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SGLT2 inhibitors in type 2 diabetes: a comprehensive review of their effects on the autonomic nervous system and cardiovascular health

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Abstract: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are antidiabetic drugs that help lower high blood sugar levels by blocking the reabsorption of glucose in the kidneys. Although their primary function is to control blood sugar in type 2 diabetes mellitus (T2DM), growing evidence suggests they may also have additional benefits, particularly in reducing neurological and cardiovascular complications related to T2DM. This study explores the neuroprotective effects of SGLT2i, which appear to improve symptoms of peripheral neuropathy by enhancing nerve conduction for both sensory and motor functions and reducing neuropathic pain. These effects are believed to occur through mechanisms such as the activation of AMP-activated protein kinase and the reduction of mitogen-activated protein kinase phosphorylation, both of which protect nerve function. In terms of cardiovascular health, SGLT2i show cardioprotective effects by lowering sympathetic nervous system activity, reducing blood pressure, and minimizing the risk of heart failure-related hospitalizations and arrhythmias. Furthermore, these inhibitors may play a role in preventing diabetic retinopathy by reducing oxidative stress and blocking inflammatory pathways in retinal tissue. Although some research has hinted at a potential link between SGLT2i use and increased risk of diabetic foot complications, the results are not definitive and require further study. Overall, SGLT2 inhibitors represent a multifaceted approach in managing T2DM, offering additional neurological and cardiovascular benefits. Ongoing research is critical to fully understand their mechanisms, enhance therapeutic outcomes, and confirm their safety for a wide range of patients.

Keywords: SGLT2 inhibitors, type 2 diabetes, glucose reabsorption, autonomic nervous system, neuroprotection, cardiovascular health.

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Introduction

Glucose is a critical energy source for the body, central to numerous metabolic processes. The sodium-glucose cotransporter 2 (SGLT2) plays a key role in glucose reabsorption, retrieving nearly all the 180 g of glucose filtered daily by the kidneys. In type 2 diabetes, SGLT2 becomes overactive, leading to hyperglycemia. SGLT2 inhibitors (SGLT2i) are a class of drugs that reduce blood glucose by inhibiting this transporter, promoting glucose excretion. Typically taken orally and often combined with other antidiabetic medications like metformin, SGLT2i are effective at controlling blood glucose level and minimizing complications in type 2 diabetes. Beyond diabetes, SGLT2i show promise in treating heart failure and possibly preventing cognitive decline and other neurological disorders, such as Parkinson's and multiple sclerosis. This work explores the potential of SGLT2 inhibitors in addressing diseases that affect the autonomic nervous system (ANS), with a focus on their neuroprotective effects, as well as comprehensively evaluate the therapeutic potential of SGLT2i in managing neurological and cardiovascular complications associated with T2DM, highlighting their broader applications beyond glycemic control and identifying areas for future research.

Methodology

This study employed a comprehensive literature review to assess the potential neuroprotective effects of SGLT2i on autonomic neurological conditions associated with type 2 diabetes mellitus. The literature search was conducted from November 2022 to April 2023 using two primary databases: PubMed and Google Scholar search engine. A systematic search was performed using specific keywords and medical subject headings (MeSH terms) related to SGLT2 inhibitors and autonomic neurological conditions. The primary search terms included: "SGLT2 inhibitors," "sodium-glucose cotransporter 2 inhibitors," "type 2 diabetes mellitus," "autonomic neuropathy," "peripheral neuropathy," "cardiac autonomic neuropathy," "diabetic retinopathy," "diabetic foot," "neuroprotection," and "neurological complications." Boolean operators such as "AND" "OR" and "NOT" were utilized to refine the search results and ensure a comprehensive retrieval of relevant studies. Articles were included if they met the following criteria: published before April 2023, written in English, peer-reviewed original research articles including clinical and laboratory research, meta-analyses, or systematic reviews and focused on the effects of SGLT2 inhibitors on neurological conditions in type 2 diabetes mellitus (T2DM) patients. Exclusion criteria were following articles not available in full text, publications in languages other than English, editorials, commentaries, and conference abstracts without full data. Titles and abstracts of the retrieved articles were screened to determine eligibility based on the inclusion and exclusion criteria. Full-text versions of potentially relevant articles were then reviewed for final inclusion. Discrepancies between reviewers were resolved through discussion.

