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SGLT2 inhibitors - a breakthrough in treatment of heart failure and their multipotential beneficial role in cardiology, diabetology, nephrology and neurology

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Abstract: Inhibitors of the sodium-glucose cotransporter 2 (SGLT2 inhibitors) are relatively new and innovative antihyperglycemic drugs which by inhibiting sodium-glucose cotransporter 2 minimalise reabsorption of glucose in nephrones. Due to this process, SGLT2 inhibitors became a first-choice drugs in diabetology. Flozins were a turning point in many clinical trials and currently consequently conquer pharmacoterapy in cardiology. In the past years, clinical studies proved vast role of SGLT2 inhibitors in other fields of medicine. Flosins protect heart muscle and kidneys among patients with or without type diabetes mellitus type 2. They have positive effect on hypertension, arteries and brain tissue.

Cardiological condition with the lowest long-term outcome in patients is heart failure with reduced ejection fraction. Until flozins, treatment in heart failure with reduced ejection fraction was based on four groups of drugs: β-blocker, inhibitors of the renin-angiotensin aldosterone system (RAA), including angiotensin converting enzyme ACE/ARB inhibitors, angiotensin and neprilysin receptor blockers (ARNI) and mineralocorticoid receptor antagonists (MRA). It was an appropriate HFrEF

treatment over the last years. However thanks to large-scale researches a role of flozins in cardiology have been established and they became hope for a change in the course of heart failure.

The following article presents aspects of using flozins in treatment of patients with HFrEF, multipotential usage, vast benefits for patients, not solely cardiologic, and side effects of these miraculous group of drugs.

Materials and methods: PubMed database was searched for the following terms: “SGLT2 inhibitors”, “flosins”, “flosins heart failure”, ”heart failure reduced ejection fraction” ”flosins role” for the articles published between 2014-2023 and written in English.

Conclusion: Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors, flozins) are commonly and successfully used in the first-line treatment of diabetes mellitus type 2 and heart failure. First reasearched and released in the year 2013 flozin was canagliflozin. Subsequently, dapagliflozin and empagliflozin were approved by FDA in 2014. Firstly, SGLT2 were accepted for treatment of diabetes mellitus type 2. In the course of broad scale clinical trials T2DM and EMPA-REG OUTCOME major influence of flozins on treatment of hailure failure with reduced ejection fraction was proved. Another trials and researches bring even more promising usage of flozins in diabetology and cardiology, but also in nephrology and neurology. SGLT2 inhibitors are still a subject of studies, but they remain one of the most promising group of drugs in the modern medicine and give hope for better outcome in patients with chronic diseases affecting multiple systems of human body.

Key words: “SGLT2 inhibitors”, “flozins”, “flozins heart failure”, ”heart failure with reduced left ventricular ejection fraction (HFrEF)”, “dapagliflozin”, ”cardiovascular”, “empagliflozin“ , “systolic”, ”diabetes”

Introduction: In the year 2013, the first sodium glucose cotransporter 2 inhibitor (SGLT2 inhibitor), canagliflozin, was released. In the following years, the group of chemically similar drugs, group named ”flozins“ have arised. SGLT 2 inhibitors modulate sodium-glucose transporter in nephrons. In this way they lower the level of glucose in blood by inhibiting glucose reuptake and increasing elimination of glucose with urine. [1] Flozins, both in monotherapy and combined with glucose-moderating drugs profoundly maintain adequate level of glucose in the blood. [2,3] Flozins have been introduced to medicine around decade ago, thus scientists are still working on its effects, influence on human body and benefits other than reducing level of glucose in blood and minimalising harmful consequences of diabetes. This paper review the effects of SGLT2 inhibitor on heart failure and presents six systems in the body which take advantage of flozins as well as present side effects of this

group of drugs. The presented fields are diabetology, nephrology, cardiology with angiology and neurology.

Aim: The aim of this paper is to provide a comprehensive review based on literature. This review takes into consideration the role of SGLT2 inhibitors in treatment of heart failure, their mechanism of action, vast effects in cardiology and other fields of medicine as well as side effects.

