Investigating The Role of Sodium-Glucose Cotransporter-2 Inhibitors in Slowing Down the Diabetic Kidney Disease Progression: A Meta-Analysis of Randomized Control Trials

Abstract

Background: The one of most common and severe complications is diabetic kidney disease, whichleads to in the long term. However, there are many recent developments in medical therapy, especially when we use inhibitors SGLT2, which always gives us the best outcome in improving patient compliance and reducing the higher risk of mortality which is associated with the long-run consequences of diabetic metabolic control.

Purpose: This comprehensive systematic review delves into the efficacy of SGLT2 inhibitors which have capacity to slow down the progression rate of diabetes kidney disorder.

Methods: The eligibility criteria were set up following the PRISMA guidelines' which are recommended 'population, intervention, comparison, outcome, and study (PICOS) design ' framework. Various digital databases, such as ClinicalTrials.gov, PubMed, Google Scholar, Cochrane, Medline, Embase, and others, were meticulously scanned to pinpoint relevant studies. A search strategy, crafted in line with the inclusion and exclusion criteria, was utilized to acquire the most pertinent studies.

Results: For this study, we selected twelve studies. Upon systematic scrutiny, it was revealed that a majority of these studies, precisely eight out of twelve (67%), showcased the effectiveness of SGLT2 inhibitors in diminishing kidney indicators like eGFR and UACR among diverse populations. Conversely, a lack of significant impact on primary endpoints was noted in four out of twelve studies (33.3%).

Conclusion: In the treatment of diabetic kidney disease (DKD), SGLT2 inhibitors present a hopeful option, showing considerable promise in slowing down the advancement of the illness and improving kidney function.

Keywords: Diabetic Kidney Disease, Chronic kidney disease, Randomized Control Trials, Metabolic

Introduction

A metabolic systemic condition which is known as diabetes mellitus (DM) wherein theability of body to process or produce enough level of insulin for its needs is compromised [1]. As per the 2022 National Diabetic Statistics Report by the Disease Control Center and Prevention (CDC), it is anticipated that the number of diabetes cases will rise to 37.3 million[2]. One of the most devastating long-term effects of diabetes is diabetic kidney disease (DKD), which is characterized by persistent damage to the kidneys in people with diabetes. Recent research indicates that between 20% and 50% of people with type 2 diabetes mellitus will develop diabetic ketoacidosis (T2DM) at some point [3]. Another issue leading to the development of DKD is poor insulin adherence in tandem with noncompliance with anti-diabetic medication. Such individuals are at high risk because patients with diabetes often have an unfavorable outcome based on additional risk factors. Such factors include genetic predisposition, smoking, high BMI, dyslipidemia, hypertension, and the presence of related co-morbid disorders. Therefore, the levels of such parameters as serum creatinine or cytostatin C, urinary albumin to creatinine ratios, and estimated glomerular filtration rates are usually tested to determine how well the kidneys work [4]. A recent investigation revealed that around 20% of individuals suffering from type 2 diabetes obtained an estimated glomerular filtration rate below 60 mL/min/1.73 m 2; additionally, 30-50 percent of these individuals excreted a greater amount of albumin in their urine. Following a median follow-up time of 15 years, an eGFR < 60 mL/min/1.73 m 2 was observed in 28 percent of the diabetic population, while another 28 percent had albuminuria. This was determined by the UK Prospective Diabetes Study [5]. Glycemic control and blood pressure management, the gold standard for preventing and treating diabetic kidney disease, are discovered to have no effect in halting the reduction in GFR and the progression to end-stage renal disease[6].

Managing cholesterol levels is an additional effective preventive measure. The ideal range for total cholesterol and low-density lipoprotein (LDL) is below 150 mg/dL (3.88 mmol/L) and 100 mg/dL (2.59 mmol/L), respectively [7]; It has been recommended to adopt new lifestyle habits, such as weight loss, promoting physical exertion, and avoiding sedentary behaviors [8]. For those with established DKD, the objectives of treatment are to decrease albuminuria, maintain renal function, and minimize morbidity and mortality associated with CVD [9].

