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Review Article

SGLT2 inhibitors: A review article

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Abstract

In the beginning, SGLT2 inhibitors were regarded as anti-diabetic agents. But after demonstration of the cardiovascular benefit of SGLT2 inhibitors in EMPAREG-OUTCOME trial, a whole new era of heart failure therapy opened up. It became an integral part of heart failure treatment protocol. Several studies demonstrated its beneficial role in HFrEF until EMPEROR PRESERVED trail. It showed the benefit of SGLT2 inhibitors in HFpEF group of patients. It was consolidated by PRESERVED HF trial and recently concluded DELIVER trial. SGLT2 inhibitors are a single group of medication that is effective in all types of heart failure patients irrespective of their ejection fraction and diabetic status. Several mechanisms of action of SGLT2 inhibitors have been proposed that can explain its cardiovascular benefits. But still, studies to elucidate molecular and genetic mechanisms are going on which may open newer avenues of heart failure management in the future.

Keywords: Heart failure, SGLT2 inhibitors, Review, Trials.

Introduction

With the advent of new oral hypoglycemic drugs, SGLT2 inhibitors have come to the limelight for their dual role as a hypoglycemic agent along with cardiovascular benefits. The first SGLT2i approved for use in humans were Canagliflozin (US FDA March 2013) and Dapagliflozin (EU 2012). The first evidence of the cardiovascular benefit of SGLTi was demonstrated in the EMPA-REG OUTCOME trial in 2015. Recent clinical trials have shown that sodium glucose co-transport 2 (SGLT2) inhibitors have dramatic beneficial cardiovascular outcomes. These include a reduced incidence of cardiovascular death and heart failure hospitalization in people with and without diabetes and those with and without heart failure.

Mechanism of Action

A substantial number of theories have been proposed to explain the beneficial effects of SGLT2 inhibitors. These include beneficial effects of SGLT2 inhibition on the following:

* Blood pressure lowering: The antihypertensive effect associated with SGLT2 inhibition was previously thought to be secondary to diuresis and natriuresis, but it has been suggested to be more likely secondary to improved endothelial function, reduced arterial stiffness and changes in sympathetic nervous activity as evidenced by recent studies [1].

* Increasing diuresis/natriuresis: Although SGLT2-inhibitor therapy is associated with natriuresis and diuresis, it is unclear if these benefits are sustained as there were no differences seen in serum N-terminal pro B-type natriuretic peptide (NT-pro BNP) concentrations in patients with chronic stable heart failure despite improvements in heart failure status [2]. Using mathematical modeling, a recent study showed that both dapagliflozin and bumetanide were associated with a reduction in sodium and interstitial fluid. However, dapagliflozin had little or no effect on plasma volume whereas bumetanide was associated with reductions in intravascular volume, which can pose challenges in the context of hypoperfusion [3,4].

* Improving cardiac energy metabolism: under physiological conditions, nearly 90% of cardiac energy is derived from mitochondrial oxidative metabolism and fuel is derived from free fatty acids, glucose, and to a lesser extent from lactate, ketones, and amino acids [5]. In heart failure, there is dysregulated fatty acid oxidation and impaired glucose uptake or oxidation causing myocardial dysfunction. SGLT2-inhibitor therapy increases hepatic synthesis and decreases the urinary excretion of ketones producing a mild and persistent state of hyperketonaemia. Cardiovascular benefits of SGLT2-inhibitor therapy may be related to a shift in cardiac metabolism away from fatty acids and glucose oxidation towards more oxygen-efficient ketone bodies, thereby improving cardiac efficiency [6].

* Preventing inflammation and adverse cardiac remodeling: Adverse cardiac remodeling is an important contributor to heart failure severity. Studies suggest that even short-term exposure to SGLT2 inhibitors can promote cardiac reverse remodeling [7]. Inhibition of the mammalian target of rapamycin pathway, a major pathway involved in cardiac hypertrophy, by SGLT2 inhibition may also be involved [6]. SGLT2 inhibitors exert their anti-fibrotic effect also by various anti-inflammatory actions like – decreasing macrophage inflammatory response, downregulating NLRP3 inflammasome pathway [8].

* Weight loss: Weight loss from SGLT2-inhibitor therapy occurs due to an increased glucagon:insulin ratio causing increased lipid mobilization and is thought to be one of the mechanisms involved in reduction in heart failure mortality associated with SGLT2-inhibitor therapy [4,9].