SGLT2 transporters profile in human physiology

In healthy individuals, glucose reabsorption occurs in the proximal tubule after filtration through the glomerulus, resulting in negligible glucose levels by the end of the nephron's proximal tubule. The proximal tubule's luminal membrane expresses SGLT2, a sodium-glucose cotransporter encoded by the SLC5A2 gene, part of the SLC5 gene family [1]. Approximately 50 mutations in

SGLT2 have been linked to familial renal glucosuria, a benign condition characterized by polyuria, polydipsia, nocturnal enuresis, polyphagia, and recurrent urinary tract infections [2]. The sodium-glucose cotransporter 2 reabsorbs 80–90% of the glucose filtered by the glomerulus and is predominantly found in the S1 and S2 segments of the proximal tubule, while SGLT1, responsible for the remaining 10–20%, is in the later S3 segments [3].

Fig. 1 illustrates the proximal tubule is divided into three segments: S1, S2, and S3. The S1 segment comprises the first half of the convoluted portion, while the S2 segment forms the second half. The S3 segment begins where the tubule straightens and extends into the loop of Henle. The majority of glucose reabsorption occurs in the S1 and S2 segments via both Sodium-dependent glucose cotransporter 1 (SGLT1) and GLUT2 transporters, while the remaining glucose is fully absorbed in the S3 segment by GLUT1.

The molecular structure of SGLT2 exists in five conformations, varying based on the stage of glucose transport, Na+ and glucose concentrations on both sides of the membrane, and the membrane voltage. The mechanisms underlying SGLT2-mediated glucose reabsorption can be divided into two stages, as illustrated in Fig. 2.

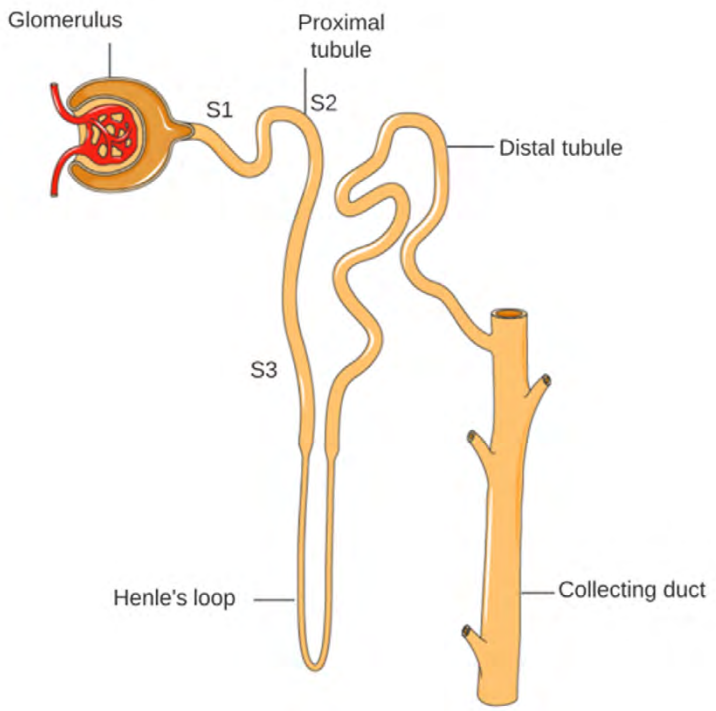

Fig. 1. Nephron structure (this figure is adapted from "Nephron" by Servier Medical Art, licensed under Creative Commons Attribution 3.0 Unported License [4], with modifications based on the text from References [5, 6]).

