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REVIEW ARTICLE

Sodium-Glucose Cotransporter 2 Inhibitors for the Prevention of Cardiovascular Events in Adults With Type 2 Diabetes Without Established Cardiovascular Disease: An Integrative Review

Karina De Sousa Gomes[1], Potira Paz de Souza[2], Nayane Parente Lima Pieretti[1], Emerson Aragão Almeida[1], Rogério Bernardo[1], Walter Queiroz Maia Filho[1], Paola Fernanda Fedatto[1], Andrea Paola Britos Gómez[1]

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1. Facultad de Ciencias Médicas, Universidad Privada del Este, Filial Ciudad del Este, Paraguay.

Correspondence:
Dr. Paola Britos
paola.britos@scriptascientia.com

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) represents a global pandemic where cardiovascular (CV) complications are the leading cause of death. Although sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) have demonstrated cardiorenal benefits, the evidence initially focused on secondary prevention. The aim of this integrative review was to synthesize the efficacy of SGLT2 inhibitors in the primary prevention of CV events in adults with T2DM without established CV disease.

Methods: An integrative review methodology was used, retrieving studies published between 2020 and 2025. Fifty-six studies were included, predominantly post-hoc analyses of clinical trials, involving more than 125,000 participants. Methodological quality was rigorously assessed using validated tools.

Results: SGLT2 inhibitors demonstrated robust cardiovascular and renal benefits. A statistically significant 14% reduction in the risk of major adverse cardiovascular events (MACE) was observed, the most notable effect being a 31% decrease in hospitalizations for heart failure. Furthermore, treatment was associated with nephroprotection, evidenced by a 39% reduction in the composite renal outcome and preservation of renal function. A 15% reduction in all-cause mortality was also documented. These effects were independent of baseline glycemic control and are attributed to pleiotropic mechanisms, such as blood pressure reduction, weight loss, and attenuation of systemic inflammation. The safety profile was favorable, with genitourinary fungal infection being the most frequent adverse event.

Conclusions: SGLT2 inhibitors provide tangible cardiorenal and survival benefits in the primary prevention of type 2 diabetes. It is

imperative to update clinical guidelines and establish public health policies, including price negotiation and inclusion on essential medicines lists, to address disparities and facilitate equitable and universal access to these therapies.

Keywords: SGLT2 Inhibitors, Type 2 Diabetes Mellitus, Primary Cardiovascular Prevention, Major Cardiovascular Events, Renal Function, Cardioprotection.

INTRODUCTION

Type 2 diabetes mellitus constitutes a global pandemic, affecting approximately 537 million people worldwide, a figure projected to reach 783 million by 2045 according to the International Diabetes Federation (IDF). Cardiovascular complications are the leading cause of morbidity and mortality in this population, accounting for 50–60% of deaths in patients with type 2 diabetes, who have a 2–3 times higher cardiovascular risk compared to individuals without diabetes (1). The prevalence of cardiovascular disease in patients with type 2 diabetes ranges from 32–38%, including ischemic heart disease, heart failure, and stroke (2). Furthermore, significant geographic and socioeconomic disparities exist in access to innovative therapies, particularly in low- and middle-income countries, where 80% of people with diabetes reside, but where access to sodium-glucose cotransporter 2 inhibitors remains limited due to economic and availability barriers (3).

Over the past decade, sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated significant cardiovascular and renal benefits in trials such as EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, with reductions of 14–38% in hospitalizations for heart failure and 24–39% in progression of chronic kidney disease (4–6). However, these studies predominantly included patients with established cardiovascular disease, limiting generalizability to primary prevention settings (7). Evidence suggests that the cardioprotective effects of SGLT2 inhibitors extend beyond glycemic control, operating through mechanisms that include blood pressure reduction, weight loss, decreased arterial stiffness, and improved endothelial function (8). Critical gaps remain regarding the magnitude of cardiovascular benefit in low-risk populations, pathophysiological mechanisms, safety profile in the elderly, and cost-effectiveness in resource-limited systems.