* Inhibiting the cardiac Na^+/H^+ exchanger and SGLT1: SGLT2-inhibitor therapy reduces cardiac cytosolic sodium content by inhibiting sodium-hydrogen exchanger 1 and SGLT1 transporters in diabetic rat and mice myocytes, thereby reversing calcium overload [10,11]. Intriguingly, this effect on sodium-hydrogen exchanger 1 and SGLT1 is independent of diabetes status [12].

* Increasing autophagy and lysosomal degradation: Experimental induction of autophagy has favorable effects in heart failure as it leads to efficient disposal of dysfunctional mitochondria, which are a major source of reactive oxygen species, promoting oxidative stress and inflammation [13]. The pathways of autophagy induction involve activation of adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (SIRT1) and hypoxia-inducible factors (HIF-1alfa and HIF-2alfa). Various SGLT2-inhibitor therapies have upregulated the expression of AMPK, SIRT1 and HIF-1 alfa [14,15].

* Decreasing epicardial fat mass and altered adipokine regulation: Epicardial fat deposition due to altered adiponectin and leptin regulation is one of the theories implicated in the development of heart failure [16]. Increased serum leptin concentrations are seen in patients with heart failure, and they are associated with cardiac remodeling due to cardiac fibrosis and inflammation. SGLT2 inhibition reduces serum leptin and increases adiponectin concentrations [17].

* Increasing hematocrit: SGLT2-inhibitor therapy is associated with increases in renal erythropoietin production, red blood cell mass and hematocrit [18].

* Increasing circulating vascular progenitor cells and improving vascular endothelial function.

* Mechanism of reno-protection: SGLT2 inhibitors inhibit the coupled reabsorption of sodium and glucose from the proximal tubules, thereby increasing renal glucose and sodium excretion, but they have more widespread renal effects, including inhibition of the sodium proton exchanger. SGLT2 increases activity of NHE3(sodium hydrogen exchanger) as well as the sodium-phosphate exchanger type IIa, the organic cation transporter, the chloride-formate exchanger, the urate-anion exchanger, and the cystic fibrosis transmembrane regulator of Cl– transport [19,20]. These widespread effects on the PT may explain why SGLT2is reduce BP in CKD stage 3 or 4 despite little glycosuria. In CKD there is hyperfiltration that contributes to renal barotrauma and the loss of renal function. Diabetes mellitus increases intrarenal Ang II that contributes to an increased efferent arteriolar resistance and impairment of tubuloglomerular feedback. SGLT2i reduces estimated GFR early during treatment of diabetes mellitus, consistent with activation of TGF [21,22]. This is followed by stabilization of estimated GFR in long duration. SGLT2 inhibitors prevent intrarenal angiotensinogen upregulation while maintaining RAA axis [23]. SGLT2 inhibitors also exert their reno-protective action by stabilizing podocyte morphology, exerting anti-inflammatory, anti-fibrotic, anti-proliferative action, and overall improving intrarenal hemodynamics [24].

Review of Literature

Diabetics with established ASCVD, who were administered 10 mg or 25 mg of empagliflozin over a median treatment duration of 2.6 years in the EMPA-REG OUTCOME trial [25], had significantly lower rates of MACE described as non-fatal MI, stroke or CV death, hazard ratio (HR) 0.86; 95% CI (0.74-0.99) compared to placebo [4]. The findings from this study represented a new indication for clinical use of SGLT2 inhibitors in diabetics with stable coronary artery disease, history of MI, peripheral artery disease, or stroke. Other studies supporting the result of decreased MACE incidence with SGLT2 inhibitors included results from the CANVAS Program [26], which showed that diabetic participants with ASCVD or CV risk factors had significantly fewer MACE incidences while on 100 mg or 300 mg of canagliflozin compared to placebo, HR 0.86; 95% CI (0.75-0.97). MACE reduction was the primary CV benefit and indication for use of SGLT2 inhibitors in diabetics with ASCVD during the time frame of the results from these earlier trials. Interesting results from secondary analysis of other outcomes demonstrated that there were other potential and consistent CV benefits apart from MACE. Empagliflozin reduced the key secondary outcome risk of CV death, HR 0.62; 95% CI (0.49-0.77) or hospitalization for HF, HR 0.65; 95% CI (0.50-0.85) in the EMPA-REG OUTCOME trial, which was a similar finding with canagliflozin in the CANVAS Program. Canagliflozin decreased the secondary outcome of CV mortality or hospitalization for HF, HR 0.78; 95% CI (0.67-0.91) and reduced hospitalization for HF, HR 0.67; 95% CI (0.52-0.87). Although dapagliflozin in DECLARE-TIMI 58 did not significantly reduce the risk of MACE in adults with type 2 diabetes and elevated risk factors or with ASCVD, it was shown to significantly attenuate CV mortality or HF hospitalization, HR 0.83; 95% CI (0.73-0.95) which was a finding most attributable to decreased HF hospitalization, HR 0.73; 95% CI (0.61-0.88) [27]. The CREDENCE_trial was also shown to reveal a consistent