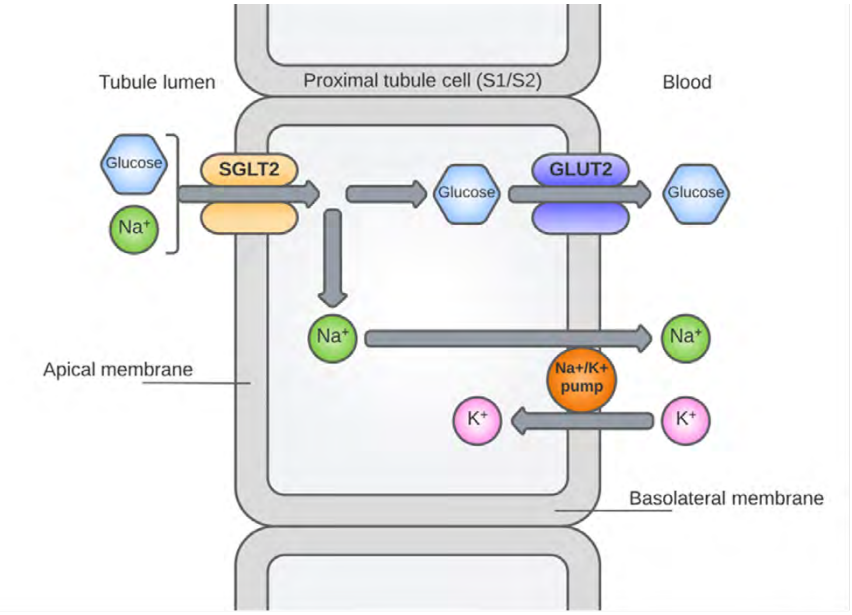

Fig. 2. Reabsorption of glucose in the proximal tubule (created based on References [1, 5]).

In the first stage, glucose is actively transported into the epithelial cells via the SGLT2 cotransporter. This leads to glucose accumulation, increasing the concentration gradient between the epithelial cell and plasma, which drives passive glucose efflux through GLUT2 transporters in the basolateral membrane, allowing glucose to re-enter the bloodstream (second stage). Sodium transport is regulated by the Na+/K+ pump in the basolateral membrane, which exchanges 3 sodium ions out of the cell for every 2 potassium ions entering.

Diabetes complications

Peripheral neuropathy is one of the most prevalent neurological conditions associated with type 2 diabetes mellitus, affecting 30–50% of diabetic patients, with 20–30% of cases being painful [7]. It predominantly affects individuals over 50 years old, as nerve degeneration requires time. In contrast, the prevalence in children under 20 years old with diabetes is lower, ranging from 7% in type 1 diabetes to 22% in type 2 diabetes [7].

Diabetic peripheral neuropathies (DPN) are classified into two groups: typical and atypical. Typical DPN includes sensory and motor neuropathies, characterized by chronic, slow progression, symmetric symptoms, and length-dependency [8]. This length-dependency primarily affects the longest nerves, contributing to complications like reduced vagal influence on the cardiac autonomic system [9] or plantar neuropathy in diabetic foot [10]. Atypical neuropathies, by contrast, lack these features; SGLT2i have shown effectiveness in improving glycemic control, which can reduce the severity of existing neuropathies and nerve palsies. However, the incidence of new neuropathies remains similar between the SGLT2i-treated and control groups (15.16% vs. 14.68%, with 334 and 323 cases, respectively) [11], While the protective effects of SGLT2i are

not consistent across all nerves, improvements in sensory and motor nerve conduction velocity have been documented [11]. Case studies have demonstrated that SGLT2i treatment successfully resolved oculomotor nerve palsy caused by uncontrolled hyperglycemia [12]. In diabetic rat studies, empagliflozin was shown to increase AMPK expression, suppressing MAPK phosphorylation, which is linked to nerve injury and targeted for neuropathic pain relief [13, 14]. Lee *et al.* demonstrated significant inhibition of hypersensitivity and preservation of neuronal function and intraepidermal nerve fiber density (IENFD) in rats treated with empagliflozin [15]. Additionally in Goto-Kakizaki rats Canagliflozin treatment improved IENFD and parasympathetic nerve density in pancreatic β-cell volume despite the absence of SGLT2 expression in these nerves, likely due to rapid glucose reduction. Despite these benefits, SGLT2i are not the primary treatment for neuropathy in T2DM, with Metformin being the most used drug in routine care and clinical trials [16]. It is worth noting that SGLT2 inhibitors are used to treat various forms of diabetes — including type 1, type 2, and mixed cases — which is an important consideration when selecting a medication for managing this diabetic complication [17].

Cardiac autonomic neuropathy and cardiovascular risk

Studies on the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) in T2DM have also included cardiac regulation. One major microvascular complication, cardiac autonomic neuropathy (CAN) [10], results from a decline in parasympathetic activity due to the pathologic atrophy of the vagus nerve, leading to sympathetic dominance [9]. Additionally, sympathetic activity is heavily regulated through afferent signals from the kidneys, where excessive glucose resorption in the proximal tubules activates renal afferent nerves, potentially causing central sympathetic hyperactivity with efferent sympathetic effects [18].