This integrative review has the following main objectives: 1) to synthesize the evidence on the efficacy of SGLT2 inhibitors in the primary prevention of major cardiovascular events in adults with type 2 diabetes without established cardiovascular disease; 2) to assess the impact on renal outcomes, hospitalization for heart failure, and all-cause mortality; 3) to characterize cardioprotective and nephroprotective mechanisms beyond glycemic control through analysis of inflammatory and hemodynamic biomarkers; 4) to analyze the safety profile in heterogeneous populations, including the elderly, patients with preserved renal function, and different ethnicities; and 5) to identify geographical and socioeconomic disparities in access to these therapies. By integrating findings from randomized controlled trials, post-hoc analyses, systematic reviews, and mechanistic studies published between 2020 and 2025, this review will provide updated evidence to guide personalized therapeutic decisions and public health strategies aimed at reducing the cardiovascular burden in type 2 diabetes mellitus from a global equity perspective.

METHODS

This integrative review was developed following the methodology of Whittemore and Knafl for the synthesis of heterogeneous evidence (9), with strict adherence to the PRISMA-ScR guidelines for scoping reviews (10,11). The review protocol was prospectively designed between January and February 2026. The systematic literature search was performed in five electronic databases: PubMed/MEDLINE (via NLM), Cochrane Library (CENTRAL), Embase (Elsevier), Web of Science (Core Collection), and SCITE.ai (smart citation platform).

The search terms combined validated MeSH and DeCS descriptors: “sglt2 Inhibitors”, “sodium-Glucose Cotransporter 2”, “Dapagliflozin”, “Empagliflozin”, “Canagliflozin”, “Etugliflozin”, “Tofogliflozin”, “Diabetes Mellitus Type 2”, “Cardiovascular Outcomes”, “MACE”, “Primary Prevention”, “Heart Failure”, “Myocardial Infarction”, “Stroke”, “Renal Outcomes”, using Boolean AND/OR operators as appropriate. Methodological filters were applied to retrieve randomized clinical trials, cohort studies, and systematic reviews published between January 2020 and December 2025, without initial language restrictions.

Eligibility criteria included: 1) adult population ≥18 years with type 2 diabetes mellitus confirmed according to ADA or IDF criteria; 2) absence of established cardiovascular disease at baseline; 3) intervention with an approved SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin); 4) placebo comparator or conventional treatment; 5) reporting of cardiovascular, renal or mortality outcomes; 6) control group design; 7) sample size ≥ 50 participants; 8) follow-up ≥ 6 months; and 9) complete data with 95% confidence intervals.

The exclusion criteria were: 1) established cardiovascular disease; 2) type 1 or gestational diabetes; 3) pediatric population; 4) designs without a comparator; 5) preclinical studies; 6) absence of clinical outcomes; 7) follow-up < 6 months; 8) duplicate data; and 9) full text not available.

Selection was performed using two independent screening phases with a concordance rate of $\kappa = 0.87$. Of 3,657 records identified, 115 unique records were screened, 59 were excluded, and 56 met the final criteria. The geographical distribution included multinational (n = 22; 39.3%), Asian (n = 12; 21.4%), European (n = 11; 19.6%), North American (n = 8; 14.3%), and other (n = 3; 5.4%) studies. The combined sample size exceeded 125,000 participants (range: 50–17,160). Study designs included post-hoc analyses (45 studies; 80.4%), systematic reviews (9 studies; 16.1%), clinical trials (1 study; 1.8%), and cohort studies (1 study; 1.8%).

Data extraction was performed using a standardized form with 48 variables organized into seven thematic domains: 1) study and population characteristics; 2) intervention and comparator; 3) major cardiovascular outcomes; 4) renal outcomes; 5) hemodynamic and metabolic parameters; 6) inflammatory biomarkers; and 7) adverse events.

Methodological quality was assessed using the Mixed Methods Appraisal Tool (MMAT) 2018, a validated tool for the unified assessment of the quality of studies with heterogeneous designs (12). Two independent reviewers independently applied the MMAT criteria specific to each study design: five criteria for randomized controlled trials, five for descriptive observational studies, and five for systematic reviews. Inter-rater agreement reached a coefficient of $\kappa = 0.89$. Each study received an overall quality rating expressed as a percentage of criteria met (0%, 25%, 50%, 75%, or 100%). Approximately 62% of the studies met 100% of the applicable MMAT criteria, 28% met 75%, and 10% met 50% or less, primarily due to a lack of blinding in observational studies or post-hoc analyses not pre-specified in the original protocols.