key secondary outcome in participants with type 2 diabetes and diabetic nephropathy of decreased HF hospitalization or CV death, HR 0.69; 95% CI (0.57-0.83), decreased HF hospitalization, HR 0.61; 95% CI (0.47-0.80), and decreased MACE, HR 0.80; 95% CI (0.67-0.95) [28].

Arnott et al. performed a meta-analysis of the four major trials, EMPA-REG OUTCOME, CANVAS Program, CREDENCE, and DECLARE-TIMI 58. Of the efficacy outcome studied including MACE, CV death, fatal and non-fatal MI, fatal and non-fatal stroke, HF hospitalization, CV death or HF hospitalization, and all-cause mortality, SGLT2 inhibitors had the greatest impact on reducing hospitalization for HF with an overall 32% reduction compared with placebo, HR 0.68; 95% CI (0.60-0.76) without evidence of heterogeneity between these studies [29]. These earlier trials demonstrating reduced HF hospitalization or CV death were performed exclusively in type 2 diabetes participants, however, subgroup analysis of diabetics with the previous diagnosis of HF suggested that this finding might benefit patients more with a history of HF most notably HFrEF. This approach was compromised by the fact that the subgroup of participants with HF represented a minority of the study size with diabetes and was not investigated accurately enough because they were not the primary objective of the design. For this reason, there was a need to define a specific study population of patients with HF by including study selection criteria such as ejection fraction and N-terminal-pro hormone B-type natriuretic peptide levels.

Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) was the first study involving the use of SGLT2 inhibitors in symptomatic patients with HFrEF to evaluate the effect of dapagliflozin on the outcome of worsening HF, hospitalization for HF, or CV death [30]. All participants had established HFrEF with a mean EF of about 30% and were previously on guideline-directed HF medications consisting of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), or sacubitril-valsartan with a beta-blocker (BB) and a mineralocorticoid receptor antagonist (MRA) if tolerated. The results of the DAPA-HF trial were followed subsequently by the EMPEROR-Reduced trial, a similarly constructed clinical trial involving a relatively greater severity of decreased left ventricular (LV) systolic function, mean EF of less than 30% [31]. In both trials, SGLT2 inhibitors reduced the composite outcome of HF hospitalization or CV death, DAPA-HF: HR, 0.74; 95% CI (0.65 to 0.85) and EMPEROR-Reduced: HR, 0.75; 95% CI (0.65 to 0.86) although the duration of follow-up was relatively shorter in the EMPEROR-Reduced trial. Hypoglycemic adverse events defined as plasma glucose level less than 70 mg/dl or symptoms that required intervention were more common in diabetic participants on empagliflozin (2.2%) than those without diabetes (0.7%) in the EMPEROR-Reduced trial. This infers that chronic HFrEF patients without diabetes are unlikely to develop hypoglycemia compared to diabetics with HFrEF particularly when the latter concomitantly administer insulin. The most consistently reported adverse effects among study participants have been hypotension, dehydration, genital yeast infection, and UTI. On May 5, 2020, dapagliflozin was approved by the US FDA to reduce the risk of HF hospitalization and CV deaths in adults with chronic New York Heart Association (NYHA) class II-IV HFrEF. This approval was followed subsequently by a similar FDA-approved indication for the use of empagliflozin.