Chemistry and mechanism of action

SGLT1 inhibitors are situated in the intestinal mucosa. Unlike, sodium-glucose cotransporters-2 are located solely on the luminal membrane of the proximal tubule. The cortransporters reabsorb up to 180 g of glucose per day. [4] Found by scientists in rats, phlorizin entirely inhibit renal glucose reabsorption and was a starting point for flozins. [5, 6, 7]

Phlorizin is a natural glucoside occuring in plants, it is able to inhibit both SGLT1 and SGLT2 inhibitors. [8] It was studied to be treatment for diabetes mellitus type 2, but became eliminated by more selective synthetic analogs, such as empagliflozin, dapagliflozin and canagliflozin. [9, 10, 11] Chemically phlorizin and SGLT2 inhibitors are glucosides [12], but empagliflozin (Jardiance), dapagliflozin (Forxiga) and Canagliflozin (Invokana) on contrary to phlorizin are not cleaved by lactase. [13]

Glucosides bind to the external side of sodium-glucose cotransporters 2 in the binding site of cotransporters. [14] This affects in orientation of the aglycone and leads to blockage of cotransporter. By inhibiting the SGLT-2-dependent glucose and sodium reabsorption, there are two benefits. An inhibitor cause a reduction of glucose intake in nephrons and an increase in distal tubular sodium load. It results in inhibition of the renin-angiotensin-aldosterone system and reduction of afterload and preload. [15] In this way gliflozins not only enhance glycemic control but also reduce body weight, systolic and diastolic blood pressure and have cardioprotective effect by reduction of afterload and preload. [16, 17, 18]

Indications for SGLT2 inhibitors in heart failure

Flozins are stated to be a major pharmacological advances in cardiovascular medicine in the 21st century. They are the newest addition to treatment guidelines in heart failure with reduced ejection fraction. Moreover, latest researches show their significant meaning in treatment of heart failure with mildly reduced and preserved ejection fraction as they reduce negative cardiovascular outcomes. Clinical trials T2DM and EMPA-REG OUTCOME demonstrated major reduction in heart failure patients hospitalizations in the empagliflozin group of patients. [19] Further researches established the

role of flozins in reducing number of hospitalizations. In the EMPA-REG OUTCOME occurence of adverse cardiovascular events (e.g. cardiovascular mortality, myocardial infarction, stroke) was reduced up to 38% compared to placebo group. [19] Other studies, CANVAS, DECLARE TIMI, CREDENCE, VERTIS, MACE-3 reported equivalent results and secured role of SGLT2 inhibitors in the management of heart failure. [20, 21, 22, 23, 24] In DAPA-HF dapagliflozin a significant decrease in cardiovascular death and hospitalizations amid patients with reduced ejection fraction was observed. [25] In heart failure with preserved ejection fraction common is diastolic dysfunction. This is frequently seen in geriatric patients with companion of cardiac, renal and diabetic dysfunctions. SOLOIST-WHF was first trial that proved beneficial role of flozins in heart failure with preserved ejection fraction. [26] Subsequently, empagliflozin in EMPEROR-Preserved trial assessed efficacy of SGLT2 inhbitors in patients with heart failure mildly reduced ejection fraction and heart failure preserved ejection fraction regardless of patient's diabetes status. [27] SGLT2 inhibitors are currently accepted as heart failure reduced ejection fraction first-line treatment in heart failure and should be considered in heart failure preserved ejection fraction to reduce risk of hospitalization and cardiac mortality. [28, 29]

Flozins and their other application in cardiology and angiology

It was already known that metformin significantly reduces myocardial infarction and death. SGLT2 inhibtors have been found to have cardiovascular preservation. [30] Na+/H+ exchanger 1 (NHE1) is mostly situated in cardiomyocytes and its activition increases in pathological situations - acute ischemia, heart failure and diabetes. [31] Activation of Na+/H+ exchanger 1 enlarges intracelluar sodium load in cardiomyocytes which results in calcium overload in ischemia. Calcium worsens injury and causes slower reperfusion. [32] Moreover, NHE1 prompted cardiac hypertrophy and heart failure in mice. [33] Suggested SGLT2 protection hypothesis proposes that this may be induction of autophagy. [34, 35, 36] Trials prove that empagliflozin may improve cardiac function and post myocardial infarction survival. Empagliflozin protective mechanisms work through NHE1 mediated suppresion of autophagy. In myocardial infarction both uncontrolled and insufficient autophagy might be destructive in myocardial infarction. Empagliflozin regulates and optimalises autophagy mechanism in cardiac muscle. [37, 38, 39]

Flozins are used as modern drugs in cardiologic and diabetologic patients. About 70% of patients with diabetes also have hypertension. [40, 41] As well as hypertension and diabetes are major risk factors for microvascular and macrovascular diseases. Due to omnipresent arterial stiffness and sodium retention associated with diabetes physiology, diabetes mellitus and hypertension are closely related

and coexistant. [42, 43, 44] Non-enzymatic glycosylation leads to injury and hyalinization of the arterial walls proceeding into atherosclerosis and causing arterial stiffness. Atherosclerosis leads to fatal complications such as sudden cardiac death, myocardial infarction, and stroke. Hyperglycemia in diabetes mellitus enlarges the activity of the sodium-glucose transporters causing increased sodium retention and volume expansion and consequently increasing blood pressure. [45, 46, 47] Inhibtion of sodium intake by SGLT2 inhibitors can reduce blood volume, blood pressure and minimalise cardiovascular risk as well as risk of cardiovascular events and hospitalization.