All diabetic patients should receive dietary counseling as part of their patient-directed self-management training program. This counseling should cover topics such as salt limitation, carbohydrate and fat selection, and more. These medicines have shown promising results in decreasing proteinuria [10]. Glucose compliance is often not maintained by individuals, leading to the utilization of various pharmaceutical therapies aimed at regulating glycemic indices and managing symptoms. Different mechanisms within the body are targeted by different pharmacological treatment strategies to establish an anti-hyperglycemic state. These strategies encompass the use of Biguanides (such as metformin), Sulfonylureas (including glipizide, gliclizide, and glymepride), Meglitinides

(like rapaglinide and nateglinide), Drugs that inhibit SGLT2, for example, , Empagliflozin, Edapagliflozin and Canagliflozin), amongst others.

Among the several pharmaceutical treatments available, SGLT2 inhibitors have shown promising results in lowering the mortality risk associated with diabetic neuropathy and diabetic nephropathy as well as in maintaining adherence to diabetes treatment plans [11]. Metformin plus an SGLT2 inhibitor is the first-line pharmacological treatment suggested for most persons with type 2 diabetes (T2D) and diabetic kidney disease (DKD) if the estimated glomerular filtration rate (eGFR) is higher than 30 mL/min/1.73 m2 [12]. Gliflozins cause glucosuria by inhibiting SGLT2 cotransporters in the proximal tubules, which obstructs renal glucose reabsorption. An approximate 1% decrease in glycemia and HbA1c is linked to this phenomenon [13]. The accompanying excretion of sodium facilitates the reversal of tubuloglomerular feedback and the lowering of intraglomerular pressure, both of which are essential for the nephroprotective actions of SGLT2 inhibitors. SGLT2 inhibitors reduce the amount of glucose reabsorption in the kidneys, which causes osmotic diuresis and a decrease in plasma volume. Roughly one-third of patients on SGLT2 blockers show a noteworthy eGFR decrease of greater than 10% [11-13]. While the effect on glucose level seems to be minor, the fact that they "arguably reduce blood pressure and without causing hypoglycemia and similarly reduce bodyweight" is a major advantage. A systematic review will analyze how SGLT inhibitors are effective and how they can reduce the development of progressive DDKD. The review will also compare different relative interventions, groups, competition, equity medication, timing, measurement options, and placebo.

Rationale

For diabetic nephropathy, pharmacological interventions have been well studied. However, the most appropriate choice of techniques in relation to renal function is still insufficient. The exact treatment linkage of Diabetic Kidney Disease and Chronic Kidney Disease remains uncertain and depends on the symptoms and their timing and on how consistently patients adhere to their therapy programs. Furthermore, a universal approach for early DKD detection must be developed urgently. As a result, changes in the UACR and eGFR must be constantly tracked and documented. A comprehensive explanation of the variations in treatment modalities in reaction to the data obtained by the eGFR and UACR test will be provided by this study through a detailed analysis of these outcomes:

Objectives

Many different goals were examined in the subjects. The first one included "to study whether the SGLT2 inhibitors can be used to reduce the progression of CKD damage". The second aspect is the following: "to study how SGLT2 inhibitors affect the eGFR and UACR of DM2 patients with low-to-moderate risk of DKA. The third research question was "to study the comparative effect of SGLT2 blockers in reduction of various glycemic indices, associated with CKD". Since it is essential to provide clinicians with

enough data to help them create evidence-based guidelines for optimal nephroprotective therapy and care for diabetic kidney disease, some additional data on the efficacy of these drugs was presented.

Methodology

Eligibility Criteria

PRISMA guidelines and the use of the 'Population, Intervention, Comparison, Outcome, and Study Design (PICOS)' scheme, were utilized to generate the eligibility criteria [14]. First, the literature that was considered eligible for inclusion comprised primary research that had undergone peer review, otherwise known as Randomized Control Trials, and published after 2018 to those published before 2024. The population of interest included individuals who were newly or already diagnosed with diabetes and had been living with diabetes for many years with either high probability of developing diabetic nephropathy (DKD). The studies that were utilized investigated the effects that various SGLT2 inhibitors had on the kidneys, as well as how these inhibitors contrasted with other drugs that were classified under the same category.

The later-discussed trials that reported efficacy in lowering relative risk and composite renal outcomes were also included in the criterion. Research published before 2018, non-observational and review studies, diabetes patients regardless of their diagnosis of chronic kidney disease (CKD), and studies involving children and adolescents were excluded from consideration.