In one study, a 24-hour Holter ECG recorded a clinical group treated with SGLT2 inhibitors (n = 40; 58% empagliflozin, 42% dapagliflozin) for at least six months, compared with a control group. Results showed reduced SNS activity in the clinical group, suggesting a protective effect of SGLT2 inhibitors on the cardiac autonomic system [10]. Several studies, including the EMPA-REG OUTCOME and DECLARE-TIMI 58 trials, reported no increase in heart rate, further suggesting cardioprotection via lowered sympathetic activity [19]. The EMBODY trial compared the effects of empagliflozin versus placebo on patients with T2DM who had recently experienced an acute myocardial infarction [20]. This study analyzed two indicators of cardiac nervous system activity: heart rate variability and heart rate turbulence, both closely related to SNS and PNS function. Results indicated that empagliflozin treatment significantly decreased SNS activity while improving PNS function, thereby enhancing cardiac performance [20]. In addition to directly affecting nerve activity, SGLT2 inhibitors promote osmotic diuresis, reducing extracellular volume and lowering blood pressure [21]. Although this reduction in blood pressure should trigger homeostatic mechanisms that increase SNS activity and heart rate, this response does not occur, further supporting a decrease in SNS cardiac influence [22]. SGLT2 inhibitors have been shown to specifically reduce systolic blood pressure by an average of 2.46 mmHg and diastolic pressure by 1.46 mmHg, with 24-hour ambulatory systolic and diastolic blood pressure reductions of 3.76 mmHg and 1.83 mmHg, respectively [23, 24].

Recent studies have focused on the cardiac effects of SGLT2 inhibitors. Ang *et al.* analyzed CAN indicators in 45 participants with T2DM on metformin monotherapy [25]. The study found no significant difference in CAN measures between the group treated with dapagliflozin and those on

glimepiride, suggesting no major impact of SGLT2 inhibitors on CAN. A meta-analysis supported this finding, showing no effect on CAN indicators [26]. However, some case studies report that long-term use of SGLT2 inhibitors, such as Ipragliflozin, may reduce SNS influence on cardiac activity, offering cardioprotection in patients with chronic heart failure and T2DM. Nonetheless, the current body of research lacks sufficient statistical data to fully support this relationship, necessitating further investigation. This effect has only been verified in rat models, where metformin and pioglitazone had a beneficial impact on diabetic rats [27].

Other studies have noted empagliflozin's ability to reduce the risk of major cardiovascular incidents beyond its glucose-lowering mechanism [28], as well as its influence on reducing the risk of hospitalization for heart failure [29]. A study investigating the use of SGLT2 inhibitors in diabetic patients with atherosclerotic cardiovascular disease showed a decreased probability of major adverse cardiovascular events by 11%, a 23% reduction in the risk of cardiovascular death or heart failure hospitalization, and a 15% reduction in the risk of all-cause mortality [29]. Additionally, another study found that the reduction in hospitalization for heart failure is the most consistent benefit observed across most trials [30].

Recent clinical studies have clarified that SGLT2 inhibitors hold great potential in improving the unfavorable cardiac autonomic profile seen in T2DM — that predisposes individuals to arrhythmias, vaso-vagal syncope, and increased cardiovascular mortality. Of note, the SCAN study illustrated that in a prospective multicenter cohort of 324 type 2 diabetic patients treatment with SGLT2 inhibitors results in better glycemic control, reduced inflammatory markers, and significant improvements in cardiac autonomic indices — specifically, a lower low frequency/high frequency (LF/HF) ratio and a higher late heart-to-mediastinum ratio (H/Mlate) on 123I-MIBG scintigraphy. Notably, Cox regression analysis in this study identified an H/Mlate value of 0.710 (95% CI: 0.481–0.985) and SGLT2 inhibitor therapy with a hazard ratio of 0.550 (95% CI: 0.324–0.934) as independent predictors of reduced syncope recurrence over a 1-year follow-up period [31, 32].

