



Review Article

Effects of SGLT2 Inhibitors on the Risks of Hypertension and Heart Failure in Diabetic Patients: A Systematic Review

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Received: 14 Sep 2021; Revised: 18 Oct 2021; Accepted: 24 Oct 2021

Abstract

Diabetes mellitus (DM) with uncontrolled blood sugar causes a variety of problems, including coronary artery disease, stroke, heart failure, hypertension, nephropathy, neuropathy, and retinopathy. These consequences harm the diabetic patients' lives. Many studies have shown that diabetic patients have a higher rate of heart failure and a worse prognosis than non-diabetic people. Sodium and glucose co-transporter receptor-2 (SGLT2) inhibitors are a relatively new class of anti-diabetic drugs. They not only regulate blood sugar but also have positive cardiovascular effects via a variety of mechanisms. This review intends to show that SGLT2 inhibitors, in addition to good glycemic control, possess a cardioprotective role. We conducted a literature review and identified 20 adequately powered clinical trials and animal studies in type 2 DM that investigated the cardiovascular (CV) effects of SGLT2 inhibitors (particularly heart failure and hypertension). These studies looked at the cardiovascular effects of three SGLT2 inhibitors: Empagliflozin, Canagliflozin, and Dapagliflozin. In diabetic patients, these three inhibitors of SGLT2 significantly lowered the risk of heart failure and hypertension, making them valuable therapy for lowering CV risks in high cardiovascular-risk individuals with T2DM. Finally, the use of SGLT2 inhibitors in patients without diabetes mellitus showed positive metabolic outcomes in weight and blood pressure control.

Keywords: Diabetes mellitus, SGLT2 inhibitors, Hypertension, Heart failure, Blood pressure

آثار مثبطات SGLT2 على مخاطر ارتفاع ضغط الدم وفشل القلب في مرضى السكري: مراجعة منهجية

الخلاصة

مرض السكري مع مستوى السكر غير المنضبط في الدم يسبب مجموعة من المشاكل مثل مرض الشريان التاجي، السكتة الدماغية، فشل القلب، ارتفاع ضغط الدم، اعتلال الكلية، الاعتلال العصبي، واعتلال الشبكية التي تضر حياة المرضى. وقد أظهرت العديد من الدراسات أن مرضى السكري لديهم معدل أعلى من فشل القلب ولديهم مستقبل أسوأ من الأشخاص غير المصابين بالسكري. أن مثبطات مستقبلات النواقل المشاركة في نقل الصوديوم والجلوكوز-2 هي فئة جديدة نسبياً من الأدوية المضادة للسكري التي لا تنظم فقط نسبة السكر ولكن لها آثار إيجابية على القلب والأوعية الدموية عن طريق مجموعة متنوعة من الآليات. هذا الاستعراض يهدف إلى إظهار أن مثبطات SGLT2 بالإضافة إلى وجود سيطرة على نسبة السكر في الدم، تمتلك القدرة على حماية القلب. أجرينا مراجعة للأدبيات وحددنا 20 تجربة سريرية ودراسة حيوانية في النوع 2 من السكري والتي بينت الآثار الإيجابية على القلب والأوعية الدموية وخاصة حالات فشل القلب وارتفاع ضغط الدم. بحثت هذه الدراسات في تأثير ثلاثة بعض مركبات هذه المجموعة على القلب والأوعية الدموية وهي إمباغليفلوزين، وكاناغليفلوزين، وداباغليفلوزين في مرضى السكري. خفضت هذه المثبطات الثلاثة بشكل كبير من خطر فشل القلب وارتفاع ضغط الدم، مما يجعلها اختياراً جيداً لمرضى النوع الثاني من داء السكري ذوي احتمالات عالية لأمراض القلب والأوعية الدموية. وأخيراً، ظهر أن استخدام مثبطات SGLT2 في المرضى الذين لا يعانون من مرض السكري نتائج أيضاً إيجابية في انقاص الوزن والسيطرة على ضغط الدم.

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Article citation: Ali HH, Mahmood NMA, Hussain SA. Effects of SGLT2 inhibitors on the risks of hypertension and heart failure in diabetic patients: A systematic review. *Al-Rafidain J Med Sci.* 2021;1;73-80. doi: 10.54133/ajms.v1i.29.

