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OPTIMIZING HEALTHCARE RESOURCES: SODIUM-GLUCOSE COTRANSPORTER INHIBITORS FOR CARDIOVASCULAR RISK REDUCTION IN TYPE 2 DIABETES MELLITUS

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Abstract:

Introduction: Type 2 diabetes mellitus (T2DM) poses a significant economic burden due to its association with cardiovascular complications, making it a leading cause of premature mortality and straining healthcare systems.

Methods: A systematic electronic search was conducted for clinical trials published between January 2015 and January 2023 in PubMed, Scopus, Web of Science, and ScieLO databases. These trials evaluated the safety and efficacy of sodium-glucose cotransporter inhibitors (SGLT2i) in patients with T2DM and established cardiovascular disease, focusing on standard treatment and cost-effectiveness analysis.

Results: The addition of SGLT2i to standard therapy led to notable reductions in rates of acute myocardial infarction, stroke, cardiovascular death, and hospitalization for heart failure. The

observed decrease in cardiovascular events offset the costs associated with SGLT2i therapy, demonstrating a favorable utilization of healthcare resources.

Conclusions: Given that cardiovascular events are the primary cause of mortality in patients with T2DM and cardiovascular disease, there is a pressing need for the development of therapies that not only improve glycemic control but also mitigate cardiovascular risks. These findings underscore the emergence of an evidence-based approach to managing such patients, heralding a new era in clinical practice.

Keywords: glucose, sodium, cotransporter, diabetes, cardioprotection, cost-effectiveness.

INTRODUCTION:

One definition of diabetes mellitus (DM) is chronic hyperglycemia caused by many processes. Young people are primarily affected by type 1 diabetes mellitus (DM1), which is defined by autoimmune aggressiveness to pancreatic beta cells in those with a high hereditary vulnerability. Conversely, cellular insulin resistance is the cause of type 2 diabetes mellitus (DM2), which results in a persistently high blood sugar level. Diabetes mellitus (DM2), together with cardiovascular events, is considered the biggest worldwide health concern of the twenty-first century. It is a significant contributor to an increased risk of premature mortality and, as such, is an increasing hazard to health. Globally, the prevalence of DM is sharply rising. The number of people worldwide who have diabetes has increased from 30 million in 1985 to 382 million in 2014 over the last three decades, and current trends indicate that this number will only increase more (Fralick & Zinman, 2021; Kramer et al., 2021).

According to the International Diabetes Federation's most recent projections, 1 in 10 people, or 591 million people globally, will have diabetes by 2035. While both T1DM and T2DM rates are rising, T2DM is disproportionately more responsible for the increased prevalence of DM worldwide than T1DM. A significant financial burden on the patient and the healthcare system is one effect of the rise in DM prevalence. The average annual cost of diabetes in the United States is $2,108 per patient, about twice as much as that of non-diabetic patients. The economic burden associated with diabetes-related morbidity and mortality is significant, encompassing direct medical care expenses as well as indirect costs resulting from reduced productivity (Garz et al., 2021).

After ischemic heart disease, diabetes mellitus (DM) is the leading cause of mortality in Ecuador, accounting for 2,533 deaths in 2000 and 4,895 deaths as of 2017, with a growing trend expected over the coming years. The Ministry of Public Health of Ecuador (MSP) released a document titled "Cost of Type 2 Diabetes Mellitus Disease" in 2013. It states that the State spends about $826 annually and $27,600 on life expectancy for a patient with type 2 diabetes who has no complications and is treated with simple pharmaceuticals. Conversely, the cost and life expectancy for a patient with diabetes-related chronic problems are about $22,520 and $296,005, respectively (Neuen et al., 2022).

Both macrovascular and microvascular consequences, including coronary heart disease, myocardial infarction, hypertension, peripheral vascular disease, retinopathy, end-stage renal disease, and neuropathy, are responsible for the direct costs of this illness. When cardiac glucotoxicity and poor metabolic control coexist, it can seriously impair a diabetic patient's quality of life, increasing their risk of death, frequent hospital stays, and high absenteeism from work. Consequently, ischemic heart disease, heart failure, stroke, and coronary and peripheral artery disease, all of which result in death in 50% of cases, are the central cardiovascular disorders (CVD) linked to DM2 (Shaman et al., 2022).

