https://doi.org/10.31925/farmacia.2026.2.2 **REVIEW**

COMPARISON OF EFFICACY OF SGLT2 INHIBITORS AND GCRA ANTAGONISTS IN CARDIOVASCULAR AND RENAL OUTCOMES FOR PATIENTS WITH DIABETIC NEPHROPATHY: A META-ANALYSIS

DAN ZHANG, YANYAN WU *

Department of Endocrinology, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui Municipal Central Hospital, Lishui, 323000, Zhejiang, China

**corresponding author: wuyanyanzj@yeah.net*

Manuscript received: December 2025

Abstract

This meta-analysis evaluated the effects of sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on major adverse cardiovascular events (MACE) and renal outcomes in patients with diabetic nephropathy (DN). A systematic search of Embase, PubMed, MEDLINE, and Web of Science identified relevant studies published up to February 2024. Eligible trials comparing SGLT2 inhibitors or GLP-1 RAs with control therapies were analyzed using RevMan 5.3. Thirteen studies involving 69,754 patients with diabetes and impaired renal function were included. SGLT2 inhibitors significantly reduced the risk of MACE, cardiovascular death, fatal or non-fatal myocardial infarction, stroke, and composite renal outcomes compared with controls. GLP-1 RAs also lowered MACE, cardiovascular death, and stroke risk, although no significant benefit was observed for myocardial infarction or renal composite endpoints. Safety analysis showed no significant differences in urinary tract infections *versus* controls; however, SGLT2 inhibitors were associated with a higher risk of severe hypoglycemia, while GLP-1 RAs showed no notable safety concerns. Overall, both drug classes demonstrate cardiovascular benefits in DN, and treatment selection should be individualized according to patient characteristics and clinical context.

Rezumat

Studiul a evaluat efectele inhibitorilor co-transportorului sodiu–glucoză de tip 2 (SGLT2) și ale agoniștilor receptorilor glucagon-like peptide-1 (GLP-1 RA) asupra evenimentelor cardiovasculare adverse majore (MACE) și asupra efectelor renale la pacienții cu nefropatie diabetică (ND). O căutare sistematică în Embase, PubMed, MEDLINE și Web of Science a identificat studii relevante publicate până în februarie 2024. Studiile eligibile care comparau inhibitorii SGLT2 sau agoniștii GLP-1 RA cu terapii de control au fost analizate utilizând RevMan 5.3. Au fost incluse treisprezece studii, însumând 69.754 de pacienți cu diabet și funcție renală afectată. Inhibitorii SGLT2 au redus semnificativ riscul de MACE, deces cardiovascular, infarct miocardic fatal sau non-fatal, accident vascular cerebral și rezultatele renale compozite comparativ cu grupul de control. Agoniștii GLP-1 RA au redus, de asemenea, riscul de MACE, deces cardiovascular și accident vascular cerebral, însă fără beneficii semnificative asupra infarctului miocardic sau rezultatelor renale compozite. Analiza siguranței nu a evidențiat diferențe privind infecțiile urinare; totuși, inhibitorii SGLT2 au fost asociați cu un risc mai mare de hipoglicemie severă. Alegerea terapiei trebuie individualizată în funcție de caracteristicile pacientului și contextul clinic.

Keywords: sodium-glucose cotransporter 2, glucagon-like peptide-1 receptor agonists, meta-analysis, cardiovascular outcomes, renal outcome

Introduction

Diabetic nephropathy (DN) stands as a prevalent and severe complication among individuals with diabetes, showcasing an escalating annual incidence and posing a substantial threat to both the quality of life and overall health of affected patients. The World Health Organization (WHO) reports indicate that diabetes has evolved into a global epidemic. Projections estimate that by 2030, the diabetic population will soar to 440 million, with approximately one-third of them encountering kidney impairment (1, 2). In the realm of advancing medical technology, the emphasis of diabetes treatment has transcended mere glycemic control. A renewed focus has emerged, emphasizing the development of strategies to safeguard cardiovascular health and renal function, with the ultimate goal of enhancing the overall quality of life.

The Sodium-glucose cotransporter 2 (SGLT2) is a membrane protein located in the proximal tubules S1 and S2 segments of the kidneys, attracting widespread attention in diabetes treatment (3). The primary function of SGLT2 is to reabsorb glucose in the renal tubules, accounting for approximately 90% of tubular

glucose reabsorption (4, 5). Under normal circumstances, SGLT2 reabsorbs filtered glucose from the urine back into the bloodstream, maintaining stable blood glucose levels. Due to its mechanism of action leading to urinary glucose excretion, SGLT2 inhibitors can also induce mild diuresis, contributing to blood pressure reduction (6, 7). Research suggests that SGLT2 inhibitors may have cardiovascular protective effects, reducing the incidence of cardiovascular events (8). Additionally, SGLT2 inhibitors can slow down the development of kidney dysfunction and lower mortality rates in diabetic patients (9). Currently used SGLT2 inhibitors in clinical practice include empagliflozin, dapagliflozin, and canagliflozin, among others.

GCRAs refer to glucagon-like peptide-1 (GLP-1) receptor agonists, a prevalent class of medications employed in diabetes management. These medications mimic the physiological roles of GLP-1 by activating GLP-1 receptors to lower hypoglycemia (10). GLP-1 stands as a peptide hormone secreted by enteroendocrine cells in the intestines, released into the bloodstream after meals, promoting insulin secretion, inhibiting glucagon secretion, and thus reducing hypoglycemic levels (11, 12). Studies suggest that GCRA antagonists exhibit positive effects on cardiovascular risk factors, such as reducing blood pressure and enhancing lipid metabolism (13). By increasing GLP-1 levels, these drugs can lead to arterial dilation and improvement in endothelial function, thereby reducing the incidence of cardiovascular events. Moreover, GCRAs may also exert direct protective effects on the myocardium and glomerulus (14). Studies suggest that GLP-1 RAs can reduce apoptosis of myocardial cells, promote the proliferation and regeneration of myocardial cells, thereby improving myocardial structure and function (15). Additionally, GLP-1 RAs can reduce the hyperfiltration state of glomeruli, alleviate pressure on glomerular capillaries, and thus slow down the progression of DN (16, 17). Commonly used GCRAs in clinical practice include exenatide, liraglutide, exenatide long-acting formulation, liraglutide long-acting formulation, and dulaglutide, among others.

This work is intended to comprehensively assess the impact of SGLT2 inhibitors and GCRAs on cardiovascular events and renal function in DN patients through a meta-analysis. The objective was to yield more accurate and reliable guidance for clinical practice, assisting healthcare professionals and patients in making more informed treatment decisions.

Materials and Methods

Literature searching. Relevant literature on the studies regarding the impact of SGLT2 inhibitors and GCRAs on cardiovascular and renal outcomes in DN patients was retrieved from databases such as Embase, PubMed, MEDLINE, and WoS, up to February 2024, through computer searches. The search words were set as SGLT2, GCRA, GLP-1 receptor agonists, diabetes, empagliflozin, canagliflozin, exenatide, liraglutide, Heart failure, Myocardial infarction, Stroke, Cardiovascular mortality, lixisenatide, semaglutide, albiglutide, dulaglutide, ipragliflozin, tofogliflozin, and randomized controlled trial. Actually, all these studies screened had to be published from the establishment of the database up to February 2024.