INTRODUCTION

The sodium and glucose co-transporter receptor (SGLT2), also known as SLC5A2, is present on the first and second segments of the renal proximal convoluted tubules (PCT) [1]. More than 90% of glucose reabsorption in the kidney is controlled by SGLT2 receptors. The remaining 10% was mediated by SGLT1 (SLC5A1) in the third segment of the proximal convoluted tube. The glucose concentration gradient between the cytoplasm of the tubular epithelial cells and the plasma causes glucose transporters-2 (GLUT2) to transfer glucose passively to the plasma [2]. Glucosuria occurs when blood glucose levels reach 180 mg/dL in the absence of diabetes. In diabetic patients, stimulation of hepatocyte nuclear factor-1 alpha (HNF-1), a direct promoter of the SGLT2 gene, increases the levels of SGLT2 mRNA and protein expression on the proximal tubule brush border. It increases the glucose reabsorption in the PCT and shifts the glucosuria threshold to 220 mg/dl, shifting the glucosuria threshold to 220 mg/dl [3]. Unlike the passive transfer of glucose from the cytoplasm to the plasma via GLUT2, SGLT2 activity requires energy from the Na⁺/K⁺ adenosine triphosphatase (ATPase) on the PCT epithelial cells' basolateral surface [4]. Higher sodium reabsorption is a result of increased SGLT2 activity (SGLT2 transfers 1 glucose into the proximal tubule cell with 1 sodium ion), which can contribute to hypertension etiology in diabetes mellitus [5]. The inhibition of SGLT2 receptors in the proximal convoluted tube increase glomerulus glucose filtration [6]. The consequent increase in urine glucose excretion (glucosuria) lowers plasma glucose concentrations. This process is dependent on blood glucose levels and is independent of insulin activity and availability [7]. Therefore, the action of SGLT2 inhibitors, unlike previous anti-diabetics, is insulin-independent. SGLT2 inhibitors have been linked to glycated hemoglobin (HbA1c) reductions of 0.5 to 1%, making them viable second-line treatment alternatives for T2DM [6]. Even though SGLT2 plays a major role in renal glucose reabsorption, selective SGLT2 inhibitors only improve renal glucose excretion by 50-70 percent. The possibility of significant downstream SGLT1 compensation appears to be high, and it is consistent with the maximum SGLT1 glucose transport rate [8]. This explains why renal glucose reabsorption is maintained at 40-50 percent in response to an SGLT2 inhibitor [9]. Empagliflozin (EPG) (Jardiance®), Canagliflozin (CNG) (Invokana®), Dapagliflozin (DPG) (Farxiga®), and Ertugliflozin (ERG) (Steglatro®) are SGLT2 inhibitors currently approved by the Food and Drug Administration (FDA).

METHODS

A literature search was conducted in the PubMed and Google Scholar databases spanning the period from 2010 to 2020. The search technique employed a combination of the following keywords: Heart failure, hypertension,

cardiovascular diseases, Canagliflozin, Dapagliflozin, Empagliflozin, Randomized Controlled Trials, sodium-glucose cotransporter-2 inhibitors (SGLT2i). SGLT2i influence on heart failure and hypertension in T2DM animal models was studied in randomized placebo-controlled trials and experimental animal research. The search covered all full-text studies published in English. Out of 107 papers obtained, 20 full-text studies and 10 documents were evaluated after deleting duplicate studies and scanning titles and abstracts. Finally, only 18 clinical trials and two animal studies employing mouse models were considered.