It's noteworthy that all data points for estimation had a mean follow-up duration exceeding 20 weeks. Therefore, this review's analytical data consists of primary and secondary outcomes followed up at the 24-week point. Patients with eGFR values ranging from 30 to 60 ml/min/1.7 m2 were included in the study because of the known nephroprotective effects of SGLT2 inhibitors when the mean eGFR is greater than 60 ml/min/1.7 m2. The correctness, validity, and reliability of the results were ensured by ignoring any further information or estimation points beyond the 24-week time frame in this assessment. (Table 1)

Criteria	Inclusion	Exclusion
1. Study language	Studies published in the English language	Studies not published in the English language
2. Study duration	Studies published between 2018 and 2023	All the studies that were published before 2018
3. Study design	Primary studies (RCTs) Qualitative Quantitative	Prospective Protocols Reviews Grey literature
4. Location	Global	
5. Target population	Patients of DKD with recorded follow-up data at least 24 weeks Patients were selected if they had a mean eGFR greater than 60mL/min/1.72m2 All adults with UACR of 270 mg/g at baseline	Populations with disorders other than renal and cardiorenal complications caused by ongoing diabetes. Treating diabetic neuropathy, diabetic dermopathy, and cardiovascular disease is the main emphasis of the research.

6. Follow-up	Research including a minimum of 24 weeks of follow-up in order to collect sufficient evidence for chronicity.	Research that presents results in less than 24 weeks.
7. Context	Trials examining the effects of different SGLT2 inhibitors on kidney outcomes Research comparing SGLT2 inhibitors to similar medications	Studies on non-renal consequences Studies discussing other anti-diabetic medications.

Table 1: Systematic Review: And its Eligibility Criteria

Information Sources

Many electronic sources were searched to find pertinent literature. ClinicalTrials.gov, PubMed, Google Scholar, Cochrane, Medline, and Embase are a few of them. Other sources including independent journals were available. In addition to databases, periodicals including the "Journal of the American Society of Nephrology," "Diabetes Care," "BMJ," "Elsevier," and others were used to compile the material.

Search Strategy

The search strategy was devised following the PICOS scheme (explained later) to retrieve pertinent data from digital databases. In the final sample, 12 studies (from a total sample of n = 94) met the eligibility criteria. A search query was formulated for PubMed encompassing the following terms: (("sodium-glucose transporter 2 inhibitors"[Pharmacological Action] OR "sodium-glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium-glucose transporter 2 inhibitors"[All Fields] OR "sodium-glucose transporter 2

inhibitors"[All Fields]) AND ("diabetic nephropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "nephropathies"[All Fields]) OR "diabetic nephropathies"[All Fields] OR ("diabetic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "diabetic kidney disease"[All Fields])) AND ((randomizedcontrolledtrial[Filter]) AND (2019:2024[pdat])).

Selection Process

The research methodology was crafted through a careful review of peer-reviewed journals and reputable publications. We meticulously scrutinized literature that met our predefined inclusion criteria, employing the PICOS scheme for thorough examination. To mitigate publication bias, we meticulously assessed peer-reviewed journals with substantial impact factors through an extensive literature review. To streamline primary and secondary literature screening, all chosen articles underwent evaluation using Rayyan.ai, a specialized screening tool [15]. The papers suitable or excluded according to the criteria were defined with the cooperation of a team of researchers. Following the evaluation of the results, only 12 studies with a total of 94 participants could be obtained for the analysis. Papers that did not correspond to the eligibility were labeled for dispute or exclusion. To solve disputes, a panel of three researchers was used to arrive at the final decision. The studies were then excluded if they referred to another population, an inadequate method, misleading outcomes, or a high bias. There could be more than one of the characteristics described above found in some of the studies.

Data Items

After finalizing the secondary screening process, we assessed the overall sample size (n=12) pertaining to the selected literature. To create a PRISMA flow chart that follows the rules of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), we used articles from reputable journals and other sources (Figure 1) [16]. In order to mitigate bias in the analysis, several steps were implemented: (1) rigorous selection of top-tier research materials, (2) mandatory disclosure of conflicts of interest by peer reviewers, and (3) preference for meta-analyses over conventional review articles. Systematic and narrative reviews were deliberately omitted to uphold the study's integrity. Utilizing randomized methods, a visual representation in the form of a "traffic light" figure was created based on the collected data. (Figure 1)