Research types. The included experimental methods comprised studies relevant to randomized controlled trials investigating SGLT2 inhibitors and GCRAs in DN patients. There were no language restrictions for the publications.

Study participants. The study participants needed to meet the following criteria simultaneously: (1) aged 18 years or older; (2) definitively diagnosed with diabetes and concomitant compromised renal function, meaning they met the WHO's diagnostic criteria for diabetes while having an estimated glomerular filtration rate (eGFR) less than 90 mL/min/1.73 m^2 (18, 19).

Interventions. The experimental group received treatment with SGLT2 inhibitors or GCRAs, including but not limited to empagliflozin, dapagliflozin, canagliflozin, dulaglutide, and ipragliflozin. The control group patients were administered a placebo or other antidiabetic medications. The duration of treatment was not restricted, and the method of drug administration was not specified.

Outcome indicators. Cardiovascular outcomes: They primarily included major adverse cardiovascular events (MACE), fatal myocardial infarction (FMI) and non-fatal myocardial infarction (NFMI), fatal stroke (FS) and non-fatal stroke (NFS), as well as cardiovascular death (CVD); Renal outcomes: The involved indicators were renal composite outcomes, which were eGFR reduction > 40% and renal death; Safety outcomes: The severe hypoglycemia and urinary tract infections of patients were counted.

Literature screening. Literature review and screening were independently implemented by two researchers. Non-randomized controlled trials were eliminated by reviewing their titles and abstracts. A rigorous examination and screening of the full text of the literature were carried out based on the criteria mentioned below, which were outlined below.

Studies enrolled in this work had to satisfy all the following conditions: (1) conformity to a randomized controlled trial; (2) study participants aged 18 or older and meeting the WHO's diagnostic criteria for diabetes with an eGFR less than 90 mL/min/1.73 m^2; and (3) inclusion of at least one outcome measure.

Studies with any of following conditions had to be excluded: (1) studies designed as non-randomized controlled trials, including cross-sectional studies,

retrospective analyses, case reports, empirical summaries, conference records, review articles, and other types of literature, such as meta-analyses; (2) inability to access complete original data or difficulty in data extraction; and (3) duplicate literature. The selected literature and data were cross-verified, and for any disputed literature, decisions on inclusion in this work were made through discussion or seeking the opinion of a third researcher.

Procedures for extracting required data. Required data from the encompassed literature were extracted, and cross-verification was conducted. The specific information extracted included: (1) baseline information, comprising basic details of the included literature (publication year, authors, intervention time, and intervention measures), baseline information of study participants (age, gender, and sample size), and outcome measures (cardiovascular, renal, and safety outcomes).

Procedures for assessing the literature quality. Evaluating the quality of literature and assessing bias is crucial for enhancing the persuasiveness and credibility of meta-analysis results. By including studies with high quality and low risk of bias in the meta-analysis, the impact of systematic bias can be reduced, improving the accuracy and stability of the comprehensive analysis and providing more reliable evidence to support clinical practice and policy formulation.

In this work, the quality of eligible studies was independently assessed by two authors using Cochrane's risk of bias assessment tool (20). The Cochrane risk of bias tool included the following domains: (1) random sequence generation, (2) allocation concealment, (3) completeness of outcome data, (4) selective reporting, (5) reporting bias, and (6) other bias. The assessment results were categorized as low- and high-risk or unclear risk in the context of insufficient information or uncertainty about the potential for bias. When the results of the two researchers differed, the two researchers would reach a consensus through discussion.

Statistical analysis. The final data from the enrolled randomized controlled trials were subjected to an analysis using RevMan 5.3. Counts data were analyzed for effectiveness statistics using hazard ratios (HR) or risk ratios (RR), and measurement data were analyzed using mean differences (MD). All results were presented with 95% confidence intervals (CI). Heterogeneity analysis was conducted during the analysis: when $I^2 = 0\%$, indicating no result heterogeneity, a fixed-effects model was applied for consistent findings. When $50\% > I^2 > 0\%$, indicating low study heterogeneity, a fixed-effects model was also applied. When $I^2 \geq 50\%$, indicating high heterogeneity, data were not suitable for simple pooling, and consideration of a random-effects model for meta-analysis might be necessary. Funnel plots were generated for the corresponding data, and data bias in the literature was judged based on the symmetry of the Funnel plots.

Results and Discussion

Literature selection. Through the retrieval methods mentioned earlier, 3,325 relevant articles were identified in this work. Among them, 1,294 articles were retrieved from the Embase, 793 from PubMed, 652 from MEDLINE, and 586 from the WoS. After applying the criteria given in section 2.3 and removing duplicate articles (926), screening titles and abstracts for relevance to randomized controlled trial experiments, and the main theme resulted in the exclusion of 2,032 articles. Following a detailed examination of the full text, 348 literature were further excluded. After cross-verification, 13 articles were ultimately enrolled. The above procedures are illustrated in Figure 1.

Basic features of literature finally analysed

The final set of 13 enrolled articles was as follows: Carol 2019 (21), George 2018 (22), Masakazu 2016 (23), Russell 2018 (24), Gerstein 2019 (25), Hernandez 2018 (26), Holman 2017 (27), Husain 2019 (28), Pfeffer 2015 (29), Brendon 2018 (30), Christonph 2016 (31), Deepak 2021 (32), and Perkovic 2019 (33). In total, 69,754 patients with diabetes and compromised renal function were included, with observation periods ranging from 24 weeks to 8 years. Relevant information of these studies is detailed and provided in Table I.

Risk of bias

The risk assessment results for the enrolled 13 articles were depicted in Figures 2 and 3. All 13 articles were randomized controlled trial studies, with two of them showing a high risk of incomplete outcomes, and some exhibited biases in randomization methods and allocation concealment. However, overall, they were of high quality