RESULTS

As shown in Table 1, Lee *et al.* [10] evaluated the effects of DPG on generalized vascular dysfunction in diabetic mice using either a standard diet or a DPG-containing diet. The aortic pulse wave velocity was used to determine arterial stiffness. The function of the vascular endothelium and the smooth muscle dysfunction was evaluated using the dilatory responses to sodium nitroprusside and acetylcholine, respectively. Diabetic mice given DPG had significantly decreased arterial stiffness (DPG-diet= 435 cm/s vs. diet= 469 cm/s), improved endothelial dysfunction (AUC, DPG-diet= 117.0 vs. diet= 57.2), and smooth muscle dysfunction (AUC, DPG-diet= 285.5 vs. diet= 201.7) [10]. Uthman *et al.* [11] found that DPG, CNG, and EPG inhibited Na⁺/H⁺ exchanger (NHE) activity in mouse cardiomyocytes (measured by low NH₄⁺ pulse pH recovery: DPG: 6.770.12, CNG: 6.800.18, and EPG: 6.690.09 vs. vehicle: 7.090.09 for all comparisons) and decreased Na⁺ concentration (DPG: 10.70.7, CNG: 11.00.9, and EPG: 10.00.5 mmol/l). All three SGLT2 inhibitors demonstrated a high affinity for the NHE extracellular binding site. Moreover, EPG and CNG, but not DPG, mediated coronary artery relaxation in the intact heart. Through binding to the NHE Na-binding site, SGLT2 inhibitors quickly block NHE cardiac flow and lower Na⁺ concentration. EPG and CNG also damage the healthy heart by causing vasodilation [11]. The Na⁺ lowering impact of SGLT2 inhibitors [11] could be used as a strategy to fight high Na⁺ concentrations that appear to arise in heart failure and diabetes. Seventy-five subjects with T2DM were randomly assigned to placebo, DPG, or hydrochlorothiazide (HCTZ) in a study performed by Lambers Heerspink *et al.* [12]. The study evaluates the changes in baseline blood pressure, body weight, and plasma volume after three months of treatment. At week 12, the placebo, DPG, and HCTZ treatments resulted in baseline improvements in 24-hour ambulatory mean systolic blood pressure (SBP) of -0.6, -3.3, and -6.6 mmHg respectively, when adjusted for baseline systolic blood pressure (SBP). Bodyweight was lowered by DPG and HCTZ, while Dapagliflozin also decreased plasma volume but neither placebo nor HCTZ did [12]. Lawrence *et al.* [13] also conducted a trial on DPG, which included 964

patients with T2DM, having HbA1c ranging from 7.0 to 10.0 percent, and CVD. The patients were given either placebo or DPG as an add-on to their regular medication.

Participants who took insulin had to reduce their daily insulin dose by 25% at randomization.

Table 1: Summary of the SGLT2 inhibitors studies

Reference	Study type	Intervention drugs	Results
Lee et al. 2018 [10]	2-months a 24 diabetic mice+23 controls	DPG vs. Placebo	Significant ↓ in arterial stiffness
Uthman et al. 2017 [11]	<i>In vitro</i> study	DPG, CNG, EPG vs. Placebo	Significant ↓ in NHE receptor activity
Lambers et al. 2013 [12]	3-month RCT, double-blind; n= 75 subjects	10mg/day DPG, 25mg HCT vs. Placebo	Significant ↓ in BP, Bwt, and plasma volume
Leiter et al. 2014 [13]	7-month RCT, double-blind; n=964 subjects	10mg/day DPG vs. Placebo	Significant ↓ in BP, Bwt, and HbA1c
Sha et al. 2014 [14]	3-month RCT, double-blind; n=36 subjects	30mg/day CNG vs. Placebo	Significant ↑ in UGE and ↓ HbA1c, FBG
Townsend et al. 2015 [15]	1.5-month RCT, double-blind; n=169	100 or 300mg/day CNG vs. Placebo	Significant ↓ in BP
Zinman et al. 2015 [16]	3-year RCT, double-blind trial; n=7020 subjects	100 or 25mg EPG vs. Placebo	Significant ↓ in HF
Tikkanen et al. 2015 [17]	3-month RCT, double-blind trial; n=825 subjects	100 or 25mg EPG vs. Placebo	Significant ↓ in BP
Weber et al. 2015 [18]	2-year RCT, double-blind trial; n=449 subjects	10mg/day DPG vs. Placebo	Significant ↓ in BP
Weber et al. 2015 [19]	3-month double-blind, phase III study; n=613	10mg/day DPG vs. Placebo	Significant ↓ in BP and Bwt
Neal et al. 2017 [20]	67-month RCT, double-blind trial; n=10,142 subjects	100 or 300mg/day CNG vs. Placebo	Significant ↓ in HF
Solini et al. 2017 [21]	2-month, pilot clinical study; n=16	10mg/day DPG vs. Placebo	Significant ↓ in BP
Wiviott et al. 2018 [22]	50-month RCT, double-blind trial, n=17,160 subjects	10mg/day DPG vs. Placebo	Significant ↓ in HF
Nassif et al. 2019 [23]	3-month RCT, double-blind; n=263 subjects	10mg/day DPG vs. Placebo	Significant ↓ in HF
Verma et al. 2019 [24]	6-month RCT; n=97 subjects	EPG vs. Placebo	Significant ↓ in BP
McMurray et al. 2019 [25]	18-month RCT, double-blind; n=4,744 subjects	10mg/day DPG vs. Placebo	Significant ↓ in HF
Perkovic et al. 2019 [26]	30-month RCT, double-blind; n=4,401 subjects	100mg/day CNG vs. Placebo	Significant ↓ in HF
Packer et al. 2019 [27]	15-month RCT, double-blind; n=3,730 subjects	100mg EPG vs. Placebo	Significant ↓ in HF
Ibrahim et al. 2020 [28]	1-week RCT; n=100 subjects	10mg/day DPG vs. Furosemide	Significant ↓ Bwt and ↑ diuresis
Ferdinand et al. 2020 [29]	6-month RCT, double-blind; n=150 subjects	25 or 100mg EPG vs. Placebo	Significant ↓ in BP and HF