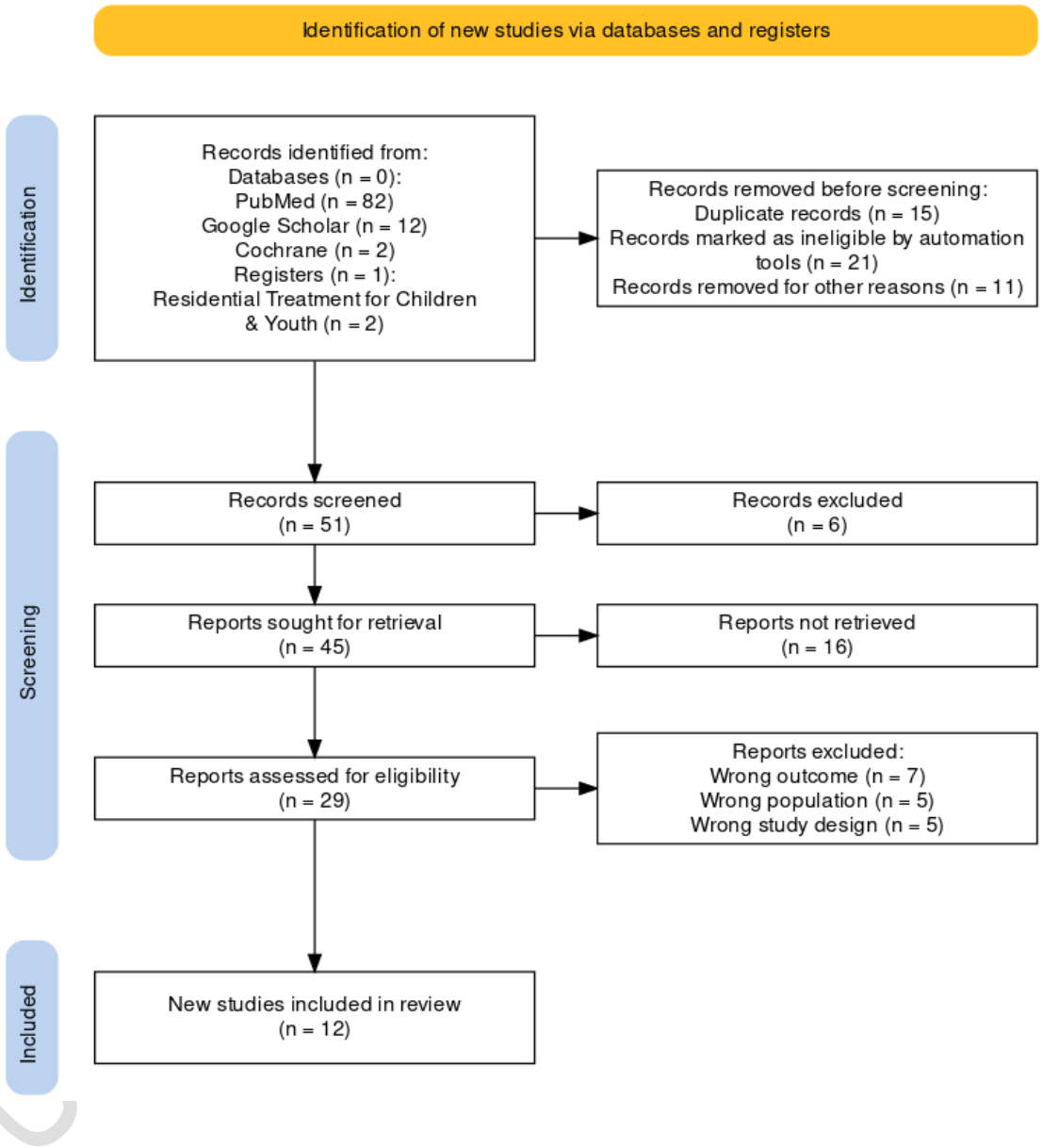
Identification of new studies via databases and registers
Identification
Records identified from:
Databases (n = 0):
PubMed (n = 82)
Google Scholar (n = 12)
Cochrane (n = 2)
Registers (n = 1):
Residential Treatment for Children & Youth (n = 2)
Records removed before screening:
Duplicate records (n = 15)
Records marked as ineligible by automation tools (n = 21)
Records removed for other reasons (n = 11)
Screening
Records screened
(n = 51)
Records excluded
(n = 6)
Reports sought for retrieval
(n = 45)
Reports not retrieved
(n = 16)
Reports assessed for eligibility
(n = 29)
Reports excluded:
Wrong outcome (n = 7)
Wrong population (n = 5)
Wrong study design (n = 5)
Included
New studies included in review
(n = 12)

Figure 1: The Literature Review: PRISMA chart

Assessment of research quality

-systematic review: We conducted a comprehensive analysis of bias in every main study selected for quality evaluation. This required analyzing the population demographics, the characteristics of the interventions, and the region where the study was conducted.

