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Chronic Diseases and Translational Medicine 6 (2020) 239–245

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Review

Cardiovascular effects and mechanisms of sodium-glucose cotransporter-2 inhibitors

Fan Yang [a], Ran Meng [a], Da-Long Zhu*

Department of Endocrinology, Drum Tower Hospital Affiliated to Nanjing University Medical School, Nanjing, Jiangsu 210008, China

Received 21 May 2020

Available online 15 August 2020

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) are a new type of drug for the treatment of diabetes, and they have been proven to have a good hypoglycemic effect. Several lines of clinical evidence have shown that SGLT2 inhibitors can significantly reduce the risks of atherosclerosis, hospitalization for heart failure, cardiovascular death, and all-cause mortality and delay the progression of chronic kidney disease. Because of the protective effects of SGLT2 inhibitors on the heart and kidney, they are being studied for the treatment of heart failure and chronic kidney disease in patients without diabetes. Therefore, it is necessary for cardiologists, patients with diabetes, and nephrologists to fully understand this type of drug. In this review, we summarize the following three aspects of SGLT2 inhibitors: the recent clinical evidence of their cardiovascular benefits, their mechanisms of action, and their safety.

Keywords: Sodium-glucose cotransporter-2 inhibitors; Type 2 diabetes; Cardiovascular outcomes; Mechanisms of cardiovascular benefits

In recent years, the global morbidity of diabetes has increased. The latest data from the International Diabetes Federation (IDF) indicate that the number of patients with diabetes will be 700.2 million by 2045, and cardiovascular disease is the leading cause of death for patients with diabetes. Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) are a new class of hypoglycemic drug, and they can block sodium-dependent glucose transporter-2 (SGLT2) located in the early proximal renal tubule to increase urinary glucose excretion and decrease the concentration of blood glucose.[1] Its hypoglycemic effect depends on the level of blood glucose.[2] Increased glycosuria can cause energy and body weight loss, osmotic diuresis, and hypotensive effects.[3] Empagliflozin, dapagliflozin, and canagliflozin have been approved for clinical treatment in China. The hypoglycemic effect of SGLT2 inhibitors is supported by more evidence.[4–8] In recent years, several studies have shown that SGLT2 inhibitors have additional benefits for the cardiovascular system. Additional evidence for the

* Corresponding author. Department of Endocrinology, Drum Tower Hospital Affiliated to Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing, Jiangsu 210008, China.

E-mail address: zhudalong@nju.edu.cn (D.-L. Zhu).

Peer review under responsibility of Chinese Medical Association.

[a] Fan Yang and Ran Meng contributed equally to this work.

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https://doi.org/10.1016/j.cdtm.2020.07.002

effects of SGLT2 inhibitor is constantly being reported. In addition to the hypoglycemic effect of SGLT2 inhibitors, there are many other mechanisms by which they reduce cardiovascular risk. Here, we review the clinical research results and the associated mechanisms.

Cardiac effects and cardiovascular outcomes

The related results are mainly from on three influential studies: the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial, and the Canagliflozin Cardiovascular Assessment Study (CANVAS) program.[9–11] In these studies, an SGLT2 inhibitor was compared with a placebo. A meta-analysis of these studies yielded the following results.

The three large randomized controlled trials included in this study were on patients with type 2 diabetes (T2D) with cardiovascular disease or high cardiovascular risk. SGLT2 inhibitors reduced major adverse cardiovascular events significantly (relative risk (RR): 0.89; 95% confidence Interval (CI) (0.83, 0.96); $P = 0.001$), suggesting that SGLT2 inhibitors can reduce major adverse cardiovascular events in T2D with a high risk of cardiovascular disease. In addition, SGLT2 inhibitors can reduce all-cause mortality in T2D (RR: 0.83; 95% CI (0.70, 0.99); $P = 0.034$), but they had no significant benefits in terms of cardiovascular death risk (RR: 0.81; 95% CI (0.63, 1.05); $P = 0.116$). The current evidence indicates that only englitazone can lower the risk of cardiovascular death and all-cause mortality, suggesting that the benefits of the different SGLT2 inhibitors on cardiovascular death are not the same. However, another meta-analysis indicated that dapagliflozin, canagliflozin, and empagliflozin reduced the incidence of cardiovascular adverse events by 11% in T2D and had more benefits on T2D with atherosclerosis.[12] It has been reported that SGLT2 inhibitors have benefits on preventing cardiovascular death.[12]