In the EMPEROR-Preserved trial [32], empagliflozin, at a dose of 10 mg daily, decreased the composite primary outcome of HF hospitalization or CV death in HFpEF, HR 0.79; 95% CI (0.69-0.90) which was mainly attributable to statistically significant reductions of hospitalization for HF, HR 0.71; 95% CI (0.60-0.83). This finding was consistent in both participants with and without diabetes. Although their efficacy was diminished by stratifying according to increasing ejection fraction subgroups. This is an important study result in HFpEF because previously known popular HF medications such as the BBs, ACEIs, and ARBs, have not been shown to improve outcomes in this subtype of HF. Of great importance is the extensive renal protective benefits that were shown in the listed trials above. SGLT2 inhibitors were shown to decrease albuminuria and the progression of CKD in diabetics with nephropathy, in addition to decreasing the renal composite outcome of end-stage kidney disease (ESKD), doubling of serum creatinine, and renal or CV death in the CREDENCE trial. SGLT2 inhibitors also decreased the key secondary renal composite outcome in the EMPEROR-Reduced trial. The progression of CKD defined by the change in slope of mean eGFR was diminished by empagliflozin in participants with CKD in both the EMPEROR-Reduced and EMPEROR-Preserved trial.

In DAPA CKD trial [33] the goal of the trial was to assess the safety and efficacy of dapagliflozin in reducing renal events among patients with chronic kidney disease (CKD) with or without diabetes mellitus (DM). The trial stopped early due to benefit. The primary endpoint, decline in eGFR ≥50%, end-stage kidney disease, death from renal causes, or cardiovascular (CV) death for dapagliflozin vs. placebo, was 9.2% vs. 14.5% (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.51-0.72; p = 0.000000028). The benefit of dapagliflozin on the primary endpoint was consistent in patients with and without type 2 DM [Decline in eGFR ≥50%: 5.2% vs. 9.3%, End-stage kidney disease: 5.1% vs. 7.5%, CV death: 3.0% vs. 3.7% (p >0.05)]. The results of this trial indicate that dapagliflozin results in salutary effects on renal function among patients with CKD, with or without DM, who are already on maximal tolerated doses of angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker. There were also beneficial effects noted on non-CV and all-cause mortality and all-cause hospitalizations. Results were sustained among patients with or without known CV disease or HF at baseline.

Other similar trials, such as DEFINE-HF, EMPERIAL-Preserved, and EMPERIAL-Reduced had smaller study enrolment ranging from a sample size of 263 to 312 participants. The VERTIS CV trial, [34] which was highly powered to investigate ertugliflozin in 8,238 patients with type 2 diabetes and ASCVD yielded non-inferior outcomes of MACE and CV death or HF hospitalizations. However, positive outcomes of decreased HF hospitalizations or CV death were shown in the SOLOIST-WHF trial [35]. The primary endpoint of total CV death, HF hospitalization, or urgent visit for HF for Sotagliflozin vs. placebo, was 70 vs. 98 events/100 patient-years (hazard ratio 0.67, 95% confidence interval 0.52-0.85, p = 0.0009 concluding that Sotagliflozin significantly reduced the rates of CV deaths and hospitalizations and urgent visits for HF in diabetics with worsening HF, compared to placebo) and the recently concluded PRESERVED-HF trial where primary endpoint was Composite CV death or HF hospitalization [36]: HR 0.79; 95% CI (0.69-0.90). It also showed reduction in total HF hospitalizations: HR 0.71; 95% CI (0.60-0.83), mean slope change in eGFR, change

in KCCQ symptom score, and any cause death. This finding was consistent in both participants with and without diabetes. The recently concluded DELIVER trial was a global, randomized, double-blind, parallel-group, event-driven trial with 6,263 patients [37]. Over a median of 2.3 years, the primary outcome occurred in 512 of 3,131 patients (16.4%) in the dapagliflozin group and in 610 of 3,132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with and without diabetes. It concluded that Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction.

Among 12,251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced composite cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73–0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77–1·00]) and first hospitalisation for heart failure (0·74 [0·67–0·83]).

SGLT2 Inhibitors and Iron Metabolism in Heart Failure

Many patients with heart failure have an iron-deficient state, which can limit erythropoiesis in erythroid precursors and ATP production in cardiomyocytes. Inflammation and oxidative stress associated with heart failure promote the synthesis of ferritin and activates hepcidin. They suppress ferritinophagy, impair duodenal absorption of iron and the release of iron from macrophages and hepatocytes thus impairing the release of intracellular iron stores and leading to the depletion of bioreactive cytosolic Fe^{2+}. By alleviating inflammation and oxidative stress, SGLT2 inhibitors down-regulate hepcidin, upregulate transferrin receptor protein 1 and reduce ferritin; the net result is to increase the levels of cytosolic Fe2+ available to mitochondria, thus enabling the synthesis of heme (in erythroid precursors) and ATP (in cardiomyocytes). Though SGLT2 inhibitors further aggravate biomarkers of iron deficiency, their net effect is favorable on iron homeostasis and helps retard progression of heart failure [38].