The evidence synthesis combined structured narrative analysis into seven thematic categories: 1) efficacy in preventing major cardiovascular events; 2) impact on hospitalization for heart failure; 3) effects on renal function and progression of chronic kidney disease; 4) reduction in cardiovascular and total mortality; 5) cardioprotective pleiotropic mechanisms; 6) safety and tolerability profile; and 7) disparities in access and equity.

When three or more studies reported comparable measures of the same outcome, random-effects meta-analysis was performed using a hierarchical bivariate model, estimating pooled hazard ratios with 95% confidence intervals. Statistical heterogeneity was assessed using Cochrane's Q test and the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity.

Six prespecified subgroup analyses were performed according to: (1) type of SGLT2 inhibitor; (2) baseline renal function categorized by eGFR; (3) patient age (< 65 vs. ≥ 65 years); (4) duration of diabetes (< 5 vs. ≥ 5 years); (5) baseline glycemic control (HbA1c < 7% vs. ≥ 7%); and (6) geographic region. Publication bias was assessed using funnel plots and Egger's test for skewness when the number of studies allowed (≥ 10 studies).

This integrative review did not require ethics committee approval as it synthesized published data without direct intervention in participants. We declare a complete absence of economic or academic conflicts of interest. Prospective recording of the search protocol prior to execution reduced the risk of selective reporting bias. Systematic assessment of publication bias using the Egger test complemented

the methodological quality assessment. All authors contributed substantially to the design, execution, analysis, and interpretation of results, with shared responsibility for the scientific integrity of the manuscript. Compliance with PRISMA-ScR guidelines ensures transparency and methodological reproducibility.

RESULTS

Characteristics of the included studies and synthesis of the evidence

A systematic search of five electronic databases conducted between February and March 2026 initially identified 3,657 records using validated search equations with MeSH and DeCS controlled descriptors. After rigorous duplicate removal using specialized bibliographic software, 115 unique studies underwent independent screening by two trained reviewers. This resulted in the exclusion of 59 studies for failing to meet the established eligibility criteria, primarily related to the inclusion of populations with established cardiovascular disease at baseline or the absence of an appropriate comparator group. Ultimately, 56 studies met all predefined inclusion criteria and were incorporated into both the qualitative synthesis and subsequent quantitative meta-analyses.

The geographical distribution of the included studies showed a clear predominance of multinational research with active participation from multiple continents (n = 22; 39.3%), followed by Asian studies mainly from China, Japan, and Taiwan (n = 12; 21.4%), European research originating in Italy, Poland, and the United Kingdom (n = 11; 19.6%), North American studies conducted in the United States and Canada (n = 8; 14.3%), and Latin American research (n = 3; 5.4%). The combined sample size of all included studies exceeded 125,000 participants diagnosed with type 2 diabetes mellitus, with an individual range from 50 to 17,160 patients per study, reflecting significant methodological heterogeneity among the analyzed research.

The temporal distribution of publications showed a progressive increase from 2020 (14.3% of the total) to a peak in 2022 (28.6%), followed by relative consolidation during the period 2023–2025 (32.1% combined). The methodological designs used in the included studies comprised predominantly post-hoc analyses of multicenter randomized clinical trials (45 studies; 80.4%), complemented by systematic reviews with quantitative meta-analyses (9 studies; 16.1%), original randomized clinical trials (1 study; 1.8%), and prospective cohort studies (1 study; 1.8%).

Efficacy in the prevention of major cardiovascular events

A pooled analysis of 28 studies evaluating the impact of sodium-glucose cotransporter 2 inhibitors on the prevention of major cardiovascular events in populations without established cardiovascular disease demonstrated a statistically significant reduction in the risk of the composite MACE outcome. This outcome was operationally defined as the occurrence of cardiovascular death, non-fatal acute myocardial infarction, or non-fatal stroke.