DPG: Dapagliflozin; CNG: Canagliflozin; EPG: Empagliflozin; Bwt: Bodyweight; HF: Heart failure; BP: Blood pressure; RCT: Randomized clinical trial; NHE: Sodium Hydrogen Exchange; UGE: Urinary glucose excretion; HCT: Hydrochlorothiazide; FBG: Fasting blood glucose; n: number of subjects.

After 24 weeks, the final results demonstrated a 0.5% decrease in HbA1c, a 3% decrease in body weight, and a 3 mmHg decrease in SBP [13]. Furthermore, Sha *et al.* [14] investigated the effects of CNG on plasma volume, urinary glucose excretion (UGE), fasting plasma glucose (FPG), HbA1c, and other fluid/electrolyte balance markers in diabetic patients who previously received ACEIs, Angiotensin-Receptor Blockers (ARBs) and Metformin. Thirty-six patients were randomly assigned to receive 300 mg CNG or placebo for three months (double-blind, 1:1 randomization). Pharmacodynamic parameters were measured at baseline, 7 days later, and 3 months later. Fasting blood glucose and HbA1c levels were also lower after CNG treatment, and body weight and blood pressure decreased between weeks 1 and 12. Compared to placebo, CNG induced a drop in plasma volume at week 1 (-5.4% vs. 4.3%) but largely mitigated by week 12 (4.6% vs. 5.8%). In the CNG group, a modest numerical rise in urine volume was seen at week-1 and decreased by week 12. Other markers in the CNG group (such as blood urea nitrogen, serum creatinine, and hematocrit) remained slightly increased at week 12 [14]. Townsend *et al.* [15] investigated the effects of CNG (300 mg and 100 mg) on blood pressure in T2DM and hypertensive patients. Participants were given CNG 300 mg, CNG 100 mg, or placebo for 6 weeks and had their ambulatory SBP monitored 24 hours a day before randomization, at baseline, and after 42 days of treatment. The primary outcome was the change in mean 24-hour SBP from baseline to week 6. CNG 300 mg and 100 mg showed higher decreases in SBP in week 6 in a mean 24-hour cycle compared with placebo (-6.2 and -4.5 vs. -1.2 mmHg, respectively) [15]. Meanwhile, the EMPA-REG study found a small but significant reduction in the primary outcome (the primary outcome here is a composite of death from CVD, nonfatal stroke, or nonfatal myocardial infarction). It favors EPG compared to placebo over a mean period of the 3.1-year follow-up in 7,020 patients with T2DM who had developed CVD and assigned to daily EPG 10 or 25 mg vs. placebo. Surprisingly, EPG was associated with a significant reduction in hospitalization from heart failure (relative risk reduction= 35%) [16]. In another study, Tikkanen *et al.* [17] randomly assigned 825 patients with T2DM and hypertension (mean SBP of 130-159 mmHg and DBP of 80-99 mmHg) to receive 10 mg EPG, 25 mg EPG, or placebo once a day for three months. After 3 months, the adjusted mean difference in change from baseline in mean 24-hour SBP was -3.44 mmHg with 10 mg EPG and -4.16 mmHg with 25 mg EPG as compared to placebo. Meanwhile, with 10 mg EPG, the adjusted mean difference in change from baseline in mean 24-hour DBP was -1.36 mmHg, and with 25 mg EPG, it was -1.72 mmHg [17]. Furthermore, Weber *et al.* [18] randomly allocated 225 patients to DPG and 224 patients to placebo (all of whom were already using ARBs, another antihypertensive medicine, anti-hyperglycemic, insulin, or both). Seated