Current Status of SGLT2i in Cardiology - 2022 ACC/AHA

In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes (COR 1, LOE A). In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (COR 2a, LOE B-R). In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (COR 2a, LOE B-R) [39].

Side-effects

Genital infections (UTI and fungal infections) seem to be the most common adverse effect [40]. The FDA issued a warning that SGLT2i can increase risk of diabetic ketoacidosis (euDKA) especially in perioperative period. Canagliflozin, in some trials, decreased bone mineral density and increased risk of lower limb amputation [41].

Conclusion

SGLT2 inhibitors are very promising and effective drugs in the management of heart failure. Its role in HFrEF is well established and in HFmrEF, HFpEF is being established (also in guidelines). SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalizations for heart failure in a broad range of patients with heart failure, supporting their role as a foundational therapy for heart failure, irrespective of ejection fraction or care setting. Its mechanism of action in heart failure and renal protection is still to be elaborated fully. Its pathway of action in heart failure may open up avenues and newer molecular targets for therapeutic intervention.

Declarations

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Declaration of conflicting interests

There is no conflict of interest.

Ethical approval

Not applicable.

Informed consent

Not applicable.

References

1. Pfeifer M, Townsend RR, Davies MJ, Vijapurkar U, Ren J. Effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on blood pressure and markers of arterial stiffness in patients with type 2 diabetes mellitus: a post hoc analysis. Cardiovascular Diabetology. 2017 Dec;16:29.
2. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation. 2019 Oct 29;140(18):1463-76.
3. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJ, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes, Obesity and Metabolism. 2018 Mar;20(3):479-87.
4. Nakayama H, Ohtsuka Y, Kawahara M, Nakamura Y, Iwata S, Yoshinobu S, et al. Changes in body composition during SGLT2 inhibitor treatment and their relevance to the improvement of insulin sensitivity. Diabetes Research and Clinical Practice. 2016;1(120):S50-1.
5. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiological Reviews. 2005 Jul;85(3):1093-129.
6. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, et al. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. JACC: Basic to Translational Science. 2018 Oct;3(5):575-87.
7. Shi L, Zhu D, Wang S, Jiang A, Li F. Dapagliflozin attenuates cardiac remodeling in mice model of cardiac pressure overload. American Journal of Hypertension. 2019 Apr 22;32(5):452-9.
8. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3

inflammasome–mediated inflammatory disease. Nature Medicine. 2015 Mar;21(3):263-9.

9. Iemitsu K, Iizuka T, Takihata M, Takai M, Nakajima S, Minami N, et al. Factors influencing changes in hemoglobin A1c and body weight during treatment of type 2 diabetes with ipragliflozin: interim analysis of the ASSIGN-K study. Journal of Clinical Medicine Research. 2016 May;8(5):373-8.

10. Lee TI, Chen YC, Lin YK, Chung CC, Lu YY, Kao YH, et al. Empagliflozin attenuates myocardial sodium and calcium dysregulation and reverses cardiac remodeling in streptozotocin-induced diabetic rats. International Journal of Molecular Sciences. 2019 Apr 4;20(7):1680.

11. Uthman L, Baartscheer A, Bleijlevens B, Schumacher CA, Fiolet JW, Koeman A, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na+/H+ exchanger, lowering of cytosolic Na+ and vasodilation. Diabetologia. 2018 Mar;61:722-6.

12. Iborra-Egea O, Santiago-Vacas E, Yurista SR, Lupón J, Packer M, Heymans S, et al. Unraveling the molecular mechanism of action of empagliflozin in heart failure with reduced ejection fraction with or without diabetes. JACC: Basic to Translational Science. 2019 Nov;4(7):831-40.

13. Santulli G. Cardioprotective effects of autophagy: Eat your heart out, heart failure!. Science Translational Medicine. 2018 May 30;10(443):eaau0462.

14. Zhou H, Wang S, Zhu P, Hu S, Chen Y, Ren J. Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. Redox Biology. 2018 May 1;15:335-46.