The necessity to research medications with pleiotropic effects has arisen from this pathophysiological solid link. As a result, numerous studies have shown that sodium-glucose cotransporter 2 (SGLT2) inhibitors, a pharmacological class of oral antidiabetics, minimize the onset or progression of heart failure by lowering the risk of cardiovascular events as well as inhibiting glucose reabsorption in the renal tubules. SGLT2 inhibitors, in particular, have been demonstrated to be helpful in the treatment of renal disease and heart failure when diabetes is not the primary pathology. This systematic review aims to assess the cost-effectiveness ratio and the safety and effectiveness of SGLT2 inhibitors in patients with established cardiovascular disease and DM2 during standard treatment (Miller et al., 2020).

METHODS:

Qualification standards

Included were randomized clinical trials assessing the safety and effectiveness of using inhibitors of SGLT2 in individuals with established cardiovascular disease and DM2 in the context of standard care and its cost-effectiveness ratio. English studies from the previous five years were taken into account. Excluded from consideration were studies involving animals and individuals without DM2 with a cardiovascular disease history. Moreover, research that failed to assess the negative consequences of these oral hypoglycemic medications statistically was disregarded (Nørgaard et al., 2022).

Search techniques

A comprehensive electronic search was conducted in the PubMed, Scopus, Web of Science, and ScieLO databases for publications published between January 2024 and 2018. Cardiometabolic, inhibitors, cotransporter, sodium-glucose type 2, diabetes, acute myocardial infarction, stroke, hospitalization, cardiovascular death, cost-effectiveness, randomized controlled trial, original article were the MeSH terms used in English (Feig et al., 2020).

Choice of studies

To assess the side effects of these medications, randomized clinical trials and original articles that provide the hazard ratio (HR), confidence interval (CI), and significance level (p) of acute myocardial infarction, stroke, death from cardiovascular causes, and hospitalization for heart failure in diabetic patients were selected (Croteau et al., 2021).

Results extraction and synthesis

Forms including authors, publication year, design, usage of SGLT2 inhibitors, sample, country, study group age and sex, presence of diabetes, glycosylated hemoglobin, cardiovascular risk, and length of follow-up were used. An additional form was utilized to determine the patients' standard course of treatment (Vallianou et al., 2022).

RESULT:

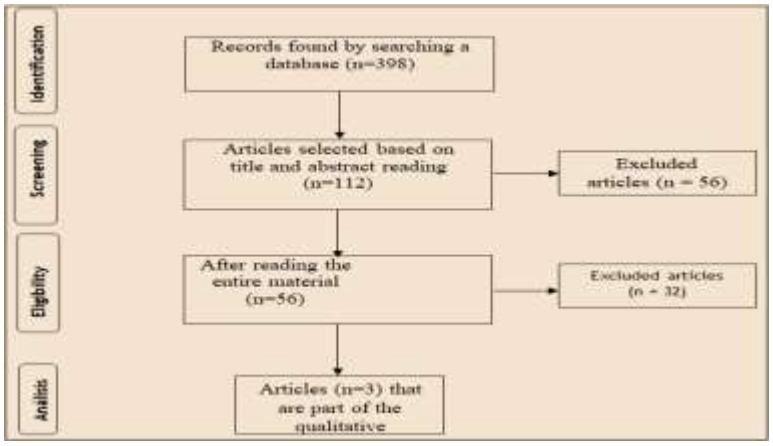

Figure 1: PRISMA study selection flowchart

Examination of SGLT2 inhibitors' cardioprotective benefits in DM2 patients

Table 1: The systematic review's primary studies are listed

NO.	1	2	3
Authors	(Zinman et al., 2015)	(Olmedo-Muñoz & Recalde-Navarrete, 2023)	(Huynh, 2019)
Qualification	EMPA-REG OUTCOME	CANVAS	DECLARE TIMI-58
Year	2015	2017	2018
Type of Study	Randomized clinical trial	Randomized clinical trial	Randomized clinical trial
SGLT2 inhibitors	Empagliflozin 10-25 mg/day	Canagliflozin 100-300 mg/day	Dapaglifozin 10 mg/day
Sample	7020 ISGLT2: 4687 Placebo: 2333	10142	17160 ISGLT2: 8582 Placebo: 8578
Country	Multicenter	Multicenter	Multicenter
Age	ISGLT2: 64,5 ± 8,8 Placebo: 64,5 ± 8,9	63,3 ± 8,3	
Sex	ISGLT2 Women: 30,7 % Men: 69,3 % Placebo Women: 28,3 % Men: 71,7 %	Women: 36 % Men: 64 %	Women: 33,5 % Men: 66,5 %
Diabetes	100 %	100 %	100 %
Glycosylated	<8,5 % ISGLT2: 3212 Placebo: 1607 >8,5 % ISGLT2: 1475 Placebo: 726	<8 % ISGLT2: 24,7 Placebo: 29,6 >8 % ISGLT2: 28,8 Placebo: 35,3	8,3 ± 1,2
hemoglobin			
Cardiovascular risk	ISGLT2: 635 Placebo: 325	ISGLT2: 34,1 Placebo: 41,3	ISGLT2: 653 Placebo: 648
Cerebrovascular disease	ISGLT2: 2732 Placebo: 1340	ISGLT2: 42,2 Placebo: 51,4	ISGLT2: 2824 Placebo: 2834
Coronary heart disease	ISGLT2: 412 Placebo: 191	ISGLT2: 33,9 Placebo: 41,3	ISGLT2: 522 Placebo: 503
Peripheral arterial disease	ISGLT2: 878 Placebo: 451	-	-
2 or 3 high-risk categories Tracking time	162 weeks	188 weeks	219 weeks

A study (Zinman et al., 2015) assessed the risk of cardiovascular events and the cardiovascular safety of empagliflozin in patients with T2DM who had been diagnosed more than ten years ago. A composite of cardiovascular mortality, myocardial infarction, or nonfatal cardiovascular incident was the primary outcome, and it varied between 10.5% and 12.1% (HR 0.86; 95% confidence interval (CI): 0.72-1.01; $p<0.001$ for non-inferiority; $p=0.04$ for superiority) when comparing empagliflozin to placebo. Hospitalization rates for unstable angina, which comprise the primary outcome and the secondary outcome, were found to be 12.8% for empagliflozin and 14.3% for placebo (HR 0.89; 95% CI: from 0.73 to 1.02; $p<0.001$ for non-inferiority; $p=0.08$ for superiority). Glycated hemoglobin (HbA1c) changed by an average of -0.5% and -0.6% with empagliflozin 10 mg and placebo, respectively, after 12 weeks, during which the hypoglycemic treatment had to stay the same (Zhang et al., 2021).

Without causing a rise in heart rate, empagliflozin was linked to slight decreases in weight, waist circumference, uric acid, and systolic and diastolic blood pressure. The patient group receiving empagliflozin and the placebo group experienced similar adverse effects. Consequently, urinary tract infection was observed in 18.1% of patients receiving placebo and 18% receiving empagliflozin. However, 6.4% of cases, compared to 1.8% had genital infections. Hypoglycemia was another side effect that affected 27.8% of people on empaglifozin and 27.9% of participants on placebo. 0.1% of individuals had diabetic ketoacidosis as opposed to less than 0.1%. 5.9% of patients taking the SGLT2 inhibitor and 4.9% receiving a placebo experienced volume-depleted states.

A composite of death from cardiovascular causes and nonfatal myocardial infarction or stroke was included as a primary outcome in the author's CANVAS study (Olmedo-Muñoz & Recalde-Navarrete, 2023). This composite occurred in 26.9% of patients treated with canagliflozin, compared to 31.5% with placebo (HR 0.86; 95% CI: 0.75 to 0.97; $p<0.001$ for non-inferiority; $p=0.02$ for superiority). Conversely, mortality from any cause, death from cardiovascular reasons, advancement of albuminuria (more than 30% rise), and the composite of hospitalization for heart failure and death from cardiovascular illnesses was the secondary outcome for evaluating the conditional sequence hypothesis. Nevertheless, no superiority was shown for deaths from any cause ($p=0.24$), defying the theory's prediction. As a result, mortality outcomes were deemed not significant. These included death from cardiovascular causes (HR 0.87, 95% CI: 0.74 to 1.01) 72 to 1.06) and death from any cause (HR 0.87, 95% CI: 0.74 to 1.01) (Vallianou et al., 2022).