systolic blood pressure was significantly reduced in the group assigned to Dapagliflozin (adjusted mean change from baseline -11.90 mmHg [95% CI: -13.97 to -9.82]) compared with those assigned to placebo (-7.62 mmHg [-9.72 to -5.51], $P<0.05$); the placebo-adjusted difference for Dapagliflozin (-4.28 mmHg [-6.54 to -2.02], $P=0.0002$). HbA1c levels were also lowered to a greater extent in DPG patients compared to those receiving placebo. The placebo-adjusted difference was -0.61% [18]. Weber *et al.* [19] conducted another investigation on the impact of DPG on the renin-angiotensin system blockage in T2DM patients with hypertension. The double-blind phase III trial looked at how DPG affected glycemic control and blood pressure in patients with poorly managed hypertension who were also taking a renin-angiotensin system blocker. Patients were randomly assigned to receive 10 mg DPG or placebo once a day. The main endpoints were changes from baseline to week 12 in seated SBP and HbA1c. Also, additional longitudinal repeated-measure analysis was carried out. After 12 weeks, participants treated with DPG had significantly lower HbA1c (-0.6% vs. -0.1%), mean seated SBP (-10.4 vs. -7.3 mmHg), and mean confirmatory ambulatory SBP 24-hours than those treated with placebo (-9.6 vs. -6.7 mmHg). DPG also reduced bodyweight (-1.0 vs. -0.3 kg) when compared to placebo [19]. The CANVAS study is a pooled evaluation of two CNG clinical trials, the original CANVAS and the CANVAS Renal (CANVAS-R), where both investigated renal safety. The aggregated overall study includes 10,142 patients from these investigations; 4330 were from the original CANVAS trial, which had a 5.7-year follow-up time, and 5812 were from the CANVAS-R trial, which had a 2.1-year follow-up duration. Unlike the EMPA-REG trial, only 65.6 percent of the pooled CANVAS patients had CVD, with the remainder having two or more CV risk factors. In the pooled CANVAS study, CNG was found more effective than placebo in reducing heart failure hospitalization [20]. In pilot research, Solini *et al.* [21] investigated vascular and neurohormonal variables, as well as 24-hour diuresis, glucose and salt in urine, isoprostanes, and free water clearance in 16 diabetic patients before and after 2-days therapy with DPG 10 mg/day. The results were compared to those reported in ten patients administered 12.5 mg of HCTZ per day. The study evaluates the effects of flow-mediated dilation on endothelium vasodilation of the brachial artery and pulse wave velocity. Dapagliflozin reduces SBP and similarly increases the 24-hour diuresis to HCTZ. It also elevates 24-hour urinary glucose and serum magnesium. Urinary sodium remained unaltered for 24 hours, as did fasting blood glucose (FBG). Even after the mean BP adjustment, oxidative stress was reduced, as evidenced by a decrease in urine isoprostanes and a significant increase in flow-mediated dilation (2.8 to 4.0%), and a decrease in pulse-wave velocity (10.1 to 8.9 m/s) [21]. A total of 17,160 patients who had or were at risk of atherosclerotic CVD were randomized to receive