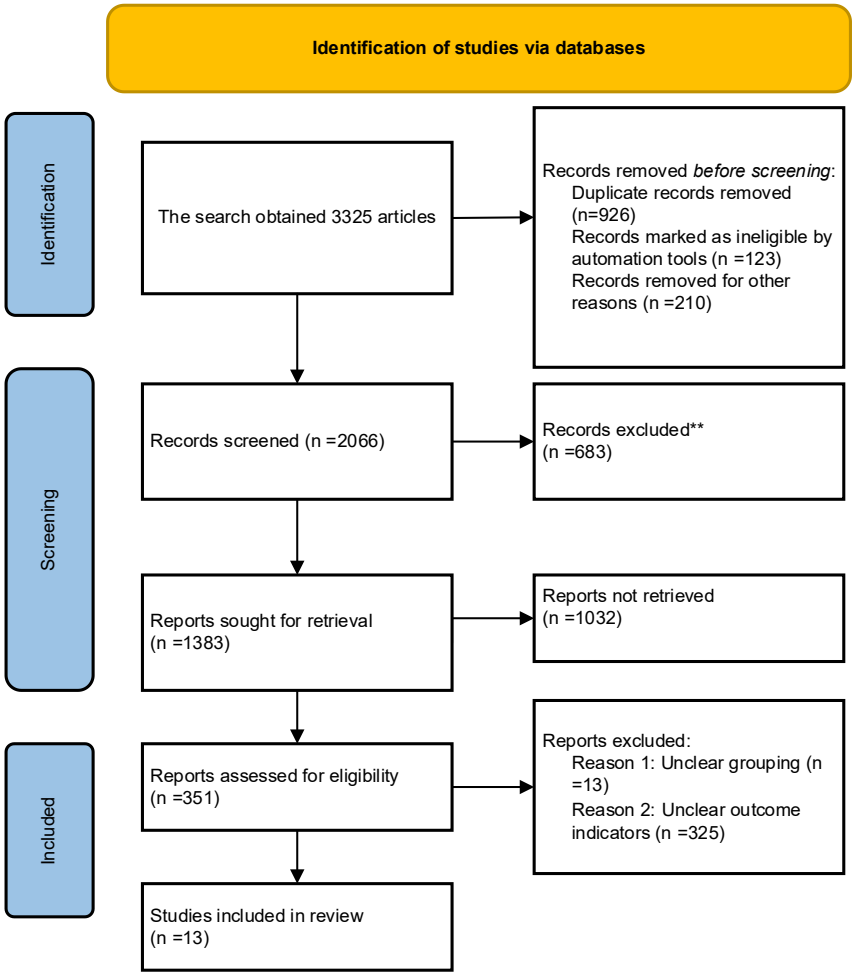

Figure 1.
Procedures for literature screening

Table I
Basic features of literature

Study	Year	Number of cases		Interventions		Outcomes
		Experimental group	Control group	Experimental group	Control group	
Carol (21)	2019	145	148	10 mg dapagliflozin	Placebo	⑥, ⑦
George (22)	2018	313	154	5 ~ 15 mg ertuglifozin	Placebo	⑥, ⑦
Masakazu (23)	2016	95	50	2.5 mg luseogliflozin	Placebo	⑥, ⑦
Russell (24)	2018	306	307	5 mg dapagliflozin	100 mg sitagliptin	⑦
Gerstein (25)	2019	4949	4952	1.5 mg dulaglutide	Placebo	①, ②, ③, ④, ⑤, ⑥, ⑦
Hernandez (26)	2018	4714	4715	30 ~ 50 mg abirutide	Placebo	①, ②, ③, ④, ⑤, ⑥, ⑦
Holman (27)	2017	7344	7372	2.0 mg exenatide	Placebo	①, ②, ③, ④, ⑤, ⑥
Husain (28)	2019	1591	1592	14 mg semaglutide	Placebo	①, ②, ③, ④, ⑤, ⑥, ⑦
Pfeffer (29)	2015	3031	3032	10 ~ 20 μg lisicenatide	Placebo	⑥, ⑦
Brendon (30)	2018	3846	3845	25 mg ertugliflozin	Placebo /100 mg canagliflozin	①, ②, ③, ④, ⑤
Christonph (31)	2016	1498	752	10 ~ 25 mg ertugliflozin	Placebo	①, ②, ③, ④, ⑤
Deepak (32)	2021	5292	5292	200 mg sotagliflozin	Placebo	①, ②, ③, ④, ⑤
Perkovic (33)	2019	2220	2199	100 mg canagliflozin	Placebo	①, ②, ③, ④, ⑤

Note: ①: MACE; ②: CVD rate; ③: FMI and NFMI; ④: FS and NFS; ⑤: rental outcomes; ⑥: severe hypoglycemia; ⑦: urinary tract infections.