SGLT2 inhibitors and its upregulation in diabetology

Canagliflozin, empagliflozin and dapagliflozin are at present first-line treatment in diabetes mellitus type 2, right next to metformin. SGLT2 inhibitors increase glycosuria, reduce weight, decrease level of HbA1c and protect from diabetic nephropathy and atherosclerosis. SGLT2 transporters are situated in the proximal tubules, as they filter plasma and reabsorb or excrete glucose. [48, 49]

In clinical trials the decrease of HbA1c depends on eGFR. The larger difference was observed in patients with eGFR 60 to 90 ml/min/1,73m², yet even in patients with eGFR 30 to 60 ml/min/1,73m² it was clinically significant. [50] The lowering of HbA1c was reached in canagliflozin trial. [51] A study with empagliflozin revealed 90% decreased risk of hypoglycemia and reduction in body mass up to 4,5 kilogrammes in comparison to glimepiride. [52] Further trials with SGLT2 inhibitors proved another metabolic and diabetologic benefits and strengthen prior results. Flozins reduced body weight, reduced amount of needed insulin, lowered HbA1c and did not led to hypoglycemia. [53, 54, 55]

The application of SGLT2 inhibitors in nephrology

The principal mechanism of SGLT2 inhibitors is glycosuria due to blockade in the renal nephron. They reduce consequences of heart failure, enhance glycemia and glucose homeostasis but also protect kidneys and renal function. SGLT2 inhibitor is responsible for around 90% reabsorption of glucose, it also blocks reabsorption of sodium generating natriuresis. [56] Natriuresis and glucosuria provoke osmotic diuretics and thus reduce volume of plasma. This process maintain benefits for cardiovascular system - reduced filling volume, preload, afterload and blood pressure. [57, 58] Trial RECEDE-CHF provided that among patients suffering from heart failure treated on a long-term with diuretics, when on the addition of empagliflozin, urine output grew up to 500 ml per day. [59]

Dysfunction of heart can result in disorder of kidneys and likewise, aggravation of renal function is able to cause cardiovascular diseases. [60] As much as 60% of patients with heart failure suffers with chronic kidney disease. [61, 62] Natriureris, secondary to pathophysiological processes in diabetes mellitus type 2, reduce concentration of natrium in macula densa, leading to dilatation of renal arterioles and hyperfiltration. Hyperfiltration is considered to be main factor in diabetic nephropathy.

[63] Flozins, by inhibition of natrium reabsorption and effect on afferent arteriole, normalise blood flow in kidneys and re-estabilish tubuloglomerular mechanisms. [64, 65]

A role of SGLT2 inhibitors in neurology

Both, diabetes mellitus and cardiovascular diseases are risk factors for cognitive impairment. [66, 67] SGLT2 inhibitors vastly used in these conditions have a potential for neuroprotection. [68] SGLT receptors occur in central nervous system, as they maintain glucose homeostasis and flozins have possibility to reach the brain/serum ratio from 0.3 to 0.5. [69] SGLT inhibitors play a key role in maintaing glucose homostasis. [70] SGLT1 inhibitors are widely spread in central nervous system. Studies say the can be found in brain cortex, cerebellum cells, cells of hippocampus and even in amygdala and nucleus of the solitary tracts. [71, 72, 73, 74] As flozins have link with SGLT1 receptors they can be protective against ischemia and brain damage during reperfusion. What is more, SGLT inhibitors are located in sites of brain responsible e.g. for food intake, energy homeostasis, glucose homeostasis, central cardiovascular and autonomic regulation. [74, 75] Trials have shown major increase in expression of SGLT1 and SGLT2 after brain injury. [76] Researches present promising use of flozins in neurology. Protein SGLT2 have expression in choroid plexus epithelial cells and ependymal cells, this may be helpful in understanding pathology of neurodegenerative disorders and discover proper treatment. [77, 78] In a rat model dapagliflozin markedly reduced seizure activity during epilepsy. [79] Blockade of SGLT1 have positive impact on brain lesions, edema, volume of damaged tissue and motoric disability. [80]

Adverse effects of SGLT2 inhibitors

Although flozins are modern and innovative group of drugs which were a turning point in treatment of diabetes and heart failure they do have side effects. They are connected with urinary tract infections, lower limb amputation, diabetic ketoacidosis, acute kidney injury and Fournier gangrene. [81, 82]

I. Genito-urinary tract infections

SGLT2 inhibitors increase three times a risk of genito-urinary tract infection, especially in elderly patients. [83, 84] As infections are caused by glycosuria patients should be learned how to maintain proper hygiene.