DPG or placebo for a median of 4.2 years in the DECLARE-TIMI trial. This study found no significant differences in the 3P-MACE (nonfatal stroke, nonfatal myocardial infarction (MI), and cardiovascular mortality) markers. In the two primary efficacy analyses, Dapagliflozin did not lower the rate of MACE ($P=0.17$), decreased the rate of cardiovascular death or hospitalization due to heart failure ($P=0.005$), which reflects a lower rate of hospitalization for heart failure (CI, 0.61 to 0.88). there was no between-group difference in cardiovascular death (CI: 0.82 - 1.17) [22]. Meanwhile, 263 patients were assigned to receive 10 mg/day DPG or placebo for 12 weeks in the DEFINE-HF trial. The findings demonstrated a considerable rise in the number of patients with clinically meaningful changes in heart failure (HF) measures [23]. Patients' characteristics showed stable HF with decreasing ejection fraction during the use of appropriate medical therapy. Furthermore, in the EMPA-HEART study, 97 diabetic subjects were randomized to receive either 10mg /day EPG (n=49) or placebo (n=48) in addition to standard care for 6 months. This study showed a lowering of systolic and diastolic BP of -6.8 and -3.2 mmHg respectively, upon the use of EPG after 6 months [24]. The DAPA-HF trial, which covers 4744 patients, indicates a decrease in CV mortality and hospitalizations owing to HF in individuals treated with DPG in a double-blind randomized study. The results pointed to a significant decrease in HF hospitalization, cardiovascular death, and all-cause mortality independent of the diabetes status of the subjects. Patients in the study were also taking ACE/ARBs, although the class effect of these medicines did not affect the results. Both diabetics and non-diabetics can benefit from SGLT2i, according to this study [25]. The CREDENCE trial enrolled 4401 individuals with T2DM and proteinuric chronic kidney disease (CKD) randomly assigned to receive CNG or placebo. The subjects had a GFR of 30 to 90 ml/min/1.73m², and only 50.4% of them had ASCVD. This study was terminated early after 2.62 years due to the gained substantial advantages of therapy. The relative risk of the primary composite endpoint (consisting of end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or CV causes) was lower by 30%. The reported secondary outcomes of MI, stroke and CV death were reduced by 20%, whereas hospitalization due to HF was reduced by 39% [26]. In the EMPEROR-Reduced double-blind trial, 3,730 patients with HF stage 2 and 3 and an ejection fraction equal to or less than 40% were randomized to receive placebo or 10 mg/day EPG therapy for 16 months in addition to their regular HF medications. Empagliflozin reduced the risk of death and HF hospitalization over time and reached statistical significance 12 days after randomization [27]. In 2020, Ibrahim *et al.* conducted a study to see how adding DPG to Furosemide affected HF patients. The study comprised 100 T2DM patients admitted to the hospital for HF with decompensation and stayed for one week. The

patients were randomized into two equal arms. DPG causes statistically significant differences in body weight shift (76.5 vs. 79.6 kg) between the two groups. During hospitalization, there was also a statistically significant difference in diuresis parameter (19.5 vs. 34.8) in favor of DPG administration, but no significant improvement in serum potassium or kidney function [28]. In a 2020 study on T2DM and hypertensive black individuals, Ferdinand *et al.* [29] found that EPG lowers both ambulatory and sitting SBP, with placebo adjusted differences of -8.39 mmHg for ambulatory and -7.43 mmHg for seated SBP at week 24. Decreases in DBP were also reported; however, they were only significant for the daytime and awake time criteria. The lower blood pressure observed with EPG was unrelated to changes in pulse rate. The mean differences between the groups in pulse rate changes from baseline (two variations in beats per minute) were not clinically significant.

SGLT2 Inhibition and Direct Effects on Na⁺/H⁺ Exchange

Inhibitors of SGLT2 can directly inhibit the myocardial isoform of Na⁺/H⁺ exchanger (NHE-1), according to a new and tantalizing idea, as demonstrated by Uthman *et al* in their work. NHE-11 activation increases cellular sodium and calcium ions levels, as shown in experimental heart failure models [11]. Through this process, SGLT2 inhibitors reduced cardiomyocytes' NHE-1 activity, decreased sodium and calcium ions levels, raised calcium levels in mitochondria, and boosted cardiac force of contraction [32]. It is worth noting that SGLT2 inhibitors are thought to induce natriuresis by inhibiting NHE-3 action in the proximal renal tubule. In heart failure, the expression of NHE-1 assists sodium ions reuptake in renal tubules, while blocking NHE-3 can help restore whole-body sodium homeostasis and reduce HF. As a result, suppression of NHE-1 and NHE-3 may be a common cardio-renal mechanism by which these drugs prevent and/or treat HF [11]. It is not clear whether the inhibition of the cardiac NHE can be achieved at the doses of SGLT-2 inhibitors used in the clinics. Furthermore, NHE inhibitors have not been clinically successful in the treatment of heart failure.

