e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 12, Issue 02; 2024, 15-27

Diuretics: A Review

Kajal Kumari*, Rajesh Kumar, Ajeet Pal Singh, Amar Pal Singh & Prachi Sharma

St. Soldier Institute of Pharmacy, Lidhran Campus, Behind NIT Jalandhar-Amritsar By pass Nh-1, Jalandhar-144011, Punjab, India.

Received: 15-01-2024 / Revised: 04-02-2024 / Accepted: 08-03-2024

Corresponding author: Kajal Kumari

Conflict of interest: No conflict of interest.

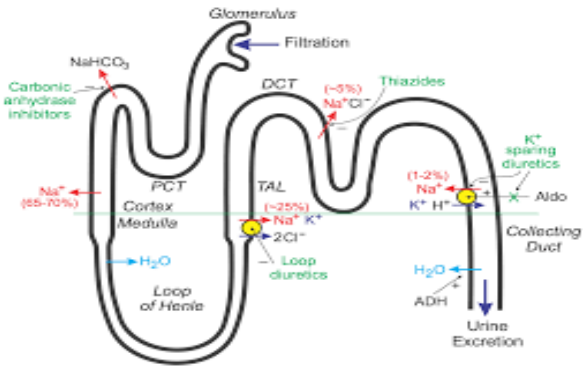
Abstract:

Diuretics represent a cornerstone in managing various conditions by enhancing diuresis and natriuresis. Acting at different segments of the renal tubule, they offer a versatile approach to fluid management. Loop diuretics, such as acetazolamide, find utility in acute heart failure, exerting antihypertensive effects and mitigating fluid overload with minimal electrolyte disturbances. Thiazide and thiazide-related diuretics, while effective antihypertensives, warrant vigilance due to potential complications like hyponatremia and hypokalemia. In contrast, mineralocorticoid receptor antagonists exhibit multifaceted benefits, including antihypertensive, nephroprotective, and cardioprotective effects, albeit increasing the risk of hyperkalemia. In contrast, mineralocorticoid receptor antagonists exhibit multifaceted benefits, including antihypertensive, nephroprotective, and cardioprotective effects , albeit increasing the risk of hyperkalemia. SGLT2 Inhibitors emerge as promising agents with antihypertensive and cardio-renal protective effects, without adverse impacts on natremia. Understanding the mechanisms and clinical implications of diuretics is crucial for optimizing therapeutic strategies in conditions such as heart failure, nephrological disease, and hypertension.

INTRODUCTION

Diuetics are drugs that increase the excretion of water and sodium in urine, known for their natriuretic effect.Different diuretics act on sodium reabsorption across various segments of the nephron, including the proximal tubule, loop of Henle, distal tubule, and collecting tubule.Diuretics affect sodium reabsorption in all sections of the nephron.

- **Regulation of Sodium Balance in the Kidneys:**
- Filtration in Glomerulus**:** 100% of sodium (Na+) is filtered.
- Proximal Tubule Reabsorption**:** 60-70% of Na+readsorption occurs via the action of 3Na+/2K+ ATPase and SGLT2.



- Loop of Henle Reabsorption**:** 20-30% of Na+ reabsorption occurs via NKCC2 , affected by loop diuretics.
- Distal Tubule Reabsorption: 5-7% of Na+ reabsorption occurs through NCC, inflenced by thiazide and thiazide-like diuretics.
- Collection Tubule Reabsorption: 2-3% of Na+ reabsorption is facilitate by ENaC, modulated by mineralocorticoid receptor antagonists.

A. SGL2 Inhibitors:

- Function**:**Sodium-glucose cotransporter 2(SGLT2) inhibitors reduce the reabsorption of glucose and sodium primarily in the proximal tubule.
- Mechanism in Proximal Tubule**:** SGLT2 Inhibitors decreases glucose and sodium reabsorption in the S1 and S2 segments of the proximal tubule.
- Increased Natriuresis**:** Use of SGLT2 inhibitors leads to dose-dependent increases in natriuresis.
- Diretic Effects**:** SGLT2 Inhibitors have been shown to increase diuresis, contributing to their overall therapeutic effect.
- Weight Loss Effect**:** Initially, SGLT2 inhibitors cause weight loss mainly due to a decrease in total body water volume. Later, weight loss may be attributed to their effects on adipose tissue metabolism, including increased lipolysis and reduced lipidaccumulation.
- Reduction of Water Content**:** SGLT2 Inhibitors reduce water content both inside cell and in the extracellular space, contributing to their diuretic and weight loss effects.

- **Site of Action of Diuretics:**These reduce glucose and Na+ reabsorption in the proximal tubule without significantly impacting extracelular space sodium levels, unlike loop diretics.
- **Effects of SGLT2 Inhibitors:**

1. Vascular Effects**:** SGLT2 inhibitors improve vascular endothelial function, reducing stiffness and stimulating nitric oxide production.
2. Reduction of Sodium Content**:**They decrease sodium content in subcutaneous tissue, mainly within intracellular and non-osmotic sodium stores.
3. Antihypertensive Effects**:** SGLT2 inhibitors have a moderate antihypertensive effect, reducing both systolic and diastolic to meta-analyses.