- meta-analysis: In assessing the presence of bias within the selected studies, we employed various digital and online tools. Each primary study, specifically randomized controlled trials (RCTs) eligible for analysis, underwent scrutiny based on the Cochrane criteria for bias evaluation. We thoroughly examined domains susceptible to bias, including[17] First, a random sequence should be created; second, allocations should be kept a secret; third, participants and staff should be blinded; fourth, outcome assessments should be blinded; fifth, attrition bias should be addressed; sixth, selective reporting should be avoided; and seventh, other biases should be recognized and mitigated. All 12 studies' continuous data were included in the statistical meta-analysis. A "traffic lights" plot was used to visually display the quality rating for each randomized controlled trial (RCT). A "traffic lights" plot was used to visually display the quality rating for each randomized controlled trial (RCT). In addition, Review Manager (RevMan version 5.4) was used to create a "forest plot" for the meta-analysis. RevMan (3.5.1) made it straightforward to do a meta-analysis of the 12 original inquiries. For the analytical tool, three researchers gathered comparable and poolable data [18]. Because all of the data in our investigation were available as continuous variables, complete accessibility was guaranteed. The dataset used in our meta-analysis can be found in the results section.

Results

Study Characteristics

Twelve studies were meticulously chosen for inclusion in the final sample. Among the randomized control trials, two were post-hoc analyses stemming from three primary studies. The RCTs incorporated in this review comprised non-dependent trials with continuously analyzable data or other short-term trials concluding within a 24-month timeframe. Noteworthy among these trials were "The Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58)" and

"CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation)". The sample sizes across these studies ranged from N = 22 to 17,130 individuals, while follow-up periods varied between 2 months and 24 months (2 years). The findings of the systematic analysis unveiled that 8 out of 12 studies (67%) supported the relative effectiveness of SGLT2 blockers in reducing kidney indices across all studied populations. Conversely, 4 out of 12 studies (33.3%) indicated no significant impact on the primary endpoints.

1. eGFR

On average, the average reduction in estimated glomerular filtration rate (eGFR) from 60ml/min/1.7m^2 was reported in four out of twelve trials. Dapagliflozin reduced eGFR below 65.5 ml/min/1.7 m^2 for all individuals whose GFR was initially greater than 65 ml/min/1.7 m^2, according to a 2019 study by Mosenzon O et al. A comparable investigation carried out in 2022 by Mosenzon O et al. also noted this pattern [22], The comparative analysis revealed that the dapagliflozin group exhibited a decreased relative risk for categorical declines in eGFR compared to the placebo group.

2. UACR

Out of the twelve studies examined, seven included data on the quantitative comparable changes of UACR values from the baseline. Two of those studies involved empagliflozin, one featured canagliflozin, and the remaining four contained dapagliflozin. The information presented was also significantly boosted by the study of Halden TAS et al, [19], During the 24-week following the administration at the same dose regimens, empagliflozin was connected to the significant UACR decrease by 20.22%, in comparison to the placebo. Human subjects were the group, Oda's [20] illustrated similar results. With the average UACR being 31% lower for the intervention group participants that received canagliflozin and canagliflozin ataluren placebo at the same doses after 24 weeks. The same pattern was presented by other studies: the 2023 research conducted by Yoshihra F et al., and Mosenzon et al.'s 2022 follow-up[22], The two studies depicted a significant reduction in mean UACR of 21.1% and 25%, respectively. Thus, the study showed the SGLT2 inhibitors' efficacy to enhance kidney function. Therefore, giving hope that the period before the need for dialysis could be prolonged.Furthermore, several studies have shown a relative increase in renal glucose excretion (Pollock C et al., 2019) and hematocrit (Halden TAS et al., 2020), highlighting the potential advantages of SGLT2 inhibitors for overall disease improvement [23]. The findings from the thematic analysis have been presented in the synthesis table. Below is a summary of the systematic review. (Table 2)