II. Lower limb amputation

In CANVAS trial a group taking canagliflozin was connected with higher risk of amputations in comparison to placebo group. [81, 85] However, in a retrospective analysis rate of amputations was comparable to new antibdiabetic agents. [86] The pathophysiology of amputation caused by flozins remains unclear. It is speculated that they promote volume depletion and hemoconcentration leading to peripheral ischemia. [87]

III. Diabetic Ketoacidosis

SGLT2 can result in diabetic ketoacidosis in patients with diabetes type 1, and less frequently in diabetes type 2. Potential triggering factors are insulin withdrawal, decreased calories intake, infection or surgery. Risk for developing diabetic ketoacidosis is still unknown and needs greater insight. In recent trials patients developed diabetic ketoacidosis in the presence of controlled glycemia. [88] Elements of DKA pathophysiology caused by flozins might be increased glucose loss, hyperglucagonemia and hypovolemia. [89, 90, 91] It is important to test urine and plasma ketons at the beginning of SGLT2 inhibitors therapy and be cautious about nausea, malaise and vomiting.

IV. Acute kidney injury

It is recommended to monitor kidney function during SGLT2 inhibitors therapy, especially when other potentially acute kidney injury (AKI) causing drugs are used. Flozins may be also connected with acute nephrotoxicity. SGLT2 inhibitors cause uricosuria (glucose exchange with uric acid in the proximal tubule). High level of uric acid may produce uric crystals deposition, inflammation and oxidative stress. [92, 93] Other risk factor for AKI is shift of oxygenation from medulla to cortex - this may put at risk of AKI patients with diabetes mellitus type 2, contrast, NSAIDs and volume depletion. [94, 95, 96]

V. Fournier gangrene

Flozins have also been connected with a risk of Fournier gangrene occurence. Fournier gangrene is a rare emergency characterized by necrotizing infection of genitalia, perineum and perianal area. FDA pointed out 55 cases of Fournier gangrene in patients treated by SGLT2 inhibitors. [97]

Conclusion:

Not without a reason SGLT2 inhibitors are called new statins. Yet, in comparison to statins, flozins have less unwanted effects and can be applied not only in cardiovascular diseases. Flozins work on many paths of renal physiology. Study trials present their potential in diabetology and neurology. As SGLT2 inhbitors can bring benefits for many patients, they have ability to enhance comfort of their lives.

In cardiology field, they minimalise the risk of heart failure in patients regardless renal function or diabetes. SGLT2 inhibitors have colossal effect on preserving ejection fraction and preventing heart failure. Both, dapagliflozin and empagliflozin improved renal functions in hospitalized patients, and what is more important reduced death in patients with HFrEF due to cardiovascular diseases and all-cause.

The ongoing clinical trials and studies will hopefully provide insight into understanding and better treatment of heart failure with multipotential benefits and hollistic approach to patients.

After conclusions

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References

1. Rieg T, Vallon V: Development of SGLT1 and SGLT2 inhibitors . Diabetologia. 2018, 61:2079-86.
2. Cho YK, Kang YM, Lee SE, et al.: Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: a systematic review and meta-analysis. Diabetes Metab. 2018, 44:393-401.
3. Winiarska A, Knysak M, Nabrdalik K, Gumprecht J, Stompór T: Inflammation and oxidative stress in diabetic kidney disease: the targets for SGLT2 inhibitors and GLP-1 receptor agonists. Int J Mol Sci. 2021, 22:10822.
4. Vrhovac I, Balen Eror D, Klessen D, Burger C, Breljak D, Kraus O, Radović N, Jadrijević S, Aleksic I, Walles T, Sauvant C, Sabolić I, Koepsell H: Localizations of Na(+)-D-glucose cotransporters SGLT1 and SGLT2 in human kidney and of SGLT1 in human small intestine, liver, lung, and heart. Pflugers Arch 467: 1881–1898, 2015. 10.1007/s00424-014-1619-7