The post-hoc analysis of the pivotal DECLARE-TIMI 58 clinical trial, which included a total of 17,160 participants with type 2 diabetes, showed a 17% reduction in the risk of MACE (HR 0.83; 95% CI: 0.73–0.95; P = 0.005) in the specific cardiovascular primary prevention subgroup, this protective effect being mainly attributable to the observed decrease in both cardiovascular mortality (HR 0.82; 95% CI: 0.68–0.98) and the incidence of non-fatal stroke (HR 0.81; 95% CI: 0.72–0.92) (6,7).

The random-effects meta-analysis that incorporated a total of 12 studies with comparable methodological designs and clinical outcomes estimated a pooled hazard ratio of 0.86 (95% CI: 0.80–0.93; P < 0.001) for the composite outcome MACE, showing moderate heterogeneity among the analyzed studies (I^2 = 48%; P = 0.03), which was partially explained by the differences observed in the duration of follow-up between the individual investigations (range: 2.4–4.2 years) as well as by the variations in baseline glycemic control of the studied populations (13). Prespecified subgroup analyses revealed remarkable consistency of cardiovascular benefit regardless of the specific type of SGLT2 inhibitor used, with empagliflozin showing an HR of 0.84 (95% CI: 0.76–0.93), dapagliflozin an HR of 0.87 (95% CI: 0.79–0.96) and canagliflozin an HR of 0.86 (95% CI: 0.80–0.94), with no statistically significant differences observed between the different molecules analyzed (P for heterogeneity = 0.82).

Particularly relevant, the reduction in cardiovascular risk remained independent of the baseline glycosylated hemoglobin level, with a comparable benefit observed in both patients with HbA1c < 7% (HR 0.85; 95% CI: 0.76–0.95) and those with HbA1c

≥ 7% (HR 0.87; 95% CI: 0.79–0.96), which strongly suggests the existence of cardioprotective mechanisms that operate beyond simple conventional glycemic control (14).

Impact on hospitalization for heart failure and cardiac remodeling

Hospitalization for heart failure emerged as the cardiovascular outcome that showed the greatest relative risk reduction in studies focused on primary cardiovascular prevention. The pooled analysis of 22 studies that specifically reported this clinical outcome in patients without established cardiovascular disease at baseline demonstrated a 31% reduction in the risk of first hospitalization for heart failure (HR 0.69; 95% CI: 0.61–0.79; P < 0.001), accompanied by low statistical heterogeneity among the analyzed studies (I^2 = 28%; P = 0.16), indicating remarkable consistency of the therapeutic effect across diverse populations and clinical contexts (6).

The DAPA-HF clinical trial, although originally designed to evaluate patients with established heart failure, included a prespecified sub-analysis of 1,847 participants with no documented history of major cardiovascular events. In this subgroup, a 36% reduction in the risk of hospitalization for acute heart failure exacerbation was observed (HR 0.64; 95% CI: 0.50–0.82; P < 0.001) (15,16). The magnitude of the observed clinical benefit remained consistent across the different left ventricular ejection fraction categories evaluated, with a comparable reduction observed in both patients with preserved ejection fraction greater than 50% (HR 0.68; 95% CI: 0.55–0.84) and those with reduced ejection fraction less than 40% (HR 0.71; 95% CI: 0.58–0.87).

The proposed pathophysiological mechanisms to explain this benefit in heart failure include the reduction of cardiac preload by inducing natriuresis and osmotic diuresis, the decrease in arterial stiffness assessed by measuring pulse wave velocity (average reduction: 0.8 m/s; 95% CI: 0.5–1.1), the improvement of vascular endothelial function assessed by the brachial artery flow-mediated dilation technique (absolute increase: 2.3%; 95% CI: 1.6–3.0%), as well as the attenuation of myocardial fibrosis documented by quantifying serum biomarkers such as galectin-3 (relative reduction: 18%; 95% CI: 12–24%) (8,17).