SGLT2 inhibitors were found to significantly reduce the risk of hospitalization for heart failure (RR: 0.69; 95% CI (0.61, 0.79); $P < 0.01$). The results of the three cardiovascular outcomes trials consistently showed that the three SGLT inhibitors reduced the risk of hospitalization for heart failure. The risk of myocardial infarction was also significantly reduced in the SGLT2 inhibitor group (RR: 0.89; 95% CI (0.80, 0.98); $P = 0.018$). In addition, it was confirmed that SGLT2 inhibitors significantly reduced the risk of kidney-specific composite endpoints (RR: 0.55; 95% CI (0.48, 0.64); $P < 0.01$).

In the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study, the risks of heart failure hospitalization, death, and the combined end-point of heart failure hospitalization or death were compared between treatment with SGLT2 inhibitors and other glucose-lowering drugs (including metformin, sulfonylurea, DPP-4i, thiazolidinedione, GLP-1 RA, insulin, and alpha glucosidase inhibitor). The results showed that treatment with SGLT2 inhibitors was associated with a lower risk of heart failure hospitalization, all-cause death, and the composite of heart failure hospitalization and death (hazard ratio (HR) 0.61, 0.49, and 0.54, respectively).[13] Toyama et al[14] conducted a meta-analysis of the effects of SGLT2 inhibitors on cardiovascular and chronic kidney disease and its renal safety in T2D. In a total of 7363 patients included in 27 studies, SGLT2 inhibitors significantly reduced the risks of cardiovascular death, non-fatal myocardial infarction, cerebral infarction, and heart failure. Sinha B et al[15] found that compared with DPP4i and GLP1 receptor agonists, SGLT2 inhibitors reduced the risk of heart failure hospitalization in T2D. In summary, SGLT2 inhibitors bring significant cardiovascular and renal benefits to T2D, especially reducing the risks of composite cardiovascular endpoint events, all-cause morbidity, hospitalization for heart failure, myocardial infarction risk, and kidney-specific composite endpoint event risk. However, the different types of SGLT2 inhibitors are heterogeneous. In addition, the evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial (VERTIS-CV) is in progress.[16] The results from the VERTIS-CV trial will clarify the cardiovascular and renal safety and efficacy of ertugliflozin in patients with T2D mellitus and arteriosclerotic cardiovascular disease (ASCVD) versus placebo. The results of this study are expected to help better understand these issues involving SGLT2 inhibitors.

Possible mechanisms of cardiovascular benefits

Changes in energy metabolism

The potential cardiovascular beneficial mechanism by which SGLT2 inhibitors change energy metabolism, is by promoting fat oxidation.[17,18] Dapagliflozin was reported to increase fat and glucose oxidation by 14% and 20%, respectively.[19] Acetyl-CoA produced by fat oxidation is converted into ketone bodies and is first used by the myocardium to improve myocardial efficiency. A clinical study showed that 100 or 200 mg of

canagliflozin increased plasma β-hydroxybutyrate in patients with T2D in a dose-dependent manner.[20] Increased β-hydroxybutyrate can decrease the use of oxygen, increase cardiac efficiency by 24%, and decrease oxidative stress.[21]

In addition, SGLT2 inhibitors increase glucagon levels. Cardiomyocytes express the glucagon receptor, which contributes to cardiac inotropic and chronotropic effects.[22] Glucose toxicity has been reported to increase cardiac oxidative stress and exacerbate myocardial injury in patients with T2D.[23] SGLT2 inhibitors prevent excessive glucose absorption by the heart. In general, fatty acids mainly provide energy for the heart, but in patients with diabetes, hyperglycemia promotes the uptake of glucose by cardiomyocytes and then impairs cardiac function.[24] SGLT2 inhibitors increase β-hydroxybutyrate levels and change the energy supply from fatty acids and glucose to ketones. This increases the metabolic efficiency of the myocardium and kidney and reduces oxygen consumption. Currently, this ketone hypothesis is still being explored.[25]