- **Benefits of SGLT2 Inhibitors in Cardiovascular and Kidney Disease:**

1. Reduction of Chronic Kidney Disease (CKD) Progression:

- Meta-analysis of 13 randomized Clinical trials involving over 90,000 patients demonstrated a reduced risk of CKD progression with SGLT2 Inhibitors.
- Significant risk reduction observed in patients without diabetes.

2. Cardiovascular Risk Reduction :

- SGLT2 Inhibitorsdecrease the risk of death from cardiovascular complications and exacerbation of heart failure, as well as all-cause mortality.

3. Effects on Urinary Albumin-to-Creatinin Ratio(UACR) :

- Dapagliflozin treatment resulted in a significant reduction in UACR compared to placebo.

- **Clinical Trials: DAPA-CKD and EMPA-KIDNEY:**

1. DAPA-CKD Study(Dapagliflozin 10 mg/day):

- Reduced risk of developing a renal function endpoint, including a permanent reduction in estimated glomerular filtration rate (eGFR) by at least 50%, end –stagerenal disease (ESRD) or death due to kidney disease.
- Also reduced the risk of death from cardiovascular complictions or heart failure exacerbation and all causes mortality.

2. EMPA-KIDNEY Study(Empagliflozin 10 mg/day):

- Showed a reduction in the risk of CKD progression and death due to cardiovascular complications.
- Decreased risk of hospitalization and well tolerated by patients.

- **Mechanism of eGFR Reduction :**

1. Hemodynamic Mechanism**:**

- Initial reduction in eGFR attributed to reversible hemodynamic effects, including decreased glomerular capillary pressure.
- Resulting from the contraction of afferent vessels and dilation of efferent vessels due to increased sodium and chloride delivery to the macula densa.

2. Tubuloglomerular Feedack **:**

- Increased release of adenosine due to activation of tubuloglomerular feedback.
- Experimental and clinical studies demonstration the impact of SGLT2 inhibitors on hyperfiltration and tubuloglomerular feedback mechanisms.

- **Impact of SGLT2 Inhibitors on Cardiovascular and Kidney Disease:**

1. Reduction in Action :

o Meta-analysis pf 13 randomized clinical trils, including over90,000 patients, confirms the ability of SGLT2 inhibitors to reduce the risk of crdiovascular and kidney disease progresion .

o Notable reductions observed in chronic kiney disease (CKD) progression, regardless of diabetes status.

2. Specific Risk Reduction:

o SGLT2 inhibitors decrease the risk of death from cardiovascular cimplications, exacerbation of heart failure, and all-cause mortality.

- **Clinical Trials Finings: DAPA-CKD and EMPA-KIDNEY:**

1. DAPA-CKD Study (Dapagliflozin 10 mg/day):

o Involving 4,304 CKD patints, dapagliflozin significantly reduced the risk of developing renal function endpoints, including a permanent reduction in estimated glomerular filtration rate (eGFR) end –stage renal disease (ESRD) or kidney related mortality.

o Also reduced the risk of death from crdiovascular complications or heart failure exacerbation and all-cause mortality.

2. EMPA-KIDNEY Study (Empagliflozin 10 mg/day):

o Conducting with, 6,609 CKD patients, empagliflozin demonstrated a reduction in CKD progression and cardiovascular-related mortality.

o Showed reduced risk of hospitalization and was well tolerated by patients.

- **Mechanism of eGFR Reduction:**

1. Hemodynamic Effects:

o SGLT2 inhibitors induce a reversible decrease in glomerular capillary pressure by affecting afferent and efferent vessel dynamics.

2. Experimental Evidence**:** Studies on diabetic mice and patients with diabates illustrate the impact of SGLT2 inhibitors on glomerular feedback mechanisms.

RESULT: SGLT2 inhibitors exhibit significant protective effects against cardiovascular and kidney diseases, supporting by robust clinical trial evidence and mechanistic understanding of their actions on renal hemodynamics.

A. Impact of Dapagliflozin on Intraglomerular Pressure:

RED Study Findings**:** Dapagliflozin usage leads to reduced intraglomerular pressure and efferent vessel wall resistance, as demonstratedbyVan Bommel etal.

B. Acetazolamide:

Mechanism of Action **:**Acetazilamide decreases hydrogen ion secretion in the proximal tubule, there by inhibiting sodium readsorption via sodium-hydrogen exchanger3 (NHE3) .It is Also used in

treating glaucoma, altitude sickness and acute congestive heart failure.

Clinical Trial(ADVOR):Mullens et al. conducted a trial with 519 patients with acute congestive heart failure, showing that acetazolamide, in combination with loop diuretics, increased natriuresis and reduced fluid retention.

- **Comparison with SGLT2 Inhibitors:**

Short-Term Treatment Duration**:** Acetazolamide treatment typically lasts aroind 3 days, unlike SGLT2 inhibitors.Meta-analysis by Schmickl et al. identified adverse effects of acetazolamide, including paresthesia, dysgeusia, polyuria and fatigue.

- **Electrolyte Balance and Diuretic Effects:**
  - Unlike other diuretics, SGLT2 inhibitors do not cause electrolyte imbalances.
  - Meta-analyses and clinical trials demonstrates no significant impact on serum sodium and potassium levels.
- **Effect on Hyperkalemia:**Studies show that SGLT2 inhibitors reduce risk of hyperkalemia, particularly in patients treated with renin-angiotensin system agents.