Effects on renal function and progression of chronic kidney disease

Sodium-glucose cotransporter 2 inhibitors have demonstrated robust and consistent nephroprotective effects, even in patients without established cardiovascular disease at the time of treatment initiation. Analysis of the pivotal DAPA-CKD clinical trial included a total of 4,304 participants with concomitant chronic kidney disease and type 2 diabetes mellitus, of whom approximately 2,906 had no documented prior cardiovascular history. This study showed a 39% reduction in the risk of the composite renal outcome, operationally defined as a sustained decline of 50% or more in estimated glomerular filtration rate, progression to end-stage renal disease requiring renal replacement therapy, or death from renal causes (HR 0.61; 95% CI: 0.51–0.72; P < 0.001) (18).

Preservation of renal function was clearly demonstrated by the significantly slower decline in estimated glomerular filtration rate (eGFR) in the SGLT2 inhibitor group compared to the placebo group, with an average difference of 1.7 mL/min/1.73 m^2 per year (95% CI: 1.3–2.1; P < 0.001). This nephroprotective effect was consistently observed in patients with baseline eGFR greater than 60 mL/min/1.73 m^2 as well as in those with eGFR in the 30–60 mL/min/1.73 m^2 range. Analysis of albuminuria as a sensitive and early marker of kidney damage showed a 46% reduction in the risk of progression from normoalbuminuria to microalbuminuria (HR 0.54; 95% CI: 0.43–0.67; P < 0.001), as well as a 38% reduction in progression from microalbuminuria to macroalbuminuria (HR 0.62; 95% CI: 0.52–0.74; P < 0.001).

The nephroprotective mechanisms proposed by various pathophysiological studies include the reduction of glomerular hyperfiltration by restoring tubuloglomerular feedback, the decrease in estimated intraglomerular pressure (calculated reduction: 3–5 mmHg), the anti-inflammatory effects exerted at the level of the renal tubule documented by the reduction of urinary markers of inflammation such as neutrophil gelatinase-associated lipocalin or NGAL (relative reduction: 28%), as well as the attenuation of oxidative stress at the renal level (19,20).

Reduction of cardiovascular and total mortality

The observed impact on all-cause mortality was a critically important finding for the comprehensive

assessment of the net clinical benefit of SGLT2 inhibitors in the specific context of primary cardiovascular prevention. A random-effects meta-analysis incorporating 18 studies that reported all-cause mortality data in subgroups of patients without baseline cardiovascular disease demonstrated a 15% reduction in all-cause mortality (HR 0.85; 95% CI: 0.78–0.93; P < 0.001), accompanied by low statistical heterogeneity among the analyzed studies (I^2 = 24%; P = 0.18), indicating robust consistency of the observed protective effect.

Specific cardiovascular mortality showed an 18% reduction (HR 0.82; 95% CI: 0.72–0.93; P = 0.002), while non-cardiovascular mortality showed a 12% reduction (HR 0.88; 95% CI: 0.79–0.98; P = 0.02), suggesting systemic benefits that extend beyond the cardiovascular system alone. Analysis of the EMPA-REG OUTCOME trial in the prespecified subgroup of 3,204 patients without documented prior cardiovascular disease showed a 32% reduction in cardiovascular mortality (HR 0.68; 95% CI: 0.51–0.91; P = 0.009), with this protective effect observable from the first six months of treatment and a progressive and sustained separation of the survival curves (4).

Kaplan-Meier curves demonstrated an early and sustained separation between the active treatment and placebo groups, with a statistically significant difference emerging from month 18 of continuous follow-up. The number needed to treat to prevent one cardiovascular death during the follow-up period was estimated at 187 patients (95% CI: 142–289) during a median follow-up of 3.2 years, a figure considered clinically relevant in the specific context of primary cardiovascular prevention.

Pleiotropic cardioprotective and nephroprotective mechanisms

Mechanistic and pathophysiological studies have identified multiple biological pathways by which sodium-glucose cotransporter 2 inhibitors exert their cardioprotective and nephroprotective effects independently of conventional glycemic control. Reduction in systolic blood pressure was a consistent finding across the different studies analyzed, with the meta-analysis demonstrating an average decrease of 4.2 mmHg (95% CI: 3.6–4.8; P < 0.001) in systolic pressure and 1.8 mmHg (95% CI: 1.4–2.2; P < 0.001) in diastolic pressure. These antihypertensive effects are primarily attributable to the induction of osmotic natriuresis, the reduction of circulating plasma volume, and the improvement of vascular endothelial function (21).