Albuminuria declined in 293.4 canagliflozin-treated individuals compared to 187.5 placebo-treated patients (HR 1.70; 95% CI: 1.51 to 1.91). The canaglifozin group's mean HbA1c level change from the placebo group's was -0.5% (95% CI: 0.61 to 0.56). Body weight differences were 1.60 kg (95% CI: 1.70 to 1.51). Additionally, direct cardiovascular advantages have been shown, with a drop in diastolic blood pressure of -1.3 mmHg (95% CI: 1.61 to 1.17; $p < 0.001$) and a decrease in systolic blood pressure of -3.9 mmHg (95% CI: 4.30 to 3.56) for all comparisons. In the canaglifozin group, the use of additional hypoglycemic medications was 9.3% lower (95% CI: 11.0 to 7.6). Adverse events, including diuresis, volume depletion, and vaginal infections, were noted in previous reports. Canagliflozin, however, was associated with a greater incidence of lower limb and toe amputation in 6.3 versus 3.4 patients, respectively (HR 1.97; 95% CI: 1.41 to 2.75) (Al-Shamasi et al., 2021).

An assessment of the cardiovascular effect in patients at risk of atherosclerotic cardiovascular disease was the goal of the DECLARE-TIMI-58 research. The main results included hospitalization for heart failure or cardiovascular death, as well as a primary safety outcome of significant adverse cardiovascular events. As a result, in 4.9% of patients treated with dapagliflozin, the rate of hospitalization for cardiovascular failure or death from cardiovascular causes was lower than in 5.8% of patients treated with placebo (HR 0.83, 95% CI: 0.73 to 0.95; $p = 0.005$). Notably, the SGLT2 inhibitor group had a poorer composite result because they were hospitalized for heart failure at a lower rate. The rate of cardiovascular death did not significantly differ between the two groups (HR 0.98, 95% CI 0.82 to 1.17) (Eraikhuemen et al., 2023).

Similar results were seen in the patient group with established atherosclerotic cardiovascular disease and several risk factors. Moreover, dapaglifozin did not outperform a placebo regarding primary safety against adverse cardiovascular events (95% CI, 0.71 to 0.98). Regarding important safety outcomes, the two groups' amputation rates, fracture, volume depletion, and hypersensitivity were comparable. On the other hand, the 0.3% dapagliflozin group experienced more cases of diabetic ketoacidosis than the 0.1% group (HR 2.18, 95% CI: 1.10 to 4.30, $p=0.02$). In both men and women, the frequency of genital infections was higher in the dapagliflozin group (0.9% vs. 0.1%; HR 8.36, 95% CI 4.19 to 16.68, $p<0.001$). Furthermore, five cases of placebo-treated Fournier's gangrene and one instance treated with dapagliflozin were recorded (Arvanitakis et al., 2022).

DISCUSSION:

The current study included three randomized clinical trials to assess the safety of SGLT2 inhibitor use in patients with DM2 and established cardiovascular disease during standard treatment compared to a placebo. The trials took into account adverse drug reactions, hospitalization for heart failure, and deaths from cardiovascular causes. The results demonstrated sound cardioprotective effects. Through the DAPA-HF clinical trial, the author assessed the probability of first hospitalization for heart failure and death from cardiovascular causes in 2019, regardless of the presence or absence of DM2. Thus, it was determined that the dapaglifozin group had a lower risk than the placebo group (Honigberg et al., 2020).

The efficacy of ertugliflozin in heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease was reported in the VERTIS CV clinical trial 2020. This showed that ertugliflozin is the fourth SGLT2 inhibitor with a cardiometabolic effect. There was a decrease in heart failure hospital admissions. However, there was no statistically significant increase in major adverse cardiac events compared to canagliflozin and empagliflozin. To assess the cardiometabolic impact of sotaglifozin in patients with T2DM and chronic renal disease, with or without albuminuria, multicenter research named SCORED was conducted in 2021. As a result, it was clear that there was a decreased risk of heart failure-related hospitalization, urgent care visits, and cardiovascular death (Kubica et al., 2023).

On the other hand, vaginal fungal infections, diarrhea, diabetic ketoacidosis, and volume depletion were the most often reported side effects associated with sotaglifozin. In terms of bone fractures, UTIs, and severe hypoglycemia, there were no changes between the SGLT2 inhibitor and placebo groups. Another research, named SOLOIST-WHF, was carried out by the authors in the same year to assess the safety and effectiveness of sotaglifozin when taken right away following an episode of decompensated heart failure. In the SGLT2 inhibitor group, the rate of new hospital admissions and deaths from cardiovascular causes was considerably lower. A meta-analysis published in 2020 verified that irrespective of renal function at the onset of treatment or history of atherosclerotic cardiovascular disease, there is a constant decrease in the risk of heart failure hospitalizations (Silva dos Santos et al., 2020).