In a companion trial, 24-week dapagliflozin treatment significantly improved HRV and heart rate turbulence parameters including an increase in SDNN by 8.79 ms ($p = 0.005$), SDANN, RMSSD, and pNN50 — as well as a reduction in the frequency of premature ventricular beats when compared to non-SGLT2 inhibitor oral antidiabetic therapies. It thus highlights the SGLT2 inhibitors' direct modulatory influence on cardiac autonomic function [33].

These findings are especially intriguing given that CAN is a common and prognostically dire complication of diabetes — its early manifestations often subclinical but progressively becoming apparent as resting tachycardia, reduced baroreflex sensitivity, and decreased parasympathetic activity, each of which has been strongly associated with significant adverse cardiovascular events and mortality with hazard ratios approaching 1.97, 1.89, and 1.77, respectively, as observed in large cohort analyses [34]. Additionally, whereas conventional CAN therapy has been based on multi-factorial interventions — from aggressive glycemic control, lifestyle intervention, and weight loss to pharmacological treatment with ACE inhibitors, β-blockers, and lipid-lowering agents — the new evidence suggests that SGLT2 inhibitors possess the singular capacity to mitigate sympathetic overactivity by lowering blood pressure without causing compensatory tachycardia and thus restoring autonomic balance [35].

Also, other cardiovascular complications noted in T2DM was worth to research in the context of SGLT2 inhibitors. A meta-analysis focused on arrhythmias found a strong association between reduced risk of atrial fibrillation and ventricular tachycardia and the use of SGLT2 inhibitors [36]. The use of SGLT2 inhibitors may also help prevent new-onset cardiac arrhythmias (NOA).

A population-based cohort study involving 399,810 patients newly diagnosed with T2DM showed that SGLT2 inhibitor use was associated with a 17% lower risk of these arrhythmias compared to non-users [37]. There is scientific evidence suggesting that the reduction in sympathetic nervous activity affecting the heart muscle is more pronounced in patients with T2DM and heart failure compared to those without heart issues (−20.2 ± 3.46 vs. −9.38 ± 3.65 bursts/100 heartbeats; $p = 0.049$) [38]. These findings further support the recommendation of SGLT2 inhibitors for treating T2DM with coexisting heart failure.

Although SGLT2 inhibitors offer numerous benefits, they are not without adverse effects. One notable side effect is the reduction in plasma volume and the alteration of compensatory mechanisms, which persist even years after treatment [39]. This effect is due to excess sodium and glucose in the renal proximal tubule, leading to homeostatic changes such as activation of the renin-angiotensin-aldosterone system, which is similar to increasing sympathetic activity [40]. This seems to contradict the previously mentioned direct effect of SGLT2 inhibitors on reducing cardiac sympathetic nervous system activity.

Collectively, these findings make a strong case for the inclusion of SGLT2 inhibitors in the treatment repertoire of diabetic subjects with CAN, as both metabolic regulation and a direct autonomic effect may ultimately lead to decreased cardiovascular morbidity and mortality.

Diabetic foot

As mentioned previously, peripheral neuropathy with nerve atrophy plays a critical role in the development of diabetic foot. This neuropathy involves sensory, motor, and autonomic dysfunctions. Sensory impairment can lead to repeated trauma, while decreased motor impulses cause muscle atrophy. Autonomic defects, such as excessive vasodilation, impaired thermoregulation, and anhidrosis, weaken affected areas. These factors contribute to increased susceptibility to wound formation and infection, raising the probability of complicated trauma.

Statistically, 20% of diabetic patients will require hospitalization due to foot ulcers, and prevention remains the most effective management strategy. Due to limited data, accurately assessing the effects of SGLT2 inhibitors on diabetic foot is challenging, particularly given the low number of recorded amputations, which introduces uncertainty [41]. Chang *et al.* [42] noted that SGLT2 inhibitors may significantly increase the risk of amputations, especially when compared to other treatment groups. In a separate study, Khouri *et al.* [43] suggested that this increased risk applies to canagliflozin, empagliflozin, and possibly dapagliflozin. However, the mechanism behind this association remains unclear and requires further research.