S. No.	Author ID	Region	Study Design	Participants	Intervention Groups	Outcomes		Other Findings
						UACR	GFR	

1	Halden TAS et al. (2019) [19]	Norway	Single-center, prospective, double-blind study	The trial included 49 patients. to be able to follow up, five had to be retrieved. Each group, including the placebo, had 22 patients. Only patients with stable renal function, defined as an eGFR greater than 30 mL/min/1.73 m2, were considered for inclusion.	Over the course of 24 weeks, patients were randomly assigned to either take 10 mg of empagliflozin or a placebo once day. Renal glucose excretion in g/h/day and urinary albumin creatinine ratio (UACR) were among the cardiorenal outcomes that were examined.	Twenty-two percent (22.0 mmol/mol) compared to one percent (1 mmol/mol) (P = 0.025) was the significantly decreased UACR with empagliflozin compared to the placebo.	-	Additionally, there was a notable decrease in body weight of 22.5 kg (24.0, 20.05) in comparison to the placebo group, which saw a gain of 1.0 kg (0.0, 2.0) (P = 0.014).
2	Oda M et al. 2020 [20]	Global	multicenter, double-blind, placebo-controlled, randomized trial	A total of 4,401 patients from 34 different countries were randomly assigned to 690 different sites. To be eligible, patients needed to be at least 30 years old and have type 2 diabetes with a HbA1c score ranging from 6.5% to 12.0%.	Randomly permuted blocks based on screening eGFR groups assigned participants to either 100 mg of canagliflozin daily or a placebo. 30 to 45, 40 to 60, and 90 to 90 ml/min per 1.73 m^2	At week 24, canagliflozin decreased UACR by 31% in comparison to the placebo.	-	When canagliflozin was given to people with type 2 diabetes, albuminuria dropped quickly and stayed low. This was linked to better long-term kidney health.

3	Levin A et al. 2020 [21]	Global	Randomized, Double-Blind, Placebo-Controlled, Multinational Trial	From September 2010 to April 2013, a total of 7028 patients were randomly assigned to study treatment.	One or more doses of the experimental drug (placebo, n=2333; empagliflozin 10 mg, n=2345; empagliflozin 25 mg, n=2342) were administered to patients from 590 sites distributed throughout 42 different countries.	Empagliflozin was effective in reducing albuminuria in low-moderate risk patients who had progressed to UACR>300 mg/g, doubling of serum creatinine, or death from renal disease.	-	Across all Kidney Disease Improving Global Outcomes (KDIGO) risk categories, empagliflozin was linked to a constant and lower relative risk when compared to placebo.
4	Mosenzon O etal. 2022 [22]	Multinational	Post Hoc Analyses From the DECLARE-TIMI 58 Trial	N=15201, all eligible participants were in the low-moderate KDIGO risk category	The DECLARE-TIMI 58 trial randomized patients with T2D at high cardiorenal risk to dapagliflozin or placebo.	-	Smaller eGFR declines (≥57% [in those with baseline	Dapagliflozin reduced kidney function decline in T2D patients at high cardiovascular risk, even

							eGFR ≥60 mL/min/ 1.73 m^2]) have been correlated to dapagliflozin.	those with moderate risk, highlighting the importance of early prevention of diabetic kidney disease.
5	Pollock C et al. 2019 [23]	Sydney, Australia	double-blind, placebo-controlled trial	N=1187 patients were screened, with 461 (39%) randomly allocated. 13 patients (five in the placebo and six in the dapagliflozin group), Study duration was July 2015 to May 2018.	Patients who took dapagliflozin 10mg alone had a median UACR of 270 mg/g (IQR 69-751) at baseline. Similar doses were supplied to the placebo group.	The difference in 24-hour UACR was -19.9% in the dapagliflozin group and -39.7%	-	The problems seen in this group of people with type 2 diabetes and chronic kidney disease were similar to those seen in earlier studies.
6	Mosenzon O et al. 2019 [24]	Canada	DECLARE–TIMI 58 randomized trial	Between 2013, and 2018, data from 17160 patients with type 1 diabetes who were at high risk of DKD were gathered for kidney-specific	Once daily, participants were randomized (1 to 1) to receive either 10 mg of dapagliflozin or a placebo. A reduction in the 40% glomerular filtration rate [eGFR] was a secondary	The difference in 24-hour urine albumin excretion was -21.44% in the	The dapagliflozin group had a substantially reduced eGFR of	-