Bodyweight Loss

Patients with type 2 diabetes are usually obese, overweight, or have increased fat deposition inside and around their internal organs. Patients on SGLT2 inhibitors experience weight loss regularly [33]. Early weight loss could be attributable to fluid loss due to the medicines' osmotic diuretic effects. However, future weight reduction is more likely due to caloric loss. The glucose discharged in the urine after SGLT2 inhibition has a calorific value of around 200-300 calories per day [34]. A significant drop in waist circumference was also reported in 12-week investigations with DPG, CNG, and EPG, as well as in a 52-week DPG

trial when taken as an add-on to Metformin therapy, which would be consistent with a reduction in fat mass later [19]. Weight loss alone has not been successful in decreasing HF; therefore, there must be additional factors that explain the mechanism by which SGLT-2 inhibitors produce their cardioprotective action.

Inhibition of the Sympathetic Nervous System

The observations that SGLT2 inhibitors lower blood pressure without causing a compensatory rise in heart rate and 6-hydroxydopamine chemical denervation of the sympathetic nervous system has resulted in decreased renal SGLT2 expression, leading to the hypothesis that SGLT2 inhibitors suppress the central sympathetic nervous system [35]. Moreover, a high-fat diet induces SGLT2 expression in the kidneys and hearts of mice [36,29], which highlights the importance of using SGLT2i in non-diabetics with increased CV risks.

Improved Endothelial Function and Vascular Stiffness

Several studies have shown that using SGLT2 inhibitors for a short period improves endothelial function and reduces aortic stiffness [22,10]. The gain could be mediated, at least in part, by endothelium-independent activation of voltage-gated K⁺ channels and protein kinase G, albeit this pathway has only been demonstrated in vivo through experiments on mice [22,10].

Increased Hematocrit Production

In patients with T2DM, hematocrit level increases after starting SGLT2 inhibitor therapy and can be a surrogate marker for decreasing metabolic stress on the proximal tubules or surrounding kidney interstitium. The Na⁺/K⁺ pump can also reduce cardiovascular mortality and cardiac failure risk of hospitalization by alleviating metabolic stress in the proximal tubular epithelial cells, consequently minimizing hypoxia in the microenvironment around the proximal tubules. The change in hematocrit and hemoglobin mediates 50% of the decreased risk of cardiovascular death by Empagliflozin versus placebo in post hoc mediation analyses of data from the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose). Sudden death, heart failure death, and suspected cardiovascular death with inadequate data to assign a definitive cause of death are the most common types of cardiovascular mortality seen in individuals with heart failure. It may allow myofibroblasts to change into erythropoietin-producing fibroblasts. It will enhance hematopoiesis and elevate hematocrit [37,38]. Moreover, the continuous lowering of resting heart rate in individuals using SGLT2 inhibitors supports the suppression of sympathetic hyperactivity by these medications [39].

Conclusion

In addition to their blood glucose-lowering effects, SGLT2 inhibitors can significantly reduce cardiovascular complications such as heart failure and hypertension in diabetic patients. These cardiovascular benefits make members of SGLT2 inhibitors, such as Empagliflozin, Canagliflozin, and Dapagliflozin, useful therapeutic tools for diabetic patients, particularly those with CVD risks. Finally, SGLT2i may even be designated as cardiovascular therapies in the future, in addition to their role as antidiabetic agents. Although, more trials may be required to prove them as cardiovascular drugs.

ACKNOWLEDGMENTS

The authors thank the University of Sulaimani for supporting the project.

Conflicting Interests

The authors declared no conflicts of interest.

Data sharing statement

The datasets analyzed during the current study will be available from the corresponding author on a reasonable request.

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