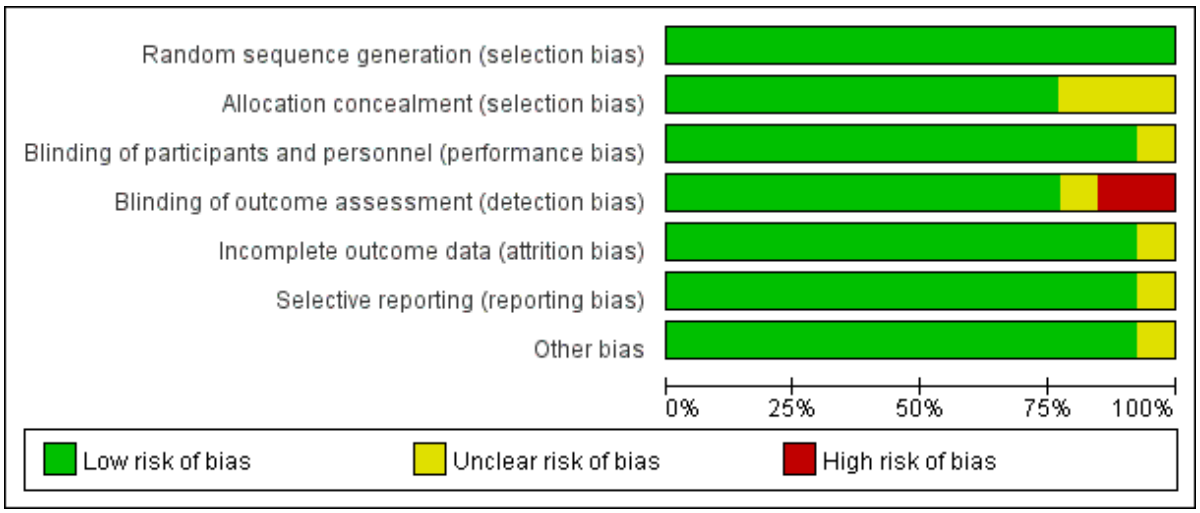

Figure 2.
Bar diagram for risk of bias

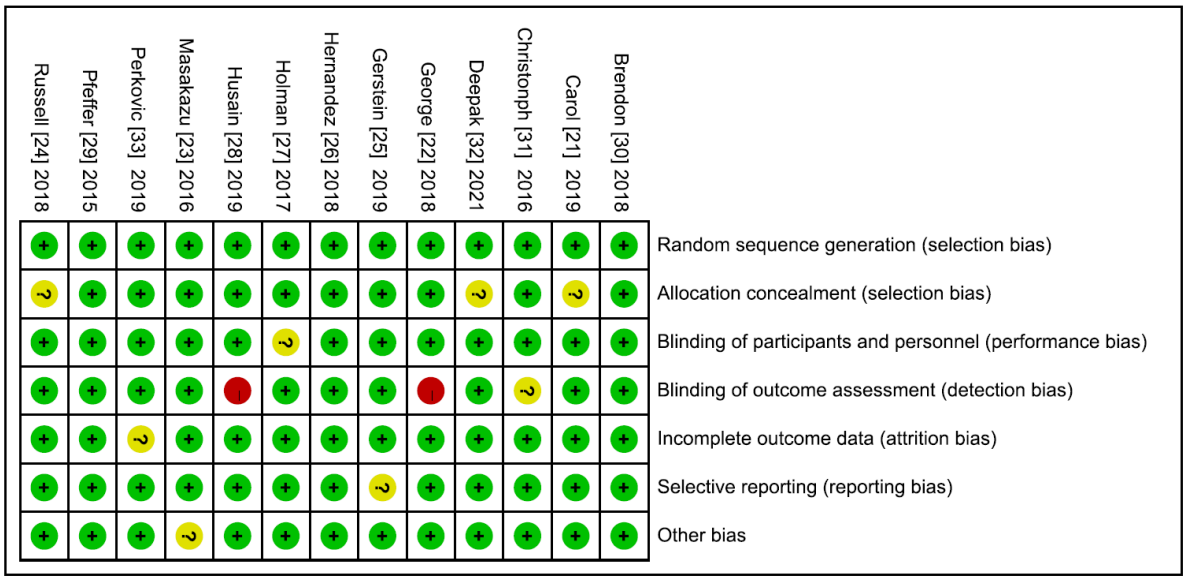

Figure 3.
Evaluation chart for risk of bias

Cardiovascular outcomes

It compiled data from four articles regarding the influence of SGLT2 inhibitors on cardiovascular outcomes in this work, with the results presented in Figure 4. Among these four articles (30-33) reporting the influence on MACE, with an I^2 of 18%, indicating no remarkable heterogeneity. It was concluded that SGLT2 inhibitors effectively reduce the MACE risk in patients, with a RR of 0.72 [95% CI (0.68, 0.78), $p < 0.00001$], showing remarkable significance. For the four articles (30-33) reporting the impact on CVD, with an I^2 of 0%, indicating no heterogeneity, the results revealed that SGLT2 inhibitors can effectively lower the CVD risk in patients. The corresponding RR reached 0.72 [95% CI (0.68, 0.77), $p < 0.00001$], so the significance was substantial. In the three articles (30, 32, 33) reporting the influence on FMI and NFMI, with an I^2 of 0%, indicating no heterogeneity. It was concluded that SGLT2 inhibitors effectively reduce the FMI and NFMI risk in patients, with a RR of 0.74 [95% CI (0.68, 0.80), $p < 0.00001$], showing remarkable significance. For three articles (30, 32, 33) reporting the impact on FS and NFS, with an I^2 of 0 %, suggesting no heterogeneity. It was concluded that SGLT2 inhibitors effectively reduce the FS and NFS risk in patients, with a RR of 0.77 [95% CI (0.70, 0.85), $p < 0.00001$].

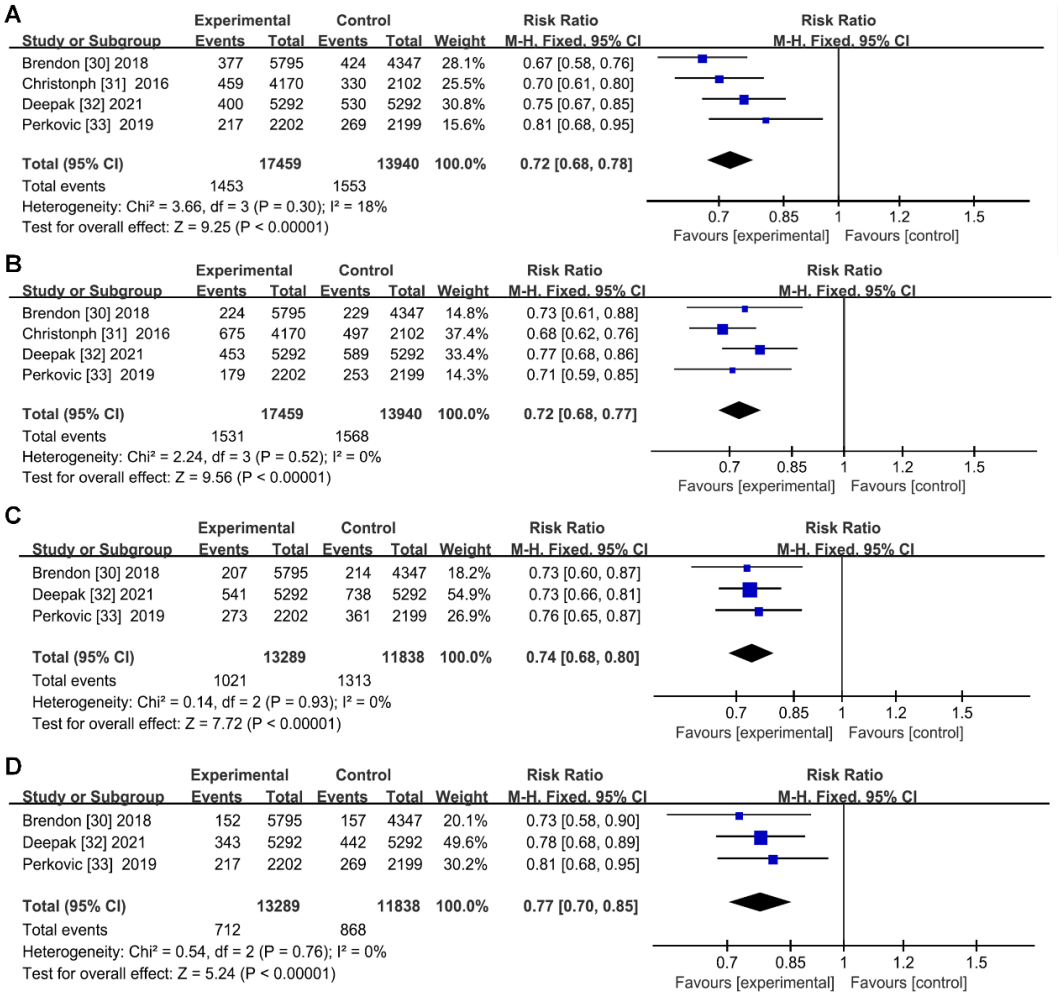

Figure 4.
Forest diagram for cardiovascular outcomes in the SGLT2 inhibitor and control group (A: MACE; B: CVD; C: FMI and NMI; D: FS and NFS)

The analysis of GCRAs on cardiovascular outcomes of patients in this work included four articles (25-28), with the results illustrated in Figure 5. The impact on MACE was as follows: the heterogeneity test $I^2 = 31\%$ ($P = 0.22$), using a fixed-effects model. The findings indicated that GCRAs can effectively reduce the MACE risk in patients, with RR = 0.89 [95% CI (0.84, 0.94), $p < 0.0001$], demonstrating a remarkable significance. For the impact on CVD, with $I^2 = 18\%$ ($p = 0.30$), there existed heterogeneity, and a fixed-effects model was applicable. The observations signified that GCRAs can effectively lower the CVD risk in patients, with RR = 0.80 [95% CI (0.82, 0.98), $p = 0.02$], demonstrating an obvious difference. In the statistics on FMI and NFMI, with $I^2 = 59\%$ ($p = 0.06$), there existed heterogeneity, so the following analysis was conducted using a fixed-effects model. The findings indicate that GCRAs do not substantially differ from the condition in the control group in reducing the possibility of MACE, with RR = 0.94 [95% CI (0.80, 1.10), $p = 0.17$]. For the impact on FS and NFS, where the heterogeneity test exhibited $I^2 = 0\%$ ($p = 0.84$), there was no heterogeneity. It implies that GCRAs can effectively reduce the potential of FS and NFS, with RR = 0.83 [95% CI (0.73, 0.93), $p < 0.002$], demonstrating a considerable difference or significance.

Renal outcomes

This work enrolled 8 articles (25-28, 30-33) for the statistical analysis of the renal outcomes associated with SGLT2 inhibitors and GCRAs in comparison to the control group, as explicated in Figure 6. The heterogeneity test for both groups showed an I^2 value of 78%. In the SGLT2 inhibitor group, the risk of renal outcomes compared to the control group exhibited RR = 0.57 [95% CI (0.39, 0.83), $p < 0.00001$], indicating a remarkable significance. On the other hand, in the GCRA group, the risk of renal outcomes relative to the control group reflected RR = 1.04 [95% CI (0.87, 1.24), $p = 0.069$], but the difference was not pivotal. This suggests that GCRAs may be more suitable for patients with poorer baseline renal conditions.