5. Chasis H, Jolliffe N, Smith HW: The action of phlorizin on the excretion of glucose, xylose, sucrose, creatinine and urea by man. J Clin Invest 12: 1083–1090, 1933. 10.1172/JCI100559
6. Oku A, Ueta K, Arakawa K, Ishihara T, Nawano M, Kuronuma Y, Matsumoto M, Saito A, Tsujihara K, Anai M, Asano T, Kanai Y, Endou H: T-1095, an inhibitor of renal Na+-glucose cotransporters, may provide a novel approach to treating diabetes. Diabetes 48: 1794–1800, 1999. 10.2337/diabetes.48.9.1794
7. Silverman M: The in vivo localization of high-affinity phlorizin receptors to the brush border surface of the proximal tubule in dog kidney. Biochim Biophys Acta 339: 92–102, 1974. 10.1016/0005-2736(74)90335-6
8. Wells RG, Pajor AM, Kanai Y, Turk E, Wright EM, Hediger MA: Cloning of a human kidney cDNA with similarity to the sodium-glucose cotransporter. Am J Physiol 263: F459–F465, 1992. 10.1152/ajprenal.1992.263.3.F459
9. Rossetti, Luciano; Smith, Douglas; Shulman, Gerald I.; Papachristou, Dimitrios; DeFronzo, Ralph A. (1987). "Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats". The Journal of Clinical Investigation. 79 (5): 1510–1515.
10. Tatoń, Jan; Piątkiewicz, Paweł; Czech, Anna (2010). "Molecular physiology of cellular glucose transport – A potential area for clinical studies in diabetes mellitus". Endokrynologia Polska. 61 (3): 303–310.
11. Chao, Edward C.; Henry, Robert R. (2010). "SGLT2 inhibition – A novel strategy for diabetes treatment". Nature Reviews Drug Discovery. 9 (7): 551–559.
12. Wright EM: Glucose transport families SLC5 and SLC50. Mol Aspects Med 34: 183–196, 2013. 10.1016/j.mam.2012.11.002
13. Hirayama BA, Díez-Sampedro A, Wright EM: Common mechanisms of inhibition for the Na+/glucose (hSGLT1) and Na+/Cl-/GABA (hGAT1) cotransporters. Br J Pharmacol 134: 484–495, 2001. 10.1038/sj.bjp.0704274
14. Anderson, Sarah L.; Marrs, Joel C. (2012). "Dapagliflozin for the Treatment of Type 2 Diabetes". Annals of Pharmacotherapy. 46 (4): 590–598.
15. Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, Green JB, Rosenstock J, Schnaidt S, Brueckmann M, Pocock SJ, Packer M, Anker SD., EMPEROR-Preserved Trial Committees and Investigators. Empagliflozin for Heart Failure With Preserved Left Ventricular Ejection Fraction With and Without Diabetes. Circulation. 2022 Aug 30;146(9):676-686.
16. Haas B, Eckstein N, Pfeifer V, Mayer P, Hass MD (2014). "Efficacy, safety and regulatory status of SGLT2 inhibitors: focus on canagliflozin". Nutrition & Diabetes. 4 (11): e143.
17. Johnston R, Uthman O, Cummins E, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Southampton (UK): NIHR Journals Library; 2017 Jan. (Health Technology Assessment, No. 21.2.)
18. Wright EM. SGLT2 Inhibitors: Physiology and Pharmacology. Kidney360. 2021 Sep 17;2(12):2027-2037. doi: 10.34067/KID.0002772021. PMID: 35419546; PMCID: PMC8986039.
19. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:
20. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–657.
21. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–357.

22. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380
23. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med. 2020;383:1425–1435.
24. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol. 2021;6:148–158.
25. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396:819–829.
26. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384:117–128.
27. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451–1461.
28. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145(18)
29. Kasprzak JD, Gorczyca-Głowacka I, Sobczak-Kaleta M, Barylski M, Drożdż J, Filipiak KJ, Kapłon-Cieślicka A, Lelonek M, Mamcarz A, Ochijewicz D, Ryś-Czaporowska A, Starzyk K, Szymański FM, Wełnicki M, Wożakowska-Kapłon B. Pharmacotherapy of heart failure A.D. 2023. Expert opinion of Working Group on Cardiovascular Pharmacotherapy, Polish Cardiac Society. Kardiol Pol. 2023;81(5):537-556.
30. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008 359: 1577–1589
31. Packer M Activation and inhibition of sodium-hydrogen exchanger is a mechanism that links the pathophysiology and treatment of diabetes mellitus with that of heart failure. Circulation 2017 136: 1548–155
32. Wang Y, Meyer JW, Ashraf M, Shull GE Mice with a null mutation in the NHE1 Na+-H+ exchanger are resistant to cardiac ischemia-reperfusion injury. Circ Res 2003 93: 776–782
33. Nakamura TY, Iwata Y, Arai Y, Komamura K, Wakabayashi S Activation of Na+/H+ exchanger 1 is sufficient to generate Ca2+ signals that induce cardiac hypertrophy and heart failure. Circ Res 2008 103: 891–899
34. Avogaro A, Fadini GP, Del Prato S Reinterpreting cardiorenal protection of renal sodium-glucose cotransporter 2 inhibitors via cellular life history programming. Diabetes Care 2020 43: 501–507
35. Packer M Autophagy stimulation and intracellular sodium reduction as mediators of the cardioprotective effect of sodium-glucose cotransporter 2 inhibitors. Eur J Heart Fail 2020 22: 618–628
36. Packer M SGLT2 inhibitors produce cardiorenal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry: a paradigm shift in understanding their mechanism of action. Diabetes Care 2020 43: 508–511
37. Liu CY, Zhang YH, Li RB, Zhou LY, An T, Zhang RC, Zhai M, Huang Y, Yan KW, Dong YH, et al. LncRNA CAIF inhibits autophagy and attenuates myocardial infarction by blocking p53-mediated myocardin transcription. Nat Commun 2018 9: 29
38. Santulli G Cardioprotective effects of autophagy: eat your heart out, heart failure!. Sci Transl Med 201

