in the therapy of treatment-resistant hypertension and , HF and CKD [45, 47].

Mineralocorticoid receptor antagonists are divided into steroidal (spironolactone and eplerenone) and non-steroidal ones (finerenone) [76].

Bazoukis et al. conducted a meta-analysis of 21 randomized clinical trials, which included 2736 patients with hypertension, and demonstrated that the use of steroidal mineralocorticoid receptor antagonists was associated with a reduction in systolic and diastolic blood pressure by 8 mmHg and 3 mmHg, respectively [77]. Agarwal et al. conducted a randomized clinical trial (AMBER) including 295 patients with CKD with eGFR 25–45 mL/min/1.73 m^2 and treatment-resistant hypertension, and showed that 25 mg of spironolactone significantly reduced blood pressure (about 11 mmHg in case of systolic blood pressure) [78].

In a meta-analysis of 7 randomized clinical trials by Navaneethan et al., which included 372 patients with CKD, the effect of using a steroidal mineralocorticoid receptor antagonist in combination with renin-angiotensin system inhibitors on urinary protein excretion was evaluated. It was shown that a ste-

roidal mineralocorticoid receptor antagonist reduced proteinuria (MD = –0.80 g; 95% CI: –1.27 to –0.33) [83]. Chung et al. conducted a meta-analysis of 14 randomized clinical trials, which included 683 patients with CKD, the effect of steroidal mineralocorticoid receptor antagonists on urinary protein excretion was also evaluated. Again, these drugs were shown to reduce proteinuria (MD = –0.51 g; 95% CI: –0.82 to –0.20) [84].

Finerenone is a new mineralocorticoid receptor antagonist, which is characterized by a non-steroidal molecule structure [80]. Bakris et al. conducted the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study, which included 5734 patients with CKD and type 2 diabetes and treated with renin-angiotensin system inhibitors, and which showed that finerenone significantly inhibits the progression of CKD and improves the prognosis of patients when compared to placebo [(primary endpoint: initiation of chronic dialysis ≥ 90 days or kidney transplantation or permanent reduction in eGFR to < 15 mL/min/1.73 m^2, permanent reduction in eGFR ≥ 40% or death from kidney disease); (secondary endpoint: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or HF hospitalization)]. A mean follow-up of 2.6 years showed that patients who were treated with finerenone had a lower risk of both the primary and secondary endpoints (HR = 0.82; 95% CI: 0.73–0.93 and HR = 0.86; 95% CI: 0.75–0.99, respectively). Finerenone reduced the urinary albumin/creatinine ratio by 31% [85]. The results of this study indicate that finerenone had nephroprotective and cardioprotective effects in patients with CKD and type 2 diabetes. The results of the FIDELIO study were confirmed in a meta-analysis of 5 randomized clinical trials, conducted by Zhang et al., which included 13078 patients. This meta-analysis found that finerenone reduced: the risk of eGFR decrease by ≥ 40% (RR = 0.85; 95% CI: 0.78–0.93), the risk of ESRD (RR = 0.80; 95% CI: 0.65–0.99), the risk of serious complications of cardiovascular disease (RR = 0.88; 95% CI: 0.80–0.95), and resulted in a decrease in urinary albumin/creatinine ratio (MD = −0.30; 95% CI: −0.32 to −0, 28). The use of finerenone in a clinical trial, in which kalemia was closely supervised, was safe. The risk of adverse reactions did not differ from placebo (RR = 1.00; 95% CI: 0.98–1.01) [86].

The use of mineralocorticoid receptor antagonists may increase the risk of electrolyte imbalances, i.e. hyponatremia and hyperkalemia. Mannheimer et al., in a study involving 11213 patients, showed that the use of mineralocorticoid receptor antagonists increased the risk of hyponatremia (OR = 1.96; 95% CI: 1.76−2.18) [53].

Antagonism of mineralocorticoid receptors leads to a decrease in the activity of the potassium channel ROMK2, which causes a decrease in urinary potassium excretion [83]. In the previously mentioned meta-analysis by Naveneethan et al., it was shown that the use of steroidal mineralocorticoid receptor antagonists significantly increased the risk of hyperkalemia (RR = 3.06; 95% CI: 1.26−7.41) [79]. Similar results were obtained in a Chung et al. meta-analysis of 17 randomized clinical trials, which included 2046 patients with CKD, where it was found that the use of steroidal mineralocorticoid receptor antagonists increased the risk of hyperkalemia (RR = 2.17; 95% CI: 1.47−3.22) [84]. A meta-analysis of 7 studies, conducted by Vukadinović et al., involving 16065 patients, showed that spironolactone was associated with a higher risk of hyperkalemia compared to eplerenone (RR = 2.45; 95% CI: 1.56−3.85 and HR = 1.91, 95% CI: 1.56−2.33), respectively [87]. The risk of hyperkalemia when using spironolactone or eplerenone depends on the dose and, consequently, on the intensity of sodium elimination from the body [86]. The use of spironolactone, compared with the same dose of eplerenone, is associated with a higher risk of hyperkalemia because the active metabolites of spironolactone have a longer plasma half-life and because spironolactone has a greater natriuretic effect [88]. Compared to finerenone, the use of steroidal mineralocorticoid receptor antagonists has a greater effect on serum potassium concentration (MD = 2.07; 95% CI: −0.04 to 4.17), as demonstrated in a meta-analysis conducted by Pei et al., including 1520 patients with heart failure [89].

In the FIDELIO-DKD study, hyperkalaemia defined as [K^+] in serum > 5.5 mmol/L occurred in 21% of patients, while defined as [K^+] in serum > 6.0 mmol/L occurred in 4.5% of patients. During a 44-month follow-up, the difference in serum potassium concentration in the finerenone and placebo groups was up to 0.25 mmol/L [90]. In the previously mentioned meta-analysis by Zhang et al., which included 13078 patients, it was demonstrated that using finerenone increased the risk of hyperkalemia (RR = 2.03; 95% CI: 1.83−2.26) [86].

Hyponatremia was found in 1.4% of patients treated with finerenone [91]. In a randomized clinical trial (ARTS) with 392 patients with HF (ejection fraction < 40%) and eGFR of 30–60 mL/min/1.73 m^2, Pitt et al. showed that finerenone (10 mg/day) compared to spironolactone (25–50 mg/day) was associated with a lower incidence of hyperkalemia (4.8% *vs.* 11.1%) [92].

In conclusion, mineralocorticoid receptor antagonists are characterized by antihypertensive, nephroprotective, and cardioprotective effects. These drugs increase the risk of hyperkalemia (lower with finerenone).

CONCLUSIONS

1. SGLT2 inhibitors are also diuretics.
2. Treatment of overhydration reduces the progression of CKD.
3. In patients with CKD and eGFR 15–30 mL/min/1.73 m^2, chlorthalidone is an effective antihypertensive drug and its use reduces proteinuria.
4. In patients with polycystic kidney disease, antihypertensive treatment with thiazide and thiazide-like diuretics should not be avoided.
5. Hyponatremia caused by thiazide and thiazide-like diuretics (TIH) is a clinically significant complication associated with the use of these drugs.
6. The use of finerenone reduces the progression of diabetic kidney disease.

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