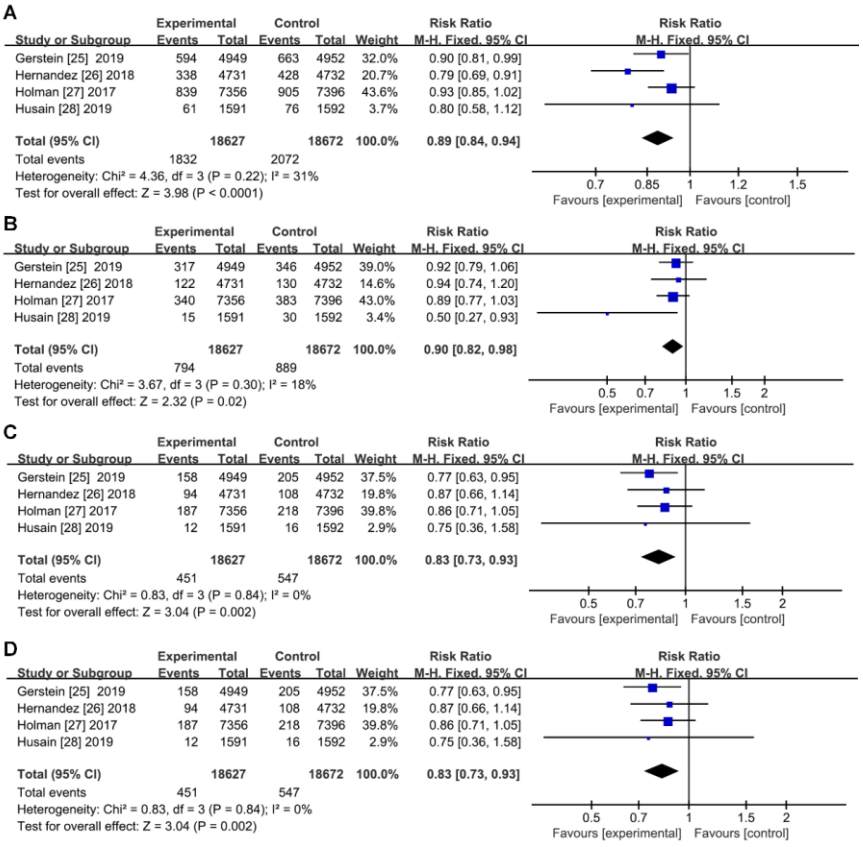

Figure 5.

Forest diagram for cardiovascular outcomes in the GCRAs and control groups (A: MACE; B: CVD; C: FMI and NMI; D: FS and NFS)

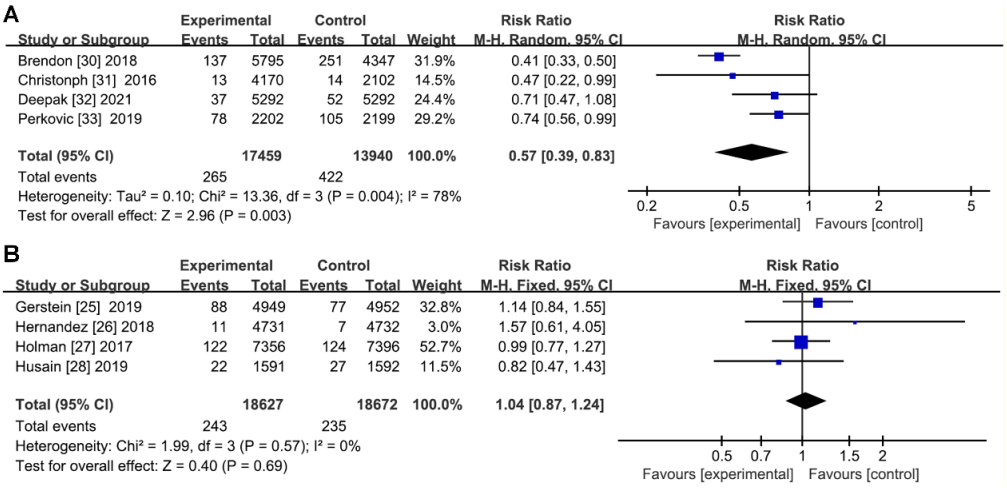

Figure 6.

Forest diagram of renal outcomes (A: SGLT2 inhibitor and control groups; B: GCRA and control groups)

Severe hypoglycemia

Eight articles (21-23, 25-29) analysing and comparing the incidence of severe hypoglycemia between the SGLT2 inhibitor and GCRA groups and the control group were enrolled in this work. The results, as explicated in Figure 7, indicated that the SGLT2 inhibitor group had a heterogeneity test with $I^2 = 66\%$ ($p = 0.02$). The risk of severe hypoglycemia in the SGLT2 inhibitor group relative to the control group exhibited RR = 0.81 [95% CI (0.62, 1.06, $p = 0.006$], exhibiting an obvious significance. In contrast, the GCRA group showed no heterogeneity ($I^2 = 0\%$, $p = 0.38$). The risk of severe hypoglycemia in the GCRA group relative to the control group demonstrated RR = 1.06 [95% CI (0.83, 1.34), $p = 0.65$], exhibiting no visible significance. This suggests that the use of SGLT2 inhibitors is more likely to lead to severe hypoglycemia.

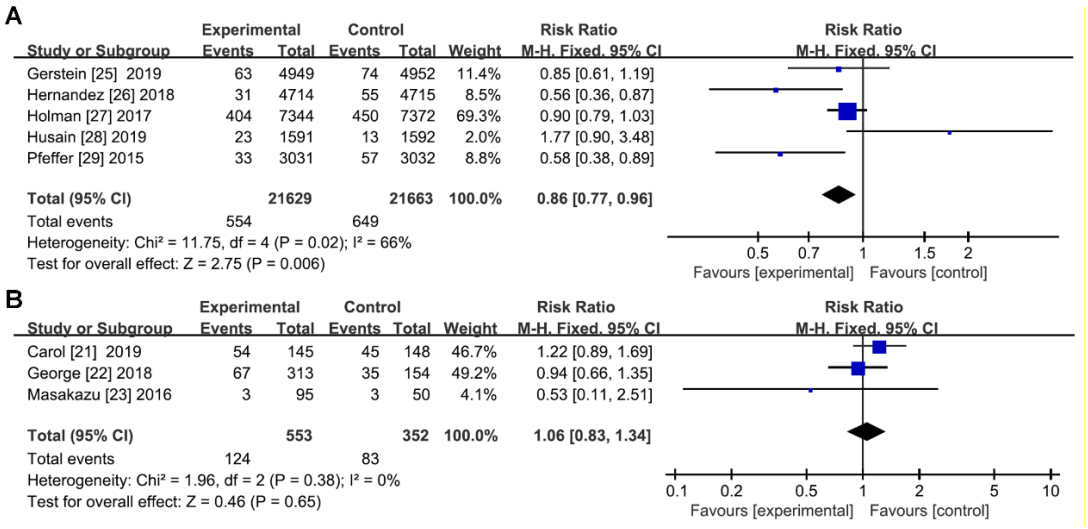

Figure 7.