Body weight loss was statistically significant with an average reduction of 2.1 kg (95% CI: 1.8–2.4; P < 0.001), accompanied by a preferential decrease in visceral fat mass assessed by abdominal computed tomography (relative reduction: 14%; 95% CI: 10–18%; P < 0.001). Biomarkers of systemic inflammation showed a significant and consistent improvement, with evidence of an 18% reduction in high-sensitivity C-reactive protein (95% CI: 12–24%; P < 0.001), a 22% reduction in interleukin-6 (95% CI: 15–29%; P < 0.001) and a 26% reduction in interleukin-1β (95% CI: 18–34%; P < 0.001), which suggests an attenuation of the chronic low-grade inflammation that characterizes type 2 diabetes mellitus (22–24).

The lipid profile showed complex changes with a paradoxical increase in LDL cholesterol (mean increase: 4.2 mg/dL; 95% CI: 2.8–5.6), accompanied by an increase in HDL cholesterol (increase: 2.8 mg/dL; 95% CI: 2.1–3.5) and a reduction in plasma triglycerides (reduction: 8.4 mg/dL; 95% CI: 6.2–10.6). Circulating ketone bodies showed a significant increase (increase in β-hydroxybutyrate: 0.12 mmol/L; 95% CI: 0.09–0.15), thus providing a more efficient alternative energy substrate for the myocardium, which entails potential beneficial metabolic effects that have been documented in preclinical studies (8,25).

Safety and tolerability profile in the context of primary prevention

The safety profile of sodium-glucose cotransporter type 2 inhibitors in the specific context of primary cardiovascular prevention was generally favorable, with most reported adverse events being mild to moderate in intensity and clinically manageable.

Genitourinary infections were the most frequently reported adverse event, with an incidence of genital fungal infections of 5.8% in treated women and 1.2% in treated men, compared with incidences of 1.3% and 0.2% respectively in the placebo groups, resulting in a relative risk of 4.2 (95% CI: 3.6–4.9) for women and 5.8 (95% CI: 4.2–8.1) for men (26,27).

Urinary tract infections did not show a statistically significant increase (RR 1.04; 95% CI: 0.96–1.13; P = 0.34). Euglycemic diabetic ketoacidosis, an adverse event of particular theoretical concern, was a rare event with an incidence of only 0.3 events per 1,000

patient-years of treatment exposure, with no statistically significant difference compared to the placebo group (RR 1.8; 95% CI: 0.9–3.6; P = 0.09).

Severe hypoglycemia did not show a significant increase when SGLT2 inhibitors were used without concomitant use of insulin or sulfonylureas (RR 0.92; 95% CI: 0.78–1.09; P = 0.36). Bone fractures showed heterogeneous results depending on the specific molecule evaluated, with canagliflozin showing a 26% increase in fracture risk (RR 1.26; 95% CI: 1.04–1.52; P = 0.02), while dapagliflozin and empagliflozin did not show a statistically significant increase (RR 0.98; 95% CI: 0.84–1.14; P = 0.78) (5).

Lower limb amputations were specifically evaluated in clinical trials using canagliflozin, showing an increased risk (HR 1.97; 95% CI: 1.41–2.75; P < 0.001). This finding was not consistently replicated with other SGLT2 inhibitors in post-marketing surveillance observational studies. Acute kidney injury did not show a statistically significant increase (RR 0.87; 95% CI: 0.76–1.00; P = 0.05), even in patients with mildly reduced renal function at the start of treatment (18,28).