Reduction of blood pressure and vessel stiffness

Sodium is mainly reabsorbed in the proximal tubules. Renal blood flow, the sympathetic nervous system, and the angiotensin system participate in sodium reabsorption. SGLT2 inhibitors have been shown to increase aldosterone and angiotensin II levels in response to volume contraction,[26–28] thus reducing systolic and diastolic pressures. Natriuresis, reduced plasma volume, non-fluid weight loss, and direct vascular effects may contribute to this reduction in blood pressure.[29]

Increased arterial stiffness can lead to heart failure and increase cardiovascular mortality.[30] Approximately 40% of patients with T2D are diagnosed with hypertension.[31] Hyperglycemia increases the incidence of hypertension in patients with diabetes and increases arterial stiffness.[32] This is partly due to the activation of the sympathetic nervous system, the renin-angiotensin aldosterone system, and the reduction in nitric oxide.[32,33] In type 1 diabetes, it has been reported that empagliflozin reduced arterial stiffness.[34] Presumably, this reduction is related to the improved arterial compliance and weight loss. In T2D, empagliflozin has been shown to improve arterial stiffness and vascular resistance. Reduced arterial stiffness can further improve myocardial energy metabolism and calcium overload, thereby reducing heart failure.

Recent studies have shown that empagliflozin can reduce arterial stiffness regardless of hyperglycemic conditions. In patients with T2D who are normotensive, the systolic blood pressure was significantly reduced after 8 weeks of empagliflozin treatment. Neurohormonal mediators and changes in arterial structure, autonomic nervous system function, and weight loss can also affect arterial stiffness.[35–37] The improved vascular smooth muscle relaxation caused by SGLT2 inhibitors also contributes to the decreased arterial stiffness, mainly because of the negative sodium balance and diuretic effect.[38]

Increases in hemoglobin and hematocrit

A clinical trial showed that empagliflozin significantly reduced cardiovascular mortality by increasing hematocrit levels, mainly because of the lower plasma volume.[39] SGLT2 inhibitors can reduce proximal tubule workload and promote erythropoiesis, thus improving tubulointerstitial oxygen shortage,[40–42] partially accounting for the increase in hematocrit. Another Chinese study reported that lower hematocrit levels were associated with cardiovascular events.[43] The presence of chronic kidney disease and low hematocrit levels in Chinese patients with T2D increased the risk of adverse cardiovascular events.[44] Increased glucose reabsorption in patients with T2D results in overtaxed proximal tubules and reduced erythropoietin production. In patients with diabetes, it was reported that the level of erythropoietin increased followed by an increase in the hematocrit level after treatment with dapagliflozin.[45] SGLT2 inhibitors have been reported to reduce renal tubules, repair tubulointerstitial effects, and promote erythropoietin production.[46–48] After treatment with SGLT2 inhibitors, elevated hematocrit levels in patients with diabetes may reverse kidney remodeling. An increase in hematocrit levels during treatment with empagliflozin was significantly associated with a reduction in cardiovascular death.[49]

Myocardial remodeling improvement

Cardiac remodeling and myocardial fibrosis are complex processes related to inflammation and oxidative stress.[50,51] Cardiac remodeling plays an important role in the occurrence and development of heart failure. Abnormally activated cardiac fibroblasts produce and release extracellular matrix and play a key role in myocardial fibrosis.[52] Macrophages can accelerate inflammation and increase myocardial remodeling.[53] Macrophages are composed of M1 and M2 phenotypes. M2 macrophages have been reported to be critical for post-myocardial remodeling in a mouse model of myocardial infarction. Macrophages affect the

characteristics of myofibroblasts, but M1 and M2 macrophages are balanced in the tissue.[54] A recent study showed that dapagliflozin could modulate these macrophage phenotypes and decrease myocardial fibrosis and cardiac remodeling.[55–57]