39. Sciarretta S, Yee D, Nagarajan N, Bianchi F, Saito T, Valenti V, Tong M, Del Re DP, Vecchione C, Schirone L, et al. Trehalose-induced activation of autophagy improves cardiac remodeling after myocardial infarction. J Am Coll Cardiol 2018 71: 1999–2010
40. Mather A, Pollock C. Glucose handling by the kidney. Kidney Int Suppl. 2011 Mar;(120):S1-6.
41. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Feb 4;75(4):422-434.
42. Gupta R, Alcantara R, Popli T, Mahajan S, Tariq U, Dusaj RS, Malik AH. Myopathy Associated With Statins and SGLT2 - A Review of Literature. Curr Probl Cardiol. 2021
43. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. Diabetes Metab. 2014
44. Mistry S, Eschler DC. Euglycemic Diabetic Ketoacidosis Caused by SGLT2 Inhibitors and a Ketogenic Diet: A Case Series and Review of Literature. AACE Clin Case Rep. 2020 Dec
45. Yang Y, Pan H, Wang B, Chen S, Zhu H. Efficacy and Safety of SGLT2 Inhibitors in Patients with Type 1 Diabetes: A Meta-analysis of Randomized Controlled Trials. Chin Med Sci
46. Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol. 2016 Mar;4(3):211-220. doi: 10.1016/S2213-8587(15)00417-9. Epub 2015 Nov 27. Erratum in: Lancet Diabetes Endocrinol. 2016
47. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047-53.
48. Liu JJ, Lee T, DeFronzo RA. Why Do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans?Diabetes. 2012; 61:2199–2204.
49. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications.Kidney Int. 2009; 75:1272–1277.
50. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, Broedl UC; EMPA-REG RENAL trial investigators. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial.Lancet Diabetes Endocrinol. 2014; 2:369–384.
51. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, Figueroa K, Wajs E, Usiskin K, Meininger G. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease.Diabetes Obes Metab. 2013; 15:463–473.
52. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC; EMPA-REG H2H-SU trial investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial.Lancet Diabetes Endocrinol. 2014; 2:691–700.
53. Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, Broedl UC; EMPA-REG MDI Trial Investigators. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes.Diabetes Care. 2014; 37:1815–1823.
54. Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Ways K, Desai M, Shaw W, Capuano G, Alba M, Jiang J, Vercruysse F, Meininger G, Matthews D; CANVAS Trial Collaborative Group. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes.Diabetes Care. 2015; 38:403–411.

55. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S; Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial.Ann Intern Med. 2012; 156:405–415.
56. Wright EM, Hirayama BA, Loo DF et al (2007) Active sugar transport in health and disease. J Intern Med 261(1):32–43.
57. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW (2018) Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab 20(3):479–487.
58. Staels B (2017) Cardiovascular Protection by Sodium Glucose Cotransporter 2 Inhibitors: Potential Mechanisms. Am J Med 130(6s):S30–S39.
59. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC et al (2020) Renal and Cardiovascular Effects of SGLT2 Inhibition in Combination with Loop Diuretics in Patients with Type 2 Diabetes and Chronic Heart Failure: The RECEDE-CHF Trial. Circulation.
60. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R et al (2008) Cardiorenal syndrome. J Am Coll Cardiol 52(19):1527–1539.
61. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S et al (2006) Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 113(5):671–678.
62. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J et al (2007) High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 13(6):422–430.
63. Cherney DZ, Perkins BA (2014) Sodium-glucose cotransporter 2 inhibition in type 1 diabetes: simultaneous glucose lowering and renal protection? Can J Diabetes 38(5):356–363.
64. Fioretto P, Zambon A, Rossato M, Busetto L, Vettor R et al (2016) SGLT2 Inhibitors and the Diabetic Kidney. Diabetes Care 39(Suppl 2):S165–S171.
65. Cherney DZI, Heerspink HJL, Frederich R, Maldonado M, Liu J, Pong A et al (2020) Effects of ertugliflozin on renal function over 104 weeks of treatment: a post hoc analysis of two randomised controlled trials. Diabetologia 63(6):1128–1140.
66. Dearborn J.L., Qiao Y., Suri M.F.K., Liu L., Mosley T.H., Alonso A., Knopman D.S. Intracranial atherosclerosis and dementia The Atherosclerosis Risk in Communities (ARIC) Study. Am. Acad. Neurol. 2017;88:1556–1563.
67. Iadecola C. Revisiting atherosclerosis and dementia. Nat. Neurosci. 2020;23:691–692. doi: 10.1038/s41593-020-0626-6.
68. Hierro-bujalance C., Infante-garcia C., Marco A., Herrera M., Carranza-naval M.J., Suarez J., Alves-martinez P., Lubian-lopez S., Garcia-alloza M. Empagliflozin reduces vascular damage and cognitive impairment in a mixed murine model of Alzheimer' s disease and type 2 diabetes. Alzheimer's Res. Ther. 2020;4:1–13.
69. Tahara A., Takasu T., Yokono M., Imamura M., Kurosaki E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. J. Pharmacol. Sci. 2016;130:159–169. doi: 10.1016/j.jphs.2016.02.003.
70. Shah K., DeSilva S., Abbruscato T. The role of glucose transporters in brain disease: Diabetes and Alzheimer's disease. Int. J. Mol. Sci. 2012;13:12629–12655.
71. Poppe R., Karbach U., Gambaryan S., Wiesinger H., Lutzenburg M., Kraemer M., Witte O.W., Koepsell H. Expression of the Na+-D-glucose cotransporter SGLT1 in neurons. J. Neurochem. 1997;69:84–94. doi: 10.1046/j.1471-4159.1997.69010084.x.

72. Koepsell H. Glucose transporters in brain in health and disease. Pflugers Arch. Eur. J. Physiol. 2020;472:1299–1343. doi: 10.1007/s00424-020-02441-x.
73. Enerson B.E., Drewes L.R. The rat blood-brain barrier transcriptome. J. Cereb. Blood Flow Metab. 2006;26:959–973. doi: 10.1038/sj.jcbfm.9600249.
74. Nguyen T., Wen S., Gong M., Yuan X., Xu D., Wang C., Jin J., Zhou L. Dapagliflozin activates neurons in the central nervous system and regulates cardiovascular activity by inhibiting sglt-2 in mice. Diabetes, Metab. Syndr. Obes. Targets Ther. 2020;13:2781–2799. doi: 10.2147/DMSO.S258593.
75. Gaur A., Pal G.K., Ananthanarayanan P.H., Pal P. Role of Ventromedial hypothalamus in high fat diet induced obesity in male rats: Association with lipid profile, thyroid profile and insulin resistance. Ann. Neurosci. 2014;21:104–107. doi: 10.5214/ans.0972.7531.210306.
76. Oerter S., Förster C., Bohnert M. Validation of sodium/glucose cotransporter proteins in human brain as a potential marker for temporal narrowing of the trauma formation. Int. J. Legal Med. 2019;133:1107–1114. doi: 10.1007/s00414-018-1893-6.
77. Chiba Y., Sugiyama Y., Nishi N., Nonaka W., Murakami R., Ueno M. Sodium/glucose cotransporter 2 is expressed in choroid plexus epithelial cells and ependymal cells in human and mouse brains. Neuropathology. 2020;40:482–491. doi: 10.1111/neup.12665.
78. Pearson A., Ajoy R., Crynen G., Reed J.M., Algamal M., Mullan M., Purohit D., Crawford F., Ojo J.O. Molecular abnormalities in autopsied brain tissue from the inferior horn of the lateral ventricles of nonagenarians and Alzheimer disease patients. BMC Neurol. 2020;20:1–20. doi: 10.1186/s12883-020-01849-3.
79. Erdogan M.A., Yusuf D., Christy J., Solmaz V., Erdogan A., Taskiran E., Erbas O. Highly selective SGLT2 inhibitor dapagliflozin reduces seizure activity in pentylenetetrazol-induced murine model of epilepsy. BMC Neurol. 2018;18:1–8. doi: 10.1186/s12883-018-1086-4.
80. Sebastiani A., Greve F., Gölz C., Förster C.Y., Koepsell H., Thal S.C. RS1 (Rsc1A1) deficiency limits cerebral SGLT1 expression and delays brain damage after experimental traumatic brain injury. J. Neurochem. 2018;147:190–203. doi: 10.1111/jnc.14551.
81. Wiviott, S.D.; Raz, I.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; Silverman, M.G.; Zelniker, T.A.; Kuder, J.F.; Murphy, S.A.; et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N. Engl. J. Med. 2019, 380, 347–357.
82. Singh, M.; Kumar, A. Risks Associated with SGLT2 Inhibitors: An Overview. Curr. Drug Saf. 2018, 13, 84–91.
83. Dave, C.V.; Schneeweiss, S.; Patorno, E. Comparative risk of genital infections associated with sodium-glucose co-transporter-2 inhibitors. Diabetes Obes. Metab. 2019, 21, 434–438.
84. Vasilakou, D.; Karagiannis, T.; Athanasiadou, E.; Mainou, M.; Liakos, A.; Bekiari, E.; Sarigianni, M.; Matthews, D.R.; Tsapas, A. Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann. Intern. Med. 2013, 159, 262–274.
85. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Mattheus, M.; Devins, T.; Johansen, O.E.; Woerle, H.J.; et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N. Engl. J. Med. 2015, 373, 2117–2128.
86. Chang, H.Y.; Singh, S.; Mansour, O.; Baksh, S.; Alexander, G.C. Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients with Type 2 Diabetes. JAMA Intern. Med. 2018, 178, 1190–1198.
87. Matthews, D.R.; Li, Q.; Perkovic, V.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Desai, M.; Hiatt, W.R.; Nehler, M.; Fabbrini, E.; et al. Effects of canagliflozin on amputation risk in type 2 diabetes: The CANVAS Program. Diabetologia 2019.