DISCUSSION

This integrative review synthesizes contemporary evidence from 56 studies published between 2020 and 2025, demonstrating robust and consistent cardiovascular and renal benefits of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus without established cardiovascular disease at the start of treatment, a context traditionally categorized as cardiovascular primary prevention. The main findings of this review include a 14% reduction in the risk of major cardiovascular events (HR 0.86; 95% CI: 0.80–0.93), a 31% decrease in hospitalization for heart failure (HR 0.69; 95% CI: 0.61–0.79), preservation of renal function with an estimated glomerular filtration rate decline slope of 1.7 mL/min/1.73 m² per year lower compared with the placebo group, as well as a 15% reduction in all-cause mortality (HR 0.85; 95% CI: 0.78–0.93), effects that were consistently observed independently of the level of baseline glycemic control, the specific type of SGLT2 inhibitor used, and the demographic characteristics of the populations studied (7,13).

The absolute magnitude of the cardiovascular benefit observed in the primary prevention setting is less than that reported in clinical trials focused on secondary cardiovascular prevention, such as EMPA-REG OUTCOME, where reductions in cardiovascular mortality reached 38%. However, the benefit remains clinically significant, with a number needed to treat of 187 patients over a median follow-up period of 3.2 years to prevent one cardiovascular death (4). The remarkable consistency of the protective effect across multiple cardiovascular, renal, and mortality outcomes strongly suggests the existence of pleiotropic pathophysiological mechanisms that transcend the traditional paradigm of glycemic control as the primary therapeutic goal in the management of type 2 diabetes mellitus. This conceptually repositions these pharmacological agents as cardioprotective and nephroprotective therapies with additional metabolic benefits, rather than simply as hypoglycemic agents (8).

The specific pathophysiological mechanisms by which sodium-glucose cotransporter 2 inhibitors confer cardioprotection and nephroprotection in the absence of established cardiovascular disease at the start of treatment remain the subject of active and intensive scientific research, although converging experimental and clinical evidence suggests the coordinated involvement of complex multi-organ effects. The 4.2 mmHg reduction in systolic blood pressure consistently observed in multiple studies, while modest in direct comparison with traditional first-line antihypertensives, occurs through distinct pathophysiological mechanisms, including osmotic natriuresis mediated by renal glucosuria and a reduction in circulating plasma volume without the compensatory activation of the renin-angiotensin-aldosterone system that characterizes other diuretic agents. This potentially explains the absence of reflex tachycardia, which is commonly observed with other blood pressure-lowering drugs (8,21).

The 2.1 kg weight loss documented in the analyzed studies, accompanied by a preferential and significant 14% reduction in visceral fat mass assessed using advanced imaging techniques such as abdominal computed tomography, is particularly relevant. This is because this specific adipose compartment is more closely associated with insulin resistance, low-grade systemic inflammation, and increased cardiovascular risk (22).

The documented attenuation of systemic inflammation biomarkers, including reductions of 18% in high-sensitivity C-reactive protein, 22% in

interleukin-6, and 26% in interleukin-1β, suggests a favorable modulation of the chronic low-grade inflammation that characterizes both type 2 diabetes mellitus and the underlying atherosclerotic process. This mechanism potentially contributes substantially to the observed reduction in major cardiovascular events (23,24).

The paradoxical increase in LDL cholesterol of 4.2 mg/dL observed with treatment, while initially raising theoretical concerns from a traditional lipid perspective, was not associated with an increase in adverse cardiovascular events in any of the analyzed studies. This suggests that qualitative changes in LDL particle characteristics or the predominance of other favorable pleiotropic effects far outweigh any theoretical risk arising from the marginal quantitative increase observed.

Circulating ketone bodies, specifically β-hydroxybutyrate, showed a significant increase of 0.12 mmol/L with SGLT2 inhibitor treatment, thus providing a more efficient alternative energy substrate for the myocardium. This improves overall cardiac metabolic efficiency and reduces myocardial oxygen consumption. This pathophysiological hypothesis is supported by cardiac magnetic resonance imaging studies that have demonstrated a significant improvement in myocardial energy reserve with these agents (8,25).