Conversely, several studies have found no correlation between SGLT2 inhibitor use and amputation risk. A study involving 714,582 individuals found that neither canagliflozin nor other SGLT2 inhibitors increased the risk of below-knee amputation. The meta-analytic hazard ratio for canagliflozin versus non-SGLT2 inhibitors was 0.75 (95% CI 0.40–1.41) in the on-treatment analysis and 1.01 (95% CI 0.93–1.10) in the intent-to-treat analysis [30]. Clinical trials assessing specific SGLT2 inhibitors, such as empagliflozin (EMPA-REG OUTCOME trial) and dapagliflozin (DECLARE-TIMI 58 trial), did not report an increased risk of amputation, though these evaluations were based on retrospective analyses [44]. Lin *et al.* suggested that the significant reductions in body weight and blood pressure associated with SGLT2 inhibitor use might elevate the risk of lower limb complications. Therefore, careful monitoring of these parameters may be necessary to ensure safe use of these medications [45].

Discussion

The pleiotropic properties of SGLT2 inhibitors are well-documented in cardiology and nephrology, where they exhibit both cardioprotective and nephroprotective effects [46–48]. Their therapeutic application continues to expand, with ongoing research into new fields [49]. One of the greatest advantages of SGLT2 inhibitors (flozins) is their exceptionally favorable safety profile. Moreover, they are structurally distinguishable from other compounds in immunoassays simultaneously providing minimal risk of adverse drug interactions in vivo [48–50]. Additionally, flozins, exhibit beneficial synergistic effects when used alongside other antidiabetic medications. Our study suggests that SGLT2 inhibitors may positively influence the nervous system through both direct and indirect pathways. This opens the possibility for their use in managing certain neurological conditions.

The most apparent benefit of SGLT2 inhibitors is their ability to reduce elevated glucose levels. These drugs were initially designed to lower blood glucose in diabetes patients by increasing renal excretion, and their effectiveness in this role has been extensively validated [51]. While glucose reduction alone is beneficial for neuronal health, SGLT2 inhibitors also exert broader effects on the nervous system, interacting with molecular targets and affecting various proteins that support neural integrity. A growing body of evidence links diabetes mellitus with an increased risk of neurological disorders [52, 53]. However, the guidelines do state that SGLT2 inhibitors should be considered for all patients with type 2 diabetes, and should be offered to those individuals with higher cardiovascular risk, or whose cardiovascular risk increases over time, or for patients with an albumin-to-creatinine ratio over 30 mg/mmol [54]. In turn, the American Diabetes Association (ADA) shares a similar point of view with NICE regarding the use of SGLT2 inhibitors in managing diabetes-related conditions such as atherosclerotic cardiovascular disease, indicators of high cardiovascular risk, heart failure, or chronic kidney disease.

The ADA guidelines also refer to the increased prevalence of Alzheimer's disease among diabetic patients but note that clinical trials with cholinesterase inhibitors and glutamatergic antagonists have not shown positive therapeutic benefits in maintaining or significantly improving cognitive function. Intranasal insulin therapy as well as metformin therapy were found to be potentially beneficial in a pilot study, providing insight for future clinical trials and mechanistic studies [55].

Despite the promising benefits, SGLT2i are not without adverse effects, such as plasma volume reduction and alterations in compensatory mechanisms, which necessitate careful patient monitoring. The current body of evidence supports the use of SGLT2i as a valuable adjunct in the comprehensive management of T2DM, particularly for patients with elevated cardiovascular risk. Nevertheless, more extensive clinical trials and long-term studies are essential to fully elucidate the mechanisms, optimize therapeutic strategies and ensure the safety of SGLT2i in diverse patient populations.

Conclusion

SGLT2i offer substantial benefits in the management of type 2 diabetes mellitus by effectively reducing blood glucose levels and minimizing diabetic complications. Their neuroprotective effects on peripheral and cardiac autonomic neuropathies, along with cardioprotective properties that lower the risk of heart failure and arrhythmias, position SGLT2i as critical agents in comprehensive diabetes care. Additionally, the potential role of SGLT2i in preventing diabetic retinopathy and mitigating oxidative stress further expands their therapeutic utility. However, the association between SGLT2i and diabetic foot complications requires further investigation to ensure patient

safety. Overall, SGLT2 inhibitors represent a promising multifaceted approach to managing both metabolic and cardiovascular aspects of type 2 diabetes, warranting continued research to fully harness their potential and address existing uncertainties.

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Conflict of interest

None declared.

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