B. Loop Diretics:

Mechanism of Action **:** Loop diuretics inhibit the sodium-potassium-chloride cotrasporter 2 (NKCC2) in the thick ascending limb of the loop of Henle, increasing sodium, potassium, and chloride excretion in urine.

Clinical Guidelines**:**Recommended for patients with heart failure with reduced ejection fraction (HFrEF) and signs/symptoms of fluid retention.It can also be used as antihypertensive drugs in specific eGFR ranges according to ECSand ESH guidelines.

RESULT: SGLT2 inhibitors offer antihypertensive and nephroprotective benefits without impacting electrolyte balance, contrasting with the adverse effects and short term usage of acetazolamide . Loop diuretics remain vital in managing heart failure and hypertension according to current clinical guidelines.

Role of Loop Diretics in CKD:

1. Impact on Overhydration:Overhydration exacerbates CKD progression due to reduced renal perfusion, increased sodium retention , elevated glomerular capillary pressure, and worsend heart failure.Loop diuretics play a crucial role in reducing overhydration in CKD patients.
2. Clinical Evidence**:** Esmeray et al. demonstrated that CKD patients without clinical signs of overhydration had a higher risk of disease progression when not treated with diuretics.Increased plasmin levels associated with significant proteinuria contribute to overhydration by stimulating sodium reabsorption, highlighting the importance of addressing underlying mechanisms.
3. Resistance Mechnisms**:** Resistance to loop diuretics may occur due to increased expression of pendrin in collecting tubules, enhancing sodium reabsorption.In hypertensive patients, loop diuetics effectively reduce both systolic and diastolic blood pressure.
4. Electrolyte Imbalance**:**Electrolyte imbalances with loop diuretics, such as hyponatremia and hypokalemia, are relatively rare in CKD patients.Studies indicate a reduced risk of hospitalization associated with hyponatremia in patients using loop diuretics.
5. Management of Resistance**:**Strategies to manage resistance include dose adjustment, frequency modification, or adding on different nephron segments.

C. Thiazide and Thiazide-like Diuretics:

- Mechanism of Action :Thiazide and thiazide-like diuretics reduce sodium and chloride reabsorption by inhibiting the

sodium-chloride symporter (NCC) in the distal tubule.

- Antihypertensive Effect**:** Thiazide monotherapy significantly reduces both systolic and diastolic blood pressure in hypertensive patients, as evidencedby clinical reials.Thiazide-like diuretics exhibit stronger antihypertensiveeffects compared to traditional thiazides.
- Thiazide and Thiazide-like Diuretics in CKD:
  - Thiazide and thiazide-like diretics significantly reduce systolic and diastolic blood pressure in hypertensive patients with CKD.
  - Meta-analyses demonstrate their efficacy in lowering mean blood pressure levels.
  - Clinical guidelines recommend chlorthalidone use in CKD patients with eGFR in the range of 15-30 mL/min/1.73mm.
  - TIH is a specific type of hyponatremia resulting from impaired prostaglandin transport, leading to increased water resorption.
  - Factors increasing TIH risk including old age, low body weight, and high diuretic doses.
  - Recent observational studies refute concerns about thiazide or thiazide-like diuretics accelerating the progression of autosomal dominant polycystic kidney disease(ADPKD) .
  - Thiazide or thiazide-like diuretic use does not hasten ADPKD progression or adversely affect renal function in patients with ADPKD and CKD.
- **Hyponatremia and Hypokalemia Risks:**

1. Hyponatremia Prevention and Management:Monitoring symptoms and educating patients about hyponatremia signs.Regular sodium testing during thiazide or thiazide-like diuetic treatment.Immediate cessation of diuretic use occurance of thiazide-include hyponatremia(THI).Avoidance of future thiazide or thiazide-like diuretic use and excessive water intake.
2. Hypokalemia Incidence and Management:Thiazide and thiazide-like diuretics increase urinary potassium excretion, leading to hypokalemia risk.Hypokalemia occurs in a small percentage of patients, with similar incidence between thiazide and thiazide-like diuretics.Close monitoring and appropriate management of hypokalemia symptoms are essential during diuretic therapy.

- **Mineralocorticoid Receptor Antagonists (MRAs) in Hypertension and CKD:**

1. Blood Preasure Reduction:Steroidal MRAs significantly reduce systolic and diastolic blood presure in hypertensive patients.Clinical trials demonstrate the efficacy of spironolactone in reducing blood pressure, particularly in CKD patients with treatment-resistant hypertension.
2. Use in Treatment-Resistant Hypertension and CKD:MRAs are effective in treating treatment-resistant hypertension and managing heart failure (HF) and CKD.They are divided into steroidal (spironolactone, eplerenon) and non-steroidal (finerenone) types.
3. Urinary Protein Excretion Reduction:Combination therapy with steroidal MRAs and renin-angiotensin system inhibitors reduces urinary protein excretion in CKD patients.

- **Skin Cancer Risk Associated with Cancer Risk:**

1. Hydrochlorothiazide and Skin Cancer Risk:Prolonged use of hydrochlorothiazide increases the risk of squamous cell carcinoma and melanoma, especially with higher cumulative doses and longer durations of use.Thiazide diuretics, particularly

hydrochlorothiazide, are associated with an increased risk of various skin cancers, necessitating regular dermatological monitoring and sun protection recommendations. In summary, while thiazide and thiazide-like diuretics effectively manage hypertension, their use requires vigilant monitoring for electrolyte imbalances and awarenessof potential skin cancer risks. Steroidal MRAs, such as spironolactone, demonstrate efficacy in reducing blood pressure and urinary protein excretion, particularly in CKD patients with treatment-resistant hypertension.