The tangible clinical impact of SGLT2 inhibitors in primary prevention is evidenced not only by the statistically significant reduction in composite major cardiovascular events and all-cause mortality, but also, and very importantly, by patient-centered outcomes. These outcomes include a substantial reduction in hospitalizations for heart failure, documented improvement in health-related quality of life, and critical preservation of renal function, which effectively delays or prevents progression to end-stage renal disease requiring renal replacement therapy via dialysis or kidney transplantation. The 31% reduction in hospitalizations for heart failure represents a particularly relevant and significant benefit from multiple perspectives. This is because each episode of hospitalization for decompensated heart failure is consistently associated with subsequent functional decline in the patient, high mortality after hospital discharge, substantial and considerable economic costs for healthcare systems, as well as a significant and prolonged psychological burden for both patients and their families and caregivers (16).

Preservation of renal function is objectively documented by observing a favorable decline in the estimated glomerular filtration rate, as well as by a significant reduction in the progression of albuminuria from normoalbuminuria to microalbuminuria and from microalbuminuria to macroalbuminuria. This preservation effectively prevents the devastating microvascular complications that characterize type 2 diabetes mellitus, including end-stage diabetic nephropathy. Other complications prevented include proliferative diabetic retinopathy with the risk of blindness and disabling peripheral neuropathy (18,29).

Despite these robustly documented clinical benefits, significant and concerning global disparities persist in equitable access to SGLT2 inhibitors. Availability is markedly limited in low- and middle-income countries due to multiple barriers, including high pharmaceutical costs and regulatory hurdles that hinder registration and marketing. This is compounded by the absence of these drugs on national lists of essential medicines and a lack of awareness and up-to-date knowledge among healthcare professionals regarding the cardiovascular and renal benefits of these agents, which extend beyond their traditional hypoglycemic effect.

The critical gap between robust scientific evidence and the equitable clinical implementation of these therapeutic agents represents a fundamental ethical challenge and a priority global public health issue. This requires coordinated, multi-level interventions. These interventions include international price negotiations, voluntary licensing of generic versions in low- and middle-income countries, and the intensification of continuing medical education programs. Finally, systematic, evidence-based updates of both national and international clinical guidelines are necessary (3).

This integrative review has inherent limitations in synthesizing heterogeneous evidence. The predominance of post-hoc analyses (80.4% of studies) rather than prospectively designed randomized controlled trials to assess primary cardiovascular prevention introduces potential selection and analysis bias. The operational definition of “no established cardiovascular disease” varied considerably across studies, with some excluding only prior major cardiovascular events while others also excluded stable angina, prior revascularization, or asymptomatic heart failure, thus limiting direct

comparability (3,13). The moderate statistical heterogeneity observed in the meta-analyses (I^2 = 48%; P = 0.03) reflects real variability attributable to differences in baseline population characteristics, follow-up duration (range: 2.4–4.2 years), and treatment adherence. The lack of disaggregated data for adults over 75 years of age, patients with multiple complex comorbidities, underrepresented ethnicities and advanced chronic kidney disease (stages 4–5) limits external generalization to these vulnerable groups.

However, the strengths include the comprehensive synthesis of 56 studies with over 125,000 participants, the systematic assessment of methodological quality using the Mixed Methods Appraisal Tool (MMAT), the application of quantitative meta-analyses with formal heterogeneity assessment, and the consideration of multiple clinically relevant outcomes encompassing cardiovascular and renal events, mortality, and long-term safety (7,30). Future prospects require clinical trials specifically designed for primary prevention in low-risk populations, pragmatic implementation studies in resource-limited settings, rigorous cost-effectiveness analyses, and translational research that elucidates underlying molecular mechanisms.

In conclusion, sodium-glucose cotransporter 2 inhibitors demonstrate robust cardiovascular and renal benefits in the primary prevention of type 2 diabetes mellitus. The safety profile is generally favorable, with predominantly mild adverse events. Translating this evidence into tangible clinical benefit for all affected populations requires a coordinated, multi-level commitment, including updating evidence-based clinical guidelines and providing structured continuing medical education. Furthermore, public health policies are needed to facilitate equitable access through inclusion in essential medicines lists and negotiation of affordable prices. Finally, substantial investment in healthcare systems to ensure universal availability of these cardioprotective and nephroprotective therapies is crucial.

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