Forest diagram of severe hypoglycemia (A: SGLT2 inhibitor and control groups; B: GCRA and control groups)

Urinary tract infections

The analysis on urinary tract infections was conducted in this work based on data extracted from 7 selected publications (21-26, 28), comparing the occurrence of urinary tract infections between the SGLT2 inhibitor and GCRA groups with that in the control group. The results, presented in Figure 8, indicated that the SGLT2 inhibitor group exhibited no heterogeneity (I^2 = 0%, p = 0.94). The possibility of urinary tract infections in the SGLT2 inhibitor group, in contrast to the control group, demonstrated RR = 0.89 [95% CI (0.79, 1.01), p = 0.07], with no marked significance observed. The GCRA group displayed some heterogeneity (I^2 = 45%, p = 0.14), and the risk of urinary tract infections in this group, in comparison to the control group, demonstrated RR = 0.89 [95% CI (0.57, 1.39), p = 0.62], also showing no substantial significance.

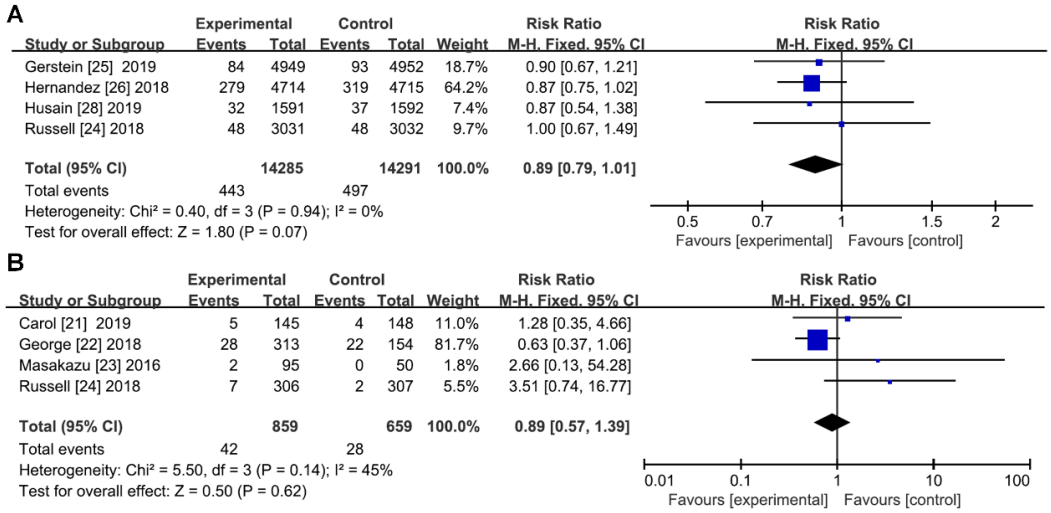

Figure 8.

Forest diagram of urinary tract infections (A: SGLT2 inhibitor and control groups; B: GCRA and control groups)

Publication bias

The Funnel plot for the included literature in the outcome indicators was generated using Revman 5.3, as illustrated in Figure 9, to assess publication bias. The symmetrical appearance on both sides of the Funnel plot suggests that the likelihood of publication bias was not influenced by the size of the effect, and no deviation of results from small-sample studies was observed at the bottom of the analyzed effect. This implies that the selected literature showed no obvious publication bias.

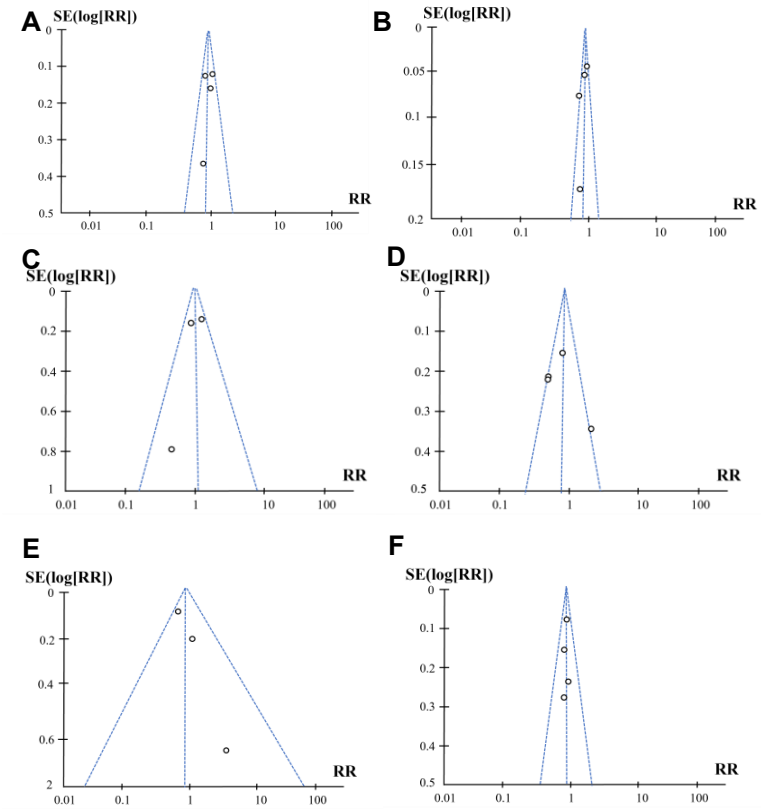

Figure 9.

Funnel plot for publication bias (A and B: renal outcomes in the SGLT2 inhibitor and GCRA groups, respectively; C and D: severe hypoglycemia in the SGLT2 inhibitor and GCRA groups, respectively; E and F: urinary tract infections in the SGLT2 inhibitor and GCRA groups, respectively)

Diabetic nephropathy is one of the most frequent complications in diabetic patients, severely affecting their quality of life and prognosis. In recent years, there has been considerable attention on cardiovascular and renal protective therapies for DN patients. Among these therapeutic approaches, SGLT2 inhibitors and GLP-1 receptor agonists are considered to have potential cardiovascular and renal protective effects. This work analyzed the impact of SGLT2 inhibitors and GLP-1 receptor agonists on cardiovascular and renal outcomes in diabetic patients.

The statistical results of this work demonstrated that SGLT2 inhibitors exert a remarkable effect in reducing cardiovascular events and CVD risk in diabetic patients. The mechanism of action includes lowering blood glucose levels, reducing cardiac workload, and possessing anti-inflammatory and antioxidant effects (34-36). By promoting the excretion of glucose through the kidneys, SGLT2 inhibitors lower blood glucose levels, mitigating the adverse effects of hyperglycemia on the cardiovascular system. Additionally, their diuretic effect leads to a reduction in blood volume, thereby alleviating cardiac workload. Moreover, SGLT2 inhibitors are believed to have anti-inflammatory and antioxidant effects. Studies have shown that they can reduce the production of inflammatory factors and alleviate oxidative stress reactions, thus protecting cardiovascular health (37). These interactions make SGLT2 inhibitors one of the important choices for cardiovascular protection therapy in DN patients. Regarding GCRA, studies also indicate their significant effectiveness in reducing cardiovascular events and CVD in patients. GCRA mimics the physiological effects of GLP-1 by promoting insulin secretion and inhibiting glucagon secretion to lower blood glucose levels, reducing the adverse effects of hyperglycemia on the cardiovascular system (38). Furthermore, activation of GLP-1 receptors has various positive effects on the cardiovascular system, including lowering blood pressure, improving lipid metabolism, and inhibiting endothelial cell proliferation, thereby reducing the progression of atherosclerosis and the risk of cardiovascular events (39). Additionally, GCRA antagonists also exert cardiovascular protective effects by reducing inflammatory responses and oxidative stress. Considering the interactions of these mechanisms, GCRA antagonists are crucial in cardiovascular protection, providing effective cardiovascular protection for diabetic patients.