- Comparison of Mineralocorticoid Receptor Antagonists:Higher risk of hyperkalemia with spironolactone.Greater risk of hyperkalemia with spironolactone due to longer plasma half-life and stronger natriuretic effect.
- Safety and Efficacy of Finerenone**:**Zhang et al. meta-analysis: Reduced risk of eGFR decrease, ESRD, and cardiovascular complications; decreased urinary albumin/creatinine ratio.Clinical trial safety: Risk of advese reactions similar to placebo(RR=1.00; 95% Cl: 0.98-1.01).
- Overall Risk of Electrolyte Imbalances:Mineralocorticoid receptor antagonists may elevate the risk of electrolyte imbalances.
- Hyponatremia Incidence with Finerenone**:**Found in 1.4 % of patients treated with finerenone.
- Overall Conclusion on Mineralocorticoid Receptor Antagonist: Characterized by antihypertensive, nephroprotectiv, and cardioprotective effects.Increase risk of hyperkalemia (lower with finerenone).
- Finerenone's Impact on Diabetic Kidney Disease Progression**:**Reduces progression of diabetic kidney disease .

REFERENCE:

1. Surma S, Więcek A, Adamczak M. Zaburzeniagos-Podarkisodowej u chorych z nadciśnieniemtętniczym. ChorobySerca I Naczyń. 2022; 19(1): 19-38, doi: 10.5603/ChSiN.2022.0003.
2. Surma S, Filipiak KJ. Plejotropowedziatanieinhitbitorów SGLT2. In: Więcek A. ed. Postępy w Nefrologii I NadciśnieniuTętniczym T. XXI. 2022:47-61.
3. Filippatos TD, Tsimihodimos V, Elisaf MS. Mechanisms of blood pressure reduction with sodium-glucose co-transporter 2 (SGLT2) inhibitors. Expert OpinPharmacother. 2016; 17(12): 1581-1583, doi: 10.1080/14656566.2016.1201073, indexed in Pubmed: 27295549.
4. Scheen AJ. Efects of reducing blood presSure on car- diovascular outcomes and mortality in patients with type 2 diabetes: Focus on SGLT2 inhibitors and EMPA-REG OUTCOME. Diabetes Res ClinPract. 2016; 121: 204- 214. Doi: 10.1016/.diabres.2016.09.016. indexed in Pubmed: 27744129.
5. Bjornstad P Greasley PJ, Wheeler DC, et al. The Potential Roles of Osmotic and Nonosmotic Sodium Handling in Mediating the Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Heart Failure. J Card Fail. 2021; 27(12): 1447-1455, doi: 10.1016/.cardfail.2021.07.003, indexed in Pubmed: 34289398.
6. Dekkers CCJ, Gansevoort RT, Heerspink HJL. New Dia- betes Therapies and Diabetic Kidney Disease Progres- sion: the Role of SGLT-2 Inhibitors. CurrDiab Rep. 2018; 18(5): 27, doi: 10.1007/s11892-018-0992-6. Indexed in Pubmed: 29589183.
7. Kawasoe S, Maruguchi Y, Kajiya S, et al. Mechanism of the blood pressure-lowering effect of sodium-glucose cotransporter 2 inhibitors in obese

patients with type 2 diabetes. BMC PharmacolToxicol. 2017; 18(1): 23, doi: 10.1186/s40360-017-0125-x, indexed in Pubmed: 28391776.