15. Hawley SA, Ford RJ, Smith BK, Gowans GJ, Mancini SJ, Pitt RD, et al. The Na+/glucose cotransporter inhibitor canagliflozin activates AMPK by inhibiting mitochondrial function and increasing cellular AMP levels. Diabetes. 2016 Sep 1;65(9):2784-94.

16. Ghantous CM, Azrak Z, Hanache S, Abou-Kheir W, Zeidan A. Differential role of leptin and adiponectin in cardiovascular system. International Journal of Endocrinology. 2015 Oct;2015:1-13.

17. Wu P, Wen W, Li J, Xu J, Zhao M, Chen H, et al . Systematic review and meta-analysis of randomized controlled trials on the effect of SGLT2 inhibitor on blood leptin and adiponectin level in patients with type 2 diabetes. Hormone and Metabolic Research. 2019 Aug;51(08):487-94.

18. Iemitsu K, Iizuka T, Takihata M, Takai M, Nakajima S, Minami N, et al. Factors influencing changes in hemoglobin A1c and body weight during treatment of type 2 diabetes with ipragliflozin: interim analysis of the ASSIGN-K study. Journal of Clinical Medicine Research. 2016 May;8(5):373-8.

19. Wilcox CS. Antihypertensive and renal mechanisms of SGLT2 (sodium-glucose linked transporter 2) inhibitors. Hypertension. 2020 Apr;75(4):894-901.

20. Onishi A, Fu Y, Darshi M, Crespo-Masip M, Huang W, Song P, et al. Effect of renal tubule-specific knockdown of the Na+/H+ exchanger NHE3 in Akita diabetic mice. American Journal of Physiology-Renal Physiology. 2019 Aug 1;317(2):F419-34.

21. Song P, Huang W, Onishi A, Patel R, Kim YC, van Ginkel C, et al . Knockout of Na+-glucose cotransporter SGLT1 mitigates diabetes-induced upregulation of nitric oxide synthase NOS1 in the macula densa and glomerular hyperfiltration. American Journal of Physiology-Renal Physiology. 2019 Jul 1;317(1):F207-17.

22. Thomson SC, Vallon V. Renal effects of sodium-glucose co-transporter inhibitors. The American Journal of Medicine. 2019 Oct 1;132(10):S30-8.

23. Isshiki M, Sakuma I, Hayashino Y, Sumita T, Hara K, Takahashi K, et al. Effects of dapagliflozin on renin-angiotensin-aldosterone system under renin-angiotensin system inhibitor administration. Endocrine Journal. 2020;67(11):1127-38.

24. Heerspink HJ, Perco P, Mulder S, Leierer J, Hansen MK, Heinzel A, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. Diabetologia. 2019 Jul;62:1154-66.

25. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015 Nov 26;373(22):2117-28.

26. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine. 2017 Aug 17;377(7):644-57.

27. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine. 2019 Jan 24;380(4):347-57.

28. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England Journal of Medicine. 2019 Jun 13;380(24):2295-306.

29. Arnott C, Li Q, Kang A, Neuen BL, Bompoint S, Lam CS, et al. Sodium-glucose cotransporter 2 inhibition for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Journal of the American Heart Association. 2020 Feb 4;9(3):e014908.

30. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2019 Nov 21;381(21):1995-2008.

31. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. New England Journal of Medicine. 2020 Oct 8;383(15):1413-24.

32. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine. 2021 Oct 14;385(16):1451-61.

33. Heerspink HJ, Stefánsson BV. Correa-Rotter Ret al. Dapagliflozin in patients with Chronic Kidney Disease. N Engl J Med. 2020;383:1436-46.

34. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. 2020 Oct 8;383(15):1425-1435.

35. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021 Jan 14;384(2):117-128.

36. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461.

37. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. European Journal of Heart Failure. 2021 Jul;23(7):1217-25.

38. Packer M. How can sodium–glucose cotransporter 2 inhibitors stimulate erythrocytosis in patients who are iron-deficient? Implications for understanding iron homeostasis in heart failure. European Journal of Heart Failure. 2022 Dec;24(12):2287-96.

39. Writing Committee Members; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Card Fail. 2022;28(5):e1-67.

40. Liu J, Li L, Li S, Jia P, Deng K, Chen W, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. Scientific Reports. 2017 Jun 6;7(1):2824.

41. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine. 2017 Aug 17;377(7):644-57.