Regarding the impact of SGLT2 inhibitors and GCRA on renal outcomes in diabetic patients, research indicates that SGLT2 inhibitors show a decreased risk of renal composite outcomes, while the

effect of GCRA in this regard is not significant. Mechanistically, SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion, which may lead to a series of kidney-related effects. Although a hyperglycemic state is damaging to the kidneys, the excretion of large amounts of glucose into the urine with SGLT2 inhibitors may increase the workload on the glomeruli, thus exerting additional pressure on the kidneys. This excessive workload may result in changes in glomerular filtration rate, damage to glomerular capillaries, and alterations in tubular function, ultimately leading to adverse changes in renal structure and function (40). The diuretic effect of SGLT2 inhibitors may lead to a decrease in blood volume and renal perfusion pressure. While moderate diuresis can alleviate blood volume overload, excessive diuresis may lead to inadequate effective blood volume, affecting renal perfusion and oxygen supply. Long-term use may increase the risk of renal composite outcomes. SGLT2 primarily acts in the S1 segment of the renal tubules, but its mechanism of action may have effects on other segments of the renal tubules, including reabsorption and secretion functions (41). These effects may lead to changes in tubular function, thereby affecting renal health and function. In contrast, the mechanism of action of GCRA does not involve influencing glomerular load or tubular function, thus not exerting additional negative effects on renal structure and function. In clinical practice, physicians need to consider the patient's renal status and risks fully when choosing treatment regimens and closely monitor changes in renal function.

Due to the mechanism of SGLT2 inhibitors, which reduce glucose reabsorption in the kidneys and increase urinary glucose excretion, blood glucose levels are lowered. However, since this mechanism does not depend on insulin, it can potentially lead to hypoglycemia, even in diabetic patients. Additionally, SGLT2 inhibitors may also affect insulin secretion and action. Research has confirmed that SGLT2 inhibitors increase the GLP-1 levels, promote insulin secretion, and enhance tissue sensitivity to insulin, further lowering blood glucose levels and increasing the risk of hypoglycemia (42). Therefore, close monitoring of blood glucose levels is necessary when using these drugs to treat DN, and medication doses and monitoring frequency should be adjusted according to the patient's condition to reduce the risk of hypoglycemia. In contrast, compared to insulin, GLP-1 has a relatively minor impact on hypoglycemia, making the use of GCRA less likely to induce hypoglycemia. Furthermore, GCRAs typically have shorter half-lives and dose-dependent effects, meaning their duration of action in the body is relatively short, and the extent of their effects is dose-dependent (43). Therefore, even if patients experience some degree of blood glucose reduction, the effects of GCRAs tend to diminish gradually over a short period, reducing the risk of severe hypoglycemia. Consequently, in treating DN patients, GCRA may be a relatively safer option, especially in populations at higher risk of hypoglycemia. This study also found that the use of SGLT2 inhibitors increases the occurrence of severe hypoglycemia, while the risk is lower with GLP-1 receptor agonists.

This work also found that neither of the two drugs showed a significant increase in the risk of urinary tract infections in DN patients. SGLT2 inhibitors lower the reabsorption of glucose in the renal tubules, leading to the excretion of a large amount of glucose in the urine. This increases the concentration of glucose in the urine, improving its osmolality and reducing the conditions for bacterial growth in the urinary tract. Furthermore, the increase in glucose in the urine forms a protective layer, preventing bacteria from adhering to and reproducing in the urinary tract, thereby reducing the incidence of urinary tract infections (44). In contrast, GCRA mimics the action of GLP-1, regulating blood glucose levels, promoting insulin secretion, and inhibiting glucagon secretion (45). Although GLP-1 receptors are also expressed in the urinary tract, their activation does not directly affect bacterial growth or immune responses in the urinary tract. Therefore, GCRAs are less likely to increase the risk of urinary tract infections by affecting the urinary tract environment. In summary, the risk impact of SGLT2 inhibitors and GCRAs on urinary tract infections in DN patients mainly involves their effects on urinary osmolality and bacterial growth in the urinary tract.

In conclusion, while both SGLT2 inhibitors and GCRAs have demonstrated efficacy in cardiovascular and renal protection, differences still exist in terms of side effects and indications. Therefore, clinicians should make choices and monitor patients based on their individual circumstances and needs.

Conclusions

Based on the findings herein, both SGLT2 inhibitors and GCRAs are highly effective in reducing cardiovascular and renal outcomes in patients with diabetic nephropathy. Both classes of drug sharply reduce the risk of major cardiovascular events and cardiovascular disease (CVD), with no obvious differences observed in other aspects. In terms of safety, there was no notable difference in urinary tract infections between the two drug classes and the control group. However, the SGLT2 inhibitor group exhibited an elevated risk of severe hypoglycaemia. This emphasises the importance of considering the efficacy and safety of medications when choosing a treatment plan. While both SGLT2 inhibitors and GCRAs showed promise as effective treatments for DN patients, individualised selection based on the patient's

specific conditions was crucial in clinical practice. On the other hand, the results of this study may not be widely applicable because it was based solely on selected literature.

Acknowledgement

Not applicable.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable

AI use disclosure

Not applicable

Conflict of interest

The authors declare no conflict of interest.