8. Fukuoka S, Dohi K, Takeuchi T, et al. Diuretic effects of s0- dium-glucose cotransporter 2 inhibitor in patients with type 2 diabetes mellitus and heart failure. Int J Cardiol. 2015;201(9): 1-3, doi: 10.1016/jcard.2015.07.072, indexed in Pubmed: 26278671.
9. Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in Heart Failure: Diuretic and Cardiorenal Effects. Circula- tion. 2020; 142(11): 1028-1039, doi: 10.1161/CIRCULA-TIONAHA.120.045691, indexed in Pubmed: 32410463.
10. Szekeres Z, Toth K, Szabados E. The Effects of SGLT2 Inhibitors on Lipid Metabolism. Metabo- lites. 2021; 11(2), doi: 10.3390/metabo11020087, indexed in Pubmed: 33535652.
11. Ohara K, Masuda I, Murakami T, et al. Effects of the so- dium-glucose cotransporter 2 inhitbitordapagliflozin on fluid distribution: A comparison study with furosemide and tolvaptan. Nephrology (Carton). 2019; 24(9): 904-911, doi: 10.1111/nep.13552, indexed in Pubmed: 30578654.
12. Karg MV, Bosch A, Kannenkeril D, et al. SGLT-2-inhibi- tion with dapagliflozin reduces tissue sodium content: a randomised controlled trial. CardiovascDiabetol. 2018; 17(1): 5, doi: 10.1186/s12933-017-0654-z, indexed in Pubmed: 29301520.
13. Noble MIM, Drake-Holland AJ, Vink H. Hypothesis: arte- rialglycocalyx dysfunction is the first step in the atherothrombotic process. QJM. 2008; 101(7): 513-518, doi: 10.1093/qjmed/hcn024, indexed in Pubmed: 18319293.
14. Fels J, Jeggle P Liashkovich I, et al. Nanomechanics of vascular endothelium. Cell Tissue Res. 2014; 355 (3): 727-737, doi: 10.1007/s00441-014-1853-5, indexed in Pubmed: 24643677.
15. Oberleithner H, Peters W., Kusche-Vihrog K, et al. Salt overload damages the glycocalyx sodium barrier of vascular endothelium. Pflugers Arch. 2011; 462(4): 519- 528, do: 10.1007/s00424-011-0999-1, indexed in Pubmed: 21796337.
16. Surma S, Romańczyk M, Baikowski E. The role of limiting sodium intake in the diet – from theory to practice. Folia Cardiologica. 2020, doi: 10.5603/tc.2020.0030.
17. Sugiyama S, Jinnouchi H, Kurinami N, et al. The SGLT2 hibitorDapagliflozin Significantly Improves the Peripheral Microvascular Endothelial Function in Patients with Uncon- trolled Type 2 Diabetes MellituS, Intern Med. 2018: 57(15): 2147-2156, doi: 10.2169/internalmedicine.0701-17, indexed in Pubmed: 29607968.
18. Shigiyama F, Kumashiro N, Miyagi M, et al. Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. CardiovascDiabetol. 2017; 16(1): 84, doi: 10.1186/s12933-017-0564-0, indexed in Pubmed: 28683796.
19. Ren B, Chen M. Effect of sodium-glucose cotrans- porter-2 inhibitors on patients with essential hyper- tension and pre-hypertension: a meta-analysis. TherAdvEndocrinolMetab. 2022: 13: 20420188221142450, doi: 10.1177/20420188221142450, indexed in Pubmed: 36533186.
20. Bjornstad P Greasley PJ, Wheeler DC, et al. The Potential Roles of Osmotic and Nonosmotic Sodium Handling in Mediating the Effects of SodiuM-

Glucose Cotransporter 2 Inhibitors on Heart Failure. J Card Fail. 2021; 27(12): 1447-1455, doi: 10.1016/.cardfail.2021.07.003, indexed in Pubmed: 34289398

21. Baigent C, Emberson J, Haynes R, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. The Lancet. 2022; 400(10365): 1788-1801, doi: 10.1016/s0140-6736(22)02074-8.
22. McMurray JJV, Wheeler DC, Stefánsson BV, et al. DA- PA-CKD Trial Commitees and Investigators, DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15): 1436-1446, doi: 10.1056/NEJMoa2024816, indexed in Pubmed: 32970396.
23. Herrington WG, Staplin N, Wanner C, et al. The EMPA-KID- NEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023; 388(2): 117-127, doi: 10.1056/NEJMoa2204233, indexed in Pubmed: 36331190.
24. Meraz-Muñoz AY, Weinstein J, Wald R. eGFR De- cline after SGLT2 Inhibitor Initiation: The Tortoise and the Hare Reimagined. Kidney360. 2021; 2(6): 1042- 1047. Doi: 10.34067/KID.0001172021, indexed in Pubmed: 35373074.
25. Jongs N, Greene T, Chertow GM, et al. DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes En- docrinol. 2021; 9(11): 755-766, doi: 10.1016/S2213-8587(21)00243-6, indexed in Pubmed: 34619106.
26. Kohn OF. Wheeler DC, Stefánsson BV, et al. DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Di- abetesEndocrinol. 2021;9(1):22-31, doi: 10.1016/S2213-8587(20)30369-7, indexed in Pubmed: 33338413.
27. Gonzalez DE, Foresto RD, Ribeiro AB. SGLT-2 inhibitors in dia- betes: afocus on renoprotection. Rev Assoc Med Bras (1992). 2020; 66Suppl 1(Suppl 1): s17-s24, doi: 10.1590/1806- 9282.66.S1.17, indexed in Pubmed: 31939531.
28. Kidokoro K, Cherney DZI, Bozovic A, et al. Evaluation of Glomerular Hemodynanic Function by Empagliflozin in Dia- betic Mice Using In Vivo Imaging. Circulation. 2019; 140(4):303-315. Doi: 10.1161/CIRCULATIONAHA.118.037418, in- dexed in Pubmed: 30773020.
29. Cherney DZI, Perkins BA, Soleymanlou N, et a. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Cir- culation. 2014; 129(5): 587-597, doi: 10.1161/CIRCULA-TIONAHA.113.005081, indexed in Pubmed: 24334175.
30. BommelEv, Muskiet M, Baar Mv, et al. The renal hemo- dynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated pa- tients with type 2 diabetes in the randomized, double-blind RED trial. Kidney International. 2020; 97(1): 202-212, doi: 10.1016/.kint.2019.09.013.