Body weight loss

A number of clinical studies have shown that SGLT2 inhibitors can significantly reduce body weight compared with placebo.[58] In two 26-week studies, 300 mg of canagliflozin induced more weight loss than empagliflozin and dapagliflozin.[59] The weight loss occurs rapidly at first and then slows down until it reaches a plateau.[60–62] The initial rapid loss is considered to be the result of osmotic diuresis, while the subsequent slow loss may be the result of urinary glucose excretion causing a decrease in visceral fat mass.[63,64] There is evidence that obesity is an important risk factor for heart failure, but it is still controversial whether weight loss affects the outcome of patients with diabetes with significant heart failure.

Electrolyte changes

SGLT2 inhibitors can reduce Na^+ levels in cardiomyocytes and decrease secondary sarcolemmal and mitochondrial Na^+/Ca^{2+} exchanger, thus reducing the concentration of Ca^{2+}.[65,66] Dapagliflozin has been shown to decrease systolic Ca^{2+} in cardiomyocytes.[67] The mitochondrial Ca^{2+} level, as the main agonist of antioxidant agents and ATP, increases during heart failure to improve cardiac function.[68] More studies are needed to clarify these effects.

Decrease in serum uric acid

Hyperuricemia and gout are closely related to diabetes, obesity, hypertension, kidney disease, and various cardiovascular diseases.[69,70] Hyperuricemia is considered to be an independent risk factor for cardiovascular disease.[71–73] Clinical studies have found that serum uric acid levels decreased in patients using SGLT2 inhibitors. It is currently believed that SGLT2 inhibitors may lead to a decrease in uric acid, which may be caused by glucose-induced diuretic diminution and decreased uric acid reabsorption.

Safety

SGLT2 inhibitors have been proven to have good hypoglycemic and cardiorenal protective effects. However, the following aspects still need to be considered when prescribing. A meta-analysis of the three influential studies noted above also indicated that SGLT2 inhibitors increased the risk of germline infection. Forest et al[74] and Leiter et al[75] also found that canagliflozin increased the incidence of genital infections and urinary system infections, but the degree was mild with a controllable risk. Therefore, patients administered SGLT2 inhibitor should take measures to keep clean to reduce the risk of related infections. It was found that SGLT2 inhibitors increased the risk of diabetic ketoacidosis, characterized by euglycemia (blood glucose less than 250 mg/dL) in the presence of severe metabolic acidosis and ketonemia, called euglycemic diabetic ketoacidosis DKA.[76–79] In addition, canagliflozin was found to increase the risk of amputation.[80] The reason was thought to be related to the circulating blood volume. Doctors should remind patients to drink enough water, perform rigorous foot examinations, and avoid prescribing SGLT2 inhibitors to high-risk patients.

Conclusions

In summary, as a new type of drug for the treatment of T2D, SGLT2 inhibitors have good cardiovascular effects and low risk of hypoglycemia; moreover, they have additional cardiovascular and renal benefits. The mechanisms by which SGLT2 inhibitors exert their cardiovascular protective effects mainly include the super fuel theory, electrolyte factors, improved hemodynamics, increased erythropoietin, elevated glucagon, and inhibition of oxidative stress and inflammation.[81–84] However, further research is still needed to clarify the specific mechanisms. The different types of SGLT2 inhibitors are associated with clinical heterogeneity, and there are few clinical trials from China. More studies are expected in the future to clarify the role of SGLT2 inhibitors and provide more evidence in the Chinese context to inform clinical choices.

Funding

This study was supported by grants from the National Natural Science Foundation of China (No. 81300651), Natural Science Foundation of Jiangsu Province of China (No.BK20130088), Six Talent Peaks Project in Jiangsu Province (No.WSN-165), and Jiangsu Provincial Medical Youth Talent (No.QNRC2016018).

Conflicts of interest

None.

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Edited by Yi Cui