References

1. Li X, Tan TE, Wong TY, Sun X. Diabetic retinopathy in China: Epidemiology, screening and treatment trends-A review. Clin Exp Ophthalmol. 2023;51(6):607-626.
2. Palmer ES, Irwin N, O'Harte FP. Potential Therapeutic Role for Apelin and Related Peptides in Diabetes: An Update. Clin Med Insights Endocrinol Diabetes. 2022;15:11795514221074679.
3. Sinha F, Federlein A, Biesold A, Schwarzfischer M, Krieger K, Schweda F, Tauber P. Empagliflozin increases kidney weight due to increased cell size in the proximal tubule S3 segment and the collecting duct. Front Pharmacol. 2023;14:1118358.
4. Tănăsescu MD, Rosu AM, Turlacu MG, Ion LC, Minca A, Rosu AL, Ionita EI, Timofte D, Ionescu D. Treatment with paricalcitol: clinical implications in patients with chronic kidney disease. Farmacia. 2025; 73(3):535-541.
5. Loutradis C, Papadopoulou E, Theodorakopoulou M, Karagiannis A, Sarafidis P. The effect of SGLT-2 inhibitors on blood pressure: a pleiotropic action favoring cardio- and nephroprotection. Future Med Chem. 2019;11(11):1285-1303.
6. Ansary TM, Nakano D, Nishiyama A. Diuretic Effects of Sodium Glucose Cotransporter 2 Inhibitors and Their Influence on the Renin-Angiotensin System. Int J Mol Sci. 2019;20(3):629.
7. Li L, Wang A, Wu S, Lv Y. Impact of GLP-1 receptor agonist semaglutide on carotid intima-media thickness in diabetes mellitus. Farmacia. 2024; 72(4):816-825.
8. Liu B, Wang Y, Zhang Y, Yan B. Mechanisms of Protective Effects of SGLT2 Inhibitors in Cardiovascular Disease and Renal Dysfunction. Curr Top Med Chem. 2019;19(20):1818-1849.
9. Davidson JA. SGLT2 inhibitors in patients with type 2 diabetes and renal disease: overview of current evidence. Postgrad Med. 2019;131(4):251-260.
10. Ja'arah D, Al Zoubi MS, Abdelhady G, Rabi F, Tambuwala MM. Role of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in Hypoglycemia. Clin Med Insights Endocrinol Diabetes. 2021;14:11795514211051697.
11. Holst JJ, Jepsen SL, Modvig I. GLP-1 - Incretin and pleiotropic hormone with pharmacotherapy potential. Increasing secretion of endogenous GLP-1 for diabetes and obesity therapy. Curr Opin Pharmacol. 2022;63:102189.
12. Holst JJ. The incretin system in healthy humans: The role of GIP and GLP-1. Metabolism. 2019;96:46-55.
13. Nagahisa T, Saisho Y. Cardiorenal Protection: Potential of SGLT2 Inhibitors and GLP-1 Receptor Agonists in the Treatment of Type 2 Diabetes. Diabetes Ther. 2019;10(5):1733-1752.
14. Sarafidis P, Ferro CJ, Morales E, Ortiz A, Malyszko J, Hojs R et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. Nephrol Dial Transplant. 2020;35(10):1825. doi: 10.1093/ndt/gfz137.
15. Wu Q, Li D, Huang C, Zhang G, Wang Z, Liu J, Yu H, Song B, Zhang N, Li B, Chu X. Glucose control independent mechanisms involved in the cardiovascular benefits of glucagon-like peptide-1 receptor agonists. Biomed Pharmacother. 2022;153:113517.
16. Puglisi S, Rossini A, Poli R, Dughera F, Pia A, Terzolo M, Reimondo G. Effects of SGLT2 Inhibitors and GLP-1 Receptor Agonists on Renin-Angiotensin-Aldosterone System. Front Endocrinol (Lausanne). 2021;12:738848.
17. Vitale M, Haxhi J, Cirrito T, Pugliese G. Renal protection with glucagon-like peptide-1 receptor agonists. Curr Opin Pharmacol. 2020;54:91-101.
18. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S14-S31.
19. Salifu RS, Hlongwa M, Hlongwana K. Implementation of the WHO's collaborative framework for the management of tuberculosis and diabetes: a scoping review. BMJ Open. 2021;11(11):e047342.
20. Crocker TF, Lam N, Jordão M, Brundle C, Prescott M, Forster A, Ensor J, Gladman J, Clegg A. Risk-of-bias assessment using Cochrane's revised tool for randomized trials (RoB 2) was useful but challenging and resource-intensive: observations from a systematic review. J Clin Epidemiol. 2023;161:39-45
21. Pollock C, Stefánsson B, Reyner D, Rossing P, Sjöström CD, Wheeler DC, Langkilde AM, Heerspink HJL. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(6):429-441.

22. Grunberger G, Camp S, Johnson J, Huyck S, Terra SG, Mancuso JP, Jiang ZW, Golm G, Engel SS, Lauring B. Ertugliflozin in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus: The VERTIS RENAL Randomized Study. Diabetes Ther. 2018;9(1):49-66.
23. Haneda M, Seino Y, Inagaki N, Kaku K, Sasaki T, Fukatsu A, Kakiuchi H, Sato Y, Sakai S, Samukawa Y. Influence of Renal Function on the 52-Week Efficacy and Safety of the Sodium Glucose Cotransporter 2 Inhibitor Luseogliflozin in Japanese Patients with Type 2 Diabetes Mellitus. Clin Ther. 2016;38(1):66-88.e20.
24. Scott R, Morgan J, Zimmer Z, Lam RLH, O'Neill EA, Kaufman KD, Engel SS, Raji A. A randomized clinical trial of the efficacy and safety of sitagliptin compared with dapagliflozin in patients with type 2 diabetes mellitus and mild renal insufficiency: The CompoSIT-R study. Diabetes Obes Metab. 2018;20(12):2876-2884.
25. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P et al; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-130.
26. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, et al; Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519-1529.
27. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al; EXSCEL Study Group. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017;377(13):1228-1239.
28. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al; PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019;381(9):841-851.
29. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015;373(23):2247-57.
30. Neuen BL, Ohkuma T, Neal B, Matthews DR, de Zeeuw D, Mahaffey KW et al. Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function. Circulation. 2018 Oct 9;138(15):1537-1550.
31. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M et al; EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34.
32. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK et al; SCORED Investigators. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021;384(2):129-139.
33. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM et al; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-2306.
34. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. Int J Mol Sci. 2020;21(5):1835.
35. Nikolic M, Zivkovic V, Jovic JJ, Sretenovic J, Davidovic G, Simovic S, Djokovic D, Muric N, Bolevich S, Jakovljevic V. SGLT2 inhibitors: a focus on cardiac benefits and potential mechanisms. Heart Fail Rev. 2022;27(3):935-949.
36. Schönberger E, Mihaljević V, Steiner K, Šarić S, Kurevija T, Majnarić LT, Bilić Ćurčić I, Canecki-Varžić S. Immunomodulatory Effects of SGLT2 Inhibitors-Targeting Inflammation and Oxidative Stress in Aging. Int J Environ Res Public Health. 2023;20(17):6671.
37. Xie L, Xiao Y, Tai S, Yang H, Zhou S, Zhou Z. Emerging Roles of Sodium Glucose Cotransporter 2 (SGLT-2) Inhibitors in Diabetic Cardiovascular Diseases: Focusing on Immunity, Inflammation and Metabolism. Front Pharmacol. 2022;13:836849.
38. Bany Bakar R, Reimann F, Gribble FM. The intestine as an endocrine organ and the role of gut hormones in metabolic regulation. Nat Rev Gastroenterol Hepatol. 2023;20(12):784-796.
39. Ma X, Liu Z, Ilyas I, Little PJ, Kamato D, Sahebka A, Chen Z, Luo S, Zheng X, Weng J, Xu S. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. Int J Biol Sci. 2021;17(8):2050-2068.
40. Duan S, Lu F, Song D, Zhang C, Zhang B, Xing C, Yuan Y. Current Challenges and Future Perspectives of Renal Tubular Dysfunction in Diabetic Kidney Disease. Front Endocrinol (Lausanne). 2021;12:661185.
41. Dai ZC, Chen JX, Zou R, Liang XB, Tang JX, Yao CW. Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease. Front Immunol. 2023;14:1213473.
42. Luna-Marco C, Iannantuoni F, Hermo-Argibay A, Devos D, Salazar JD, Víctor VM, Rovira-Llopis S. Cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists through effects on mitochondrial function and oxidative stress. Free Radic Biol Med. 2024;213:19-35.
43. Gilbert MP, Pratley RE. GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. Front Endocrinol (Lausanne). 2020;11:178.
44. Carvalho FM, Mergulhão FJM, Gomes LC. Using Lactobacilli to Fight Escherichia coli and Staphylococcus aureus Biofilms on Urinary Tract Devices. Antibiotics (Basel). 2021;10(12):1525.
45. Hjørne AP, Modvig IM, Holst JJ. The Sensory Mechanisms of Nutrient-Induced GLP-1 Secretion. Metabolites. 2022;12(5):420.