31. Kim NH, Kim NH. Renoprotective Mechanism of Sodi- um-Glucose Cotransporter 2 Inhibitors: Focusing on Renal Henmodynamics. Diabetes Metab J. 2022; 46(4): 543-551, doi: 10.4093/dm,. 2022.0209, indexed in Pubmed: 35929172.
32. Tiwary M, Milder TY, Stocker SL, et al. Sodium-glucose Co-transporter 2 inhibitor therapy: use in chronic kidney disease and adjunctive sodium restriction. Intern Med J. 2022; 52(10): 1666-1676, doi: 10.1111/imj.15727, in- dexed in Pubmed: 35257458.
33. Jongs N, Chertow GM, Greene I, et al. DAPA-CKD Trial Committees and Investigators, Members of the DAPA-CKD Trial Committees and Investigators. Cor- relates and Consequences of an Acute Change in eGFR in Response to the SGLT2 Inhibitor Dapagliflozin in Pa- tients with CKD. J Am SocNephrol. 2022; 33(11): 2094-2107, doi: 10.1681/ASN.2022030306, indexed in Pubmed: 35977807.
34. Adamczak M, Surma S, Więcek A. Hyponatremia in patients with arterial hypertension -pathophysiology and management. Archives of Medical Science. 2023, doi: 10.5114/aoms/161578.
35. H t tps: |ịdC.je f fers 0n. edu/cgi/viewcontent.cgi?article=1071&c ontext=siCtr 2023 phaset (30/3/2023).
36. Yavin Y, Mansfield TA, Ptaszynska A, et al. Effect of the SGLT2 Inhibitor Dapaglifiozin on Potassium Levels in Pa- tients with Type 2 Diabetes Mellitus: A Pooled Analysis. Di- abetesTher. 2016; 7(1): 125-137, doi: 10.1007/s13300- 015-0150-y, indexed in Pubmed: 26758563.
37. Neuen BL, Oshima M, Agarwal R, et al. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials. Cir- culation. 2022; 145(19): 1460-1470, doi: 10.1161/CIRCU-LATIONAHA.121.057736, indexed in Pubmed: 35394821.
38. Neuen BL, Oshima M, Perkovic V, et al. Effects of cana- gliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial. Eur Heart J. 2021; 42(48): 4891-4901, doi: 10.1093/eur- hearti/ehab497, indexed in Pubmed: 34423370.
39. Ferreira J, Butler J, Zannad F, et al. Mineralocorticoid Re- ceptor Antagonists and Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology. 2022; 79(12): 1129- 1137, doi: 10.1016/j,jacc.2022.01.029.
40. Adamczak M, Surma S, Więcek A. Kwasicametaboliczna u chorych z przewlektąchorobąnerek. Forum Nefrol. 2020; 13(4): 214-227.
41. . Htps:/indeks.mp.pVdesc.php?id=44.
42. Mullens W, Dauw J, Martens P et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. New England Journal of Medicine. 2022: 387(13): 1185- 1195, doi: 10.1056/nejmoa2203094.
43. Schmickl CN, Owens RL, Orr JE, et al. Side effects of acet- azolamide: a systematic review and meta-analysis assess- ing overall risk and dose dependence. BMJ Open Respir Res. 2020; 7(1), doi: 10.1136/bmjresp-2020-000557, in- dexed in Pubmed: 32332024.
44. Surma S, Więcek A, Adamczak M. Hipokaliemia u chorych Z nadciśnieniemtętniczym. Terapia. 2020; 10(393): 4-17.

45. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guide- lines the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599-3726.
46. Mancia Chairperson G, Kreutz Co-Chair R, Brunström M, et al. Authors/Task Force Members:. 2023 ESH Guidelines for the management arterial hypertension The Task Force for the management of arterial hypertension of the Euro- pean Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (SH). J Hypertens. 2023 [Epub ahead of print], doi: 10.1097/HJH.0000000000003480, indexed in Pubmed: 37345492.
47. Tykarski A, Filipiak KJ, Januszewicz A, al. Zasadypostępowania w nadciśnieniutętniczym 2019 rok. NadciśnienieTętnicze w Praktyce. 2019; 5(1): 1-86.
48. Palmer BF, Clegg DJ. Fluid overload as a therapeutic tar- get for the preservative management of chronic kidney disease. CurrOpinNephrolHypertens. 2020; 29(1): 22-28, doi: 10.1097/MNH.0000000000000563, indexed in Pubmed: 31714288.
49. Tabinor M, Elphick E, Dudson M, et al. Bioimpedance-de- fined overhydration predicts survival in end stage kidney failure (ESKF): systematic review and subgroup meta-anal- ysis. Sci Rep. 2018; 8(1): 4441, doi: 10.1038/s41598-018-21226-y, indexed in Pubmed: 29535377.
50. Esmeray K, Dizdar 0S, Erdem S, et al. Effect of Strict Volume Control on Renal Progression and Mortality Non-Dialysis-Dependent Chronic Kidney Disease Patients: A Prospective Interventional Study. Med PrincPract. 2018: 27(5): 420-427, doi: 10.1159/000493268, indexed Pubmed: 30149377.
51. Musini VM, Rezapour P Wright JM, et al. Blood pressure lowering efficacy of loop diuretics for primary hyper-tension. Cochrane Database Syst Rev. 2012: 2015(8): CDO03825, doi: 10.1002/14651858.CDO03825.pub3, in-dexed in Pubmed: 22895937.
52. Zamboli P De Nicola L, Minutolo R, et al. Effect furo- semide on left ventricular mass in non-dialysis chronic kidney disease patients: a randomized controlled trial. Nephrol Dial Transplant. 2011; 26(5): 1575-1583, doi: 10.1093/ndt/gta565, indexed in Pubmed: 20876366.
53. Mannheimer B, Falhammar H, Calissendorff J, et al. Non-thi- azide diuretics and hospitalization due to hyponatraemia: A population-based case-control study. ClinEndocrinol (Ox). 2021; 95(3): 520-526, doi: 10.1111/cen.14497, in- dexed in Pubmed: 33978246.
54. Adamczak M, Chudek J, Zejda J, et al. Prevalence of hypokalemia in older persons: results from the Pol- Senior national survey. EurGeriatr Med. 2021: 12(5): 981-987, doi: 10.1007/s41999-021-00484-6, indexed in Pubmed: 33830482.
55. Guo L, Fu B, Liu Y, et al. Diuretic resistance in patients with kidney disease: Challenges and opportunities. Biomed Pharmacother. 2023; 157: 114058, doi: 10.1016/j.bio-pha.2022.114058, indexed in Pubmed: 36473405.
56. Schork A, Woern M, Kalbacher H, et al. Associa- tion of Plasminuria with Overhydration in Patients with CKD. Clin J Am SocNephrol. 2016; 11(5): 761-769, doi: 10.2215/CJN.12261115, indexed in Pubmed: 26933188.
57. Svenningsen P Friis UG, Versland JB, et al. Mechanisms of renal NaCl retention in proteinuric disease.