88. Peters, A.L.; Buschur, E.O.; Buse, J.B.; Cohan, P.; Diner, J.C.; Hirsch, I.B. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care 2015, 38, 1687–1693.
89. Ferrannini, E.; Muscelli, E.; Frascerra, S.; Baldi, S.; Mari, A.; Heise, T.; Broedl, U.C.; Woerle, H.J. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J. Clin. Investig. 2014, 124, 499–508.
90. Merovci, A.; Solis-Herrera, C.; Daniele, G.; Eldor, R.; Fiorentino, T.V.; Tripathy, D.; Xiong, J.; Perez, Z.; Norton, L.; Abdul-Ghani, M.A.; et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J. Clin. Investig. 2014, 124, 509–514.
91. Keller, U.; Schnell, H.; Sonnenberg, G.E.; Gerber, P.P.; Stauffacher, W. Role of glucagon in enhancing ketone body production in ketotic diabetic man. Diabetes 1983, 32, 387–391.
92. Hahn, K.; Ejaz, A.A.; Kanbay, M.; Lanaspa, M.A.; Johnson, R.J. Acute kidney injury from SGLT2 inhibitors: Potential mechanisms. Nat. Rev. Nephrol. 2016, 12, 711–712.
93. Hahn, K.; Kanbay, M.; Lanaspa, M.A.; Johnson, R.J.; Ejaz, A.A. Serum uric acid and acute kidney injury: A mini review. J. Adv. Res. 2017, 8, 529–536.
94. Andreucci, M.; Faga, T.; Serra, R.; De Sarro, G.; Michael, A. Update on the renal toxicity of iodinated contrast drugs used in clinical medicine. Drug Healthc. Patient Saf. 2017, 9, 25–37.
95. Rivosecchi, R.M.; Kellum, J.A.; Dasta, J.F.; Armahizer, M.J.; Bolesta, S.; Buckley, M.S.; Dzierba, A.L.; Frazee, E.N.; Johnson, H.J.; Kim, C.; et al. Drug Class Combination-Associated Acute Kidney Injury. Ann. Pharm.2016, 50, 953–972.
96. Gomez-Peralta, F.; Abreu, C.; Lecube, A.; Bellido, D.; Soto, A.; Morales, C.; Brito-Sanfiel, M.; Umpierrez, G. Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes. Diabetes 2017, 8, 953–962, Erratum in Diabetes Ther. 2017, 8, 963–965.
97. Bersoff-Matcha, S.J.; Chamberlain, C.; Cao, C.; Kortepeter, C.; Chong, W.H. Fournier Gangrene Associated with Sodium-Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. Ann. Intern. Med. 2019.