When added to the standard treatment of individuals with high-risk diabetes mellitus, SGLT2 inhibitors have been shown in multiple studies to be cost-effective in lowering healthcare expenses related to cardiovascular problems. Thus, they created an economic model to extrapolate the costs and clinical outcomes of participants in the EMPA-REG OUTCOME study who had established cardiovascular disease and DM2, and they concluded that the cardiovascular outcomes were consistent with long-term clinical benefits at reasonable costs. Less clinical events largely offset the cost of empagliflozin, resulting in savings that allow the UK's National Health Service to use resources cost-effectively (£4,083 per quality-adjusted life year, significantly below the UK threshold of £30,000) (Ryan et al., 2020).

The author reported in 2019 the medical costs of diabetes and its consequences, as well as a cost-effectiveness analysis of therapy with empagliflozin plus conventional treatment compared to standard treatment alone in Asian patients involved in the EMPAREG-OUTCOME research. Consequently, it was noted that while traditional therapy alone produced 8.0 quality-adjusted life years, adding an SGLT2 inhibitor to the regimen produced 10.7 QLD. Over a lifetime, this translates to an increase of 2.7 quality-adjusted life years with empaglifozin. However, because there were fewer cardiovascular events due to the SGLT2 inhibitor, the average cost of these events dropped by 118,997 yen (Chen et al., 2021).

Using a Markov decision analysis model with one-year cycles and a lifetime time horizon, the Qatari healthcare system will assess the efficacy of empagliflozin plus metformin with metformin monotherapy in 2019 for patients with DM2 who are between the ages of 50 and 79 and already have cardiovascular disease. Thus, the model estimated that adding empagliflozin to standard treatment would save 1.9 extra life years and 1.5 quality-adjusted life years per person at an additional cost of QAR 56,869 ($15,619). This translates to an incremental cost-effectiveness ratio

of QAR 30,675 (USD 8,425) per life-year saved and QAR 39,245 (USD 10,779) per quality-adjusted life-year (Xu et al., 2022).

For patients with T2DM and CVD, empagliflozin plus metformin seems to be a reasonably priced therapeutic choice. The economic analysis conducted using data from the DECLARE-TIME 58 clinical trial indicated that dapagliflozin treatment was predominant in the United Kingdom, with an increase in life years from 10.43 to 10.48 and a decrease in total lifetime costs from £39,451 to £36,899, indicating a reduction in the financial burden of type 2 diabetes and its related complications. These findings are consistent with those of a prior study by the same author and other collaborators, which used data from the three major clinical trials EMPAREG-OUTCOME, CANVAS, and DECLARE-TIME 58 and found that, when used as an adjuvant to standard treatment, SGLT2 inhibitors are more costly than oral hypoglycemic medications or placebo (Kharitonova et al., 2022).

Patients with established atherosclerotic cardiovascular disease and those without a history of heart failure can both use this statement. In China and the UK, SGLLT2 inhibitors were similarly proven to be cost-effective in the subgroup with multiple risk factors. Nonetheless, the analyses conducted in the United States yielded less favorable outcomes than those reported for China and the United Kingdom. This is primarily because, compared to other nations, the list price of treatment with these kinds of pharmaceuticals is higher in the United States. This systematic review's drawback is the lack of research on the subject carried out in our nation due to the high costs of clinical trials and the often complicated procedure of obtaining ethical and regulatory permits (Bassols et al., 2023; Kharitonova et al., 2022).

However, when considering the real-world implications, the decrease in cardiovascular clinical events may partially offset the cost of SGLT2 inhibitor acquisition, saving the healthcare system money on treating potential issues. We will keep researching novel treatments aimed at preventing shared pathways in the development of problems, given the connection between the pathophysiology of DM2 and its consequences in generating cardiovascular events (Kaur et al., 2019).

CONCLUSION:

Developing new therapies that improve glycemic control and cardiovascular outcomes is critical as we enter a new era of evidence-based management of patients with T2DM and cardiovascular disease. This is because cardiovascular events are the primary cause of mortality in this population. Thus, in high-risk DM2 patients, extensive observational studies have shown the safety and effectiveness of SGLT2 inhibitors in lowering cardiovascular mortality, heart failure hospitalization, and nonfatal myocardial infarction and stroke. However, economic analyses have demonstrated that adding an SGLT2 inhibitor to standard therapy is more beneficial than assuming the expenses associated with cardiovascular problems.

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