ActaPhysiol (Oxf). 2013; 207(3): 536-545, doi: 10.1111/apha.12047, indexed in Pubmed: 23216619.
58. Wilcox CS, Testani JM, Pitt B. Pathophysiology of Diuretic Resistance and Its Implications for the Management of Chronic Heart Failure. Hypertension. 2020; 76(4): 1045- 1054, doi: 10.1161/HYPERTENSIONAHA.120.15205, in- dexed in Pubmed: 32829662.
59. Soleimani M. The mutiple roles of pendrin in the kid- ney. Nephrol Dial Transplant. 2015; 30(8): 1257-1266, doi: 10.1093/ndt/gfu307, indexed in Pubmed: 25281699.
60. Hoorn EJ, Ellison DH. Diuretic Resistance. Am J Kid- ney Dis. 2017; 69(1): 136—142, doi: 10.1053/j.ajkd.2016.08.027, indexed in Pubmed: 27814935.
61. Ernst ME, Moser M. Use of diuretics in patients with hypertension. N Engl J Med. 2009; 361(22): 2153-2164, doi: 10.1056/NEJMra0907219, indexed in Pubmed: 19940300.
62. Surma S, Adamczak M, Więcek A. Hiponatremiaspowodowanatiazydowymi I tiazydopodobnymilekamimoczopędnymi. Terapia. 2019; 10(381); 4-10.
63. Musini VM, Nazer M, Bassett K, et al. Blood pressure-low- ering efficacy of monotherapy with thiazide diuretics for pri- mary hypertension. Cochrane Database Syst Rev. 2014(5): CDO03824, doi: 10.1002/14651858.CD003824.pub2, indexed in Pubmed: 24869750.
64. Liang W, Ma H, Cao L, et al. Comparison of thiazide-like diuretics versus thiazide-type diuretics: a meta-anal- ysis. J Cell Mol Med. 2017; 21(11): 2634-2642, doi: 10.1111/jcmm.13205, indexed in Pubmed: 28631393.
65. Surma S, Więcek A, Adamczak M. Leczenienadciśnieniatętniczego u chorych z przewlektąchorobąnerek. Terapia. 2022; 7(414): 66–76.
66. Agarwal R, Sinha A, Cramer A, et al. Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease. New England Journal of Medicine. 2021; 385(27): 2507-2519, doi: 10.1056/nejmoa2110730.
67. Teles F, Peçanha de Miranda Coelho JA, Albino RM, et.Al. Effectiveness of thiazide and thiazide-like diuretics in advanced chronic kidney disease: a systematic review and meta-analysis. Ren Fail. 2023; 45(1): 2163903, doi: 10.1080/0886022X.2022.2163903, indexed in Pubmed: 36637019.
68. Kramers BJ, Koorevaar IW, De Boer et al. DIPAK Con- sortium. Thiazide diuretics and the rate of disease progression in autosomal dominant polycystic kidney disease: an observational study. Nephrol Dial Transplant. 2021; 36(10): 1828-1836, doi: 10.1093/ndt/gfaa150, indexed in Pubmed: 33150452.
69. Clayton JA, Rodgers S, Blakey J, et al. Thiazide diuretic pre- scription and electrolyte abnormalities in primary care. Br J ClinPharmacol. 2006; 61(1): 87-95, doi: 10.1111).1365- 2125.2005.02531.x, indexed in Pubmed: 16390355.
70. Palmer BE, Clegg DJ. Altered Prostaglandin Signal- ing as a Cause of Thiazide-Induced Hyponatremia. Am J Kidney Dis. 2018; 71(6): 769-771, doi: 10.1053/1. Ajkd.2017.11.026, indexed in Pubmed: 29501264.
71. Barber J. Mckeever TM, McDowell SE, et al. A system- atic review and meta-analysis of thiazide-induced hyponatraemia: time to reconsider electrolyte monitoring regi- mens after thiazide initiation? Br J ClinPharmacol. 2015; 79(4): 566-577, doi: 10.1111/bcp.12499, indexed in Pubmed: 25139696.

72. Friedman E, Shadel M, Halkin H, et al. Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. Ann Intern Med. 1989; 1101): 24-30, doi: 10.7326/0003-4819-110-1-24, in- dexed in Pubmed: 2491733.
73. Surma S, Adamczak M. Zaburzeniagospodarkipotasowej u chorych z nadciśnieniemtętniczym. ChorobySercaiNaczyń. 2021; 18(1): 1-19, doi: 10.5603/chsin.2021.0001.
74. Roush GC, Ernst ME, Kostis JB, et al. Head-to-head com- parisons of hydrochlorothiazide with indapamide and chlorthalidone: antihypertensive and metabolic effects. Hy- pertension. 2015; 65(5): 1041-1046, doi: 10.1161/HYPER-TENSIONAHA.114.05021, indexed in Pubmed: 25733245.
75. Kreutz R, Algharably EA, Douros A. Reviewing the efects of thiazide and thiazide-like diuretics as photosensitizing drugs on the risk of skin cancer. J Hypertens. 2019; 37(10): 1950-1958, doi: 10.1097/HJH.0000000000002136, in- dexed in Pubmed: 31145177.
76. Nochaiwong S, Chuamanochan M, Ruengorn C, et al. Use of Thiazide Diuretics and Risk of All Types of Skin Cancers: An Updated Systematic Review and Meta-Analysis. Cancers (Basel). 2022; 14(10), doi: 10.3390/cancers14102566, in- dexed in Pubmed: 35626169.
77. Shao SC, Lai CC, Chen YH, et al. Associations of thiazide use with skin cancers: a systematic review and meta-anal- ysis. BMC Med. 2022; 20(1): 228, doi: 10.1186/s12916- 022-02419-9, indexed in Pubmed: 35794547.
78. Azoulay L, St-Jean A, Dahl M, et al. Canadian Network for Observational Drug Effect Studies (CNODES) Investi- gators. Hydrochlorothiazide use and risk of keratinocyte carcinoma and melanoma: A multisite population-based cohort study. J Am AcadDermatol. 2023; 89(2): 243-253, doi: 10.1016/j.jaad.2023.04.035, indexed Pubmed:37105517.
79. Barrera-Chimal J. Lima-Posada l, Bakris GL, et al. Miner- alocorticoid receptor antagonists in diabetic kidney disease – mechanistic and therapeutic effects. Nat Rev Nephrol. 2022; 18(1): 56-70, doi: 10.1038/s41581-021-00490-8, indexed in Pubmed: 34675379.
80. Rico-Mesa JS, White A, Ahmadian-Tehrani A, et al. Min- eralocorticoid Receptor Antagonists: a Comprehensive Review of Finerenone. CurrCardiol Rep. 2020; 22(11): 140, doi: 10.1007/s11886-020-01399-7, indexed in Pubmed: 32910349.
81. Bazoukis G, Thomopoulos C, Tsioufis C. Effect of min- eralocorticoid antagonists on blood pressure lowering: overview and meta-analysis of randomized controlled trials in hypertension. J Hypertens. 2018; 36(5): 987- 994, doi: 10.1097/HJH.0000000000001671, indexed in Pubmed: 29356711.Romero A, et al. Patiromerver-
82. Agarwal R, Rossignol Sus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, place- bo-controlled trial. Lancet. 2019; 394(10208): 1540- 1550, doi: 10.1016/S0140-6736(19)32135-X, indexed in Pubmed: 31533906.
83. Navaneethan SD, Nigwekar SU, Sehgal AR, et al. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. Clin J Am SocNephrol. 2009; 4(3):542-551, doi:

10.2215/CJN.04750908, indexed in Pubmed: 19261819.

84. Chung EYm, Ruospo M, Natale P et al. Aldosterone antago- nists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2020; 10(10): CD007004, doi: 10.1002/14651858.CD007004.pub4., indexed in Pubmed: 33107592.
85. Bakris G, Agarwal R. Anker S. et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2020;383(23): 2219-2229, doi: 10.1056/nejmoa2025845.
86. Zhang MZ, Bao W, Zheng QY, et al. Eficacy and Safety of Fi- nerenone in Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Front Pharmacol. 2022; 13:819327, doi: 10.3389/fphar.2022.819327, indexed in Pubmed: 35197856.
87. Vukadinović D, Lavall D, Vukadinović AN, et al. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials:A meta-analysis. Am Heart J. 2017; 188: 99-108, doi: 10.1016/j.ahj.2017.03.011, indexed in Pubmed: 28577687.
88. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents eplerenone and spi- ronolactone. ClinCardiol. 2008; 31(4): 153-158, doi: 10.1002/clc.20324, indexed in Pubmed: 18404673.
89. Pei H, Wang W, Zhao Di, et al. The use of a novel non-ste- roidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure: A systematic review and meta-analysis. Medicine (Baltimore). 2018; 97(16): e0254, doi: 10.1097/MD.0000000000010254, indexed in Pubmed: 29668577.
90. Agarwal R, Joseph A, Anker SD, et al. FIDELIO-DKD In- vestigators. Hyperkalemia Risk with Finerenone: Results from the FIDELIO-DKD Trial. J Am SocNephrol. 2022: 33(1): 225-237, do: 10.1681/ASN.2021070942, indexed in Pubmed: 34732509.
91. https://www. Accessdata. Fda.gov/drugsatfda_Docs/label/2021/215341s000lbl.pdf.
92. Pitt B, Kober L, Ponikowski P et al. Safety and tolerabil- ity of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J. 2013; 34(31): 2453-2463, doi: 10.1093/eurheartij/eht187, indexed in Pubmed: 23713082.