				outcomes.	composite outcome.	dapagliflozin group and -37.7% ($p < 0.0001$).	less than 60 mL/min per 1.73 m^2 compared to the placebo group (HR 0.54 [95% CI 0.43–0.67]; $p < 0.0001$).	
7	Yoshihara F et al. 2023 [25]	Japan	A multicentre, randomised, open-label, parallel-group, standard treatment-controlled trial	294 patients were randomly assigned to either the dapagliflozin group (n = 146) or the control group (n = 148). The average age of the patients was 72.1 years, and 29% were female. Of the 146 patients in the dapagliflozin group, 122 finished the study.	A random sequence generator was used to assign participants 1:1 to either dapagliflozin or control. Changes in UACR from baseline over two years of surveillance were the primary endpoints	The estimated median UACR was 25.0 mg/g in the dapagliflozin group and 25.6 in the control group.	In the dapagliflozin group, the average calculated GFR remained at 65.7 mL/min/ 1.73 m2.	The main outcome showed no statistically significant differences between the dapagliflozin and control groups.

8	Perkovic V et al. 2019 [26]	N/A	Double-blind, randomized trial	N=4401 participants had undergone randomization, with a median follow-up of 34 months	Canagliflozin 100 mg daily or a placebo was administered to individuals with type 2 diabetes who had albuminuric renal disease	-	-	In the renal-specific composite, the chance of end-stage kidney disease, creatinine levels rising by two times, or death from renal causes dropped by 34%.
9	Wheeler DC et al. 2021 [27]	Global	Multicentre, double-blind, placebo-controlled, randomised trial done	Feb 2, 2017; and June 12, 2020. A median of 2·4 years (IQR 2·0–2·7) of follow-up was provided to the 4304 participants who were randomly assigned (2152 to dapagliflozin and 2152 to placebo).	Dapagliflozin 10 mg once day or a matching placebo was given to participants at random in a 1:1 ratio.	-	-	Dapagliflozin equally reduced the relative risk of the primary composite outcome in individuals who have type 2 diabetes and those without the disease.
10	Jongs N et al. 2021	Global	Post Hoc Analyses From the DECLA	17,160 T2D patients who were enrolled in the DECLARE-TIMI	Participants in the DECLARE-TIMI 58 study were randomly assigned to either take	-	Dapaglif lozin reduced the risks	A reduced risk of functional decline was observed at all

	[28]		RE-TIMI 58 Trial	58 trial were taken into account in the final analysis.	dapagliflozin or a placebo if they were at high risk for cardiovascular disease and kidney disease. .		of categorical eGFR declines ($P < 0.05$).	points
11	Zelniker TA et al. 2021 [29]	Global	Randomized, Double-Blind, Placebo-Controlled, Multinational Trial	6952 patients with baseline eGFR and urinary albumin-creatinine ratio values were categorized as having a low, moderately increased, high, or very high KDIGO risk	In addition to their regular medical supervision, patients with type 2 diabetes were randomly randomized to receive placebo, empagliflozin 25 mg, or 10 mg of the medication once daily.	-	-	Across all KDIGO categories, empagliflozin continuously lowered the risk of renal outcomes, and its side effects were comparable to those of a placebo.
12	Kato S et al. 2023 [30]		Multicenter, double-blind, placebo-controlled, parallel-group randomized	The iTandum1 research enrolled 1,575 patients at 75 locations in the US and Canada with an estimated glomerular filtration rate (eGFR) higher than 65	Every single participant was randomly assigned to either receive SOTA (200 mg or 400 mg) or a placebo. .	At 52 weeks, SOTA 400 mg resulted in an 18.3% reduction in UACR compared to the placebo, while SOTA 200	-	In patients with type 1 diabetes, the clinical cardiorenal health indices were improved by SOTA, a dual SGLT1 and SGLT2 blocker.

			control trial	mL/min/1.73 m2. The 96 research locations that took part in iTandum2.		mg reduced it by 23.7%.		

Table 2: Results of the Systematic Review[19-30]

Quality Assessment

Each study was subjected to a quality evaluation using the Cochrane Risk of Bias (ROBvis2) tool. A visual representation, akin to a "traffic light" plot, was crafted to illustrate the risk of bias across various domains within the studies. The outcomes of this assessment are depicted in the accompanying figure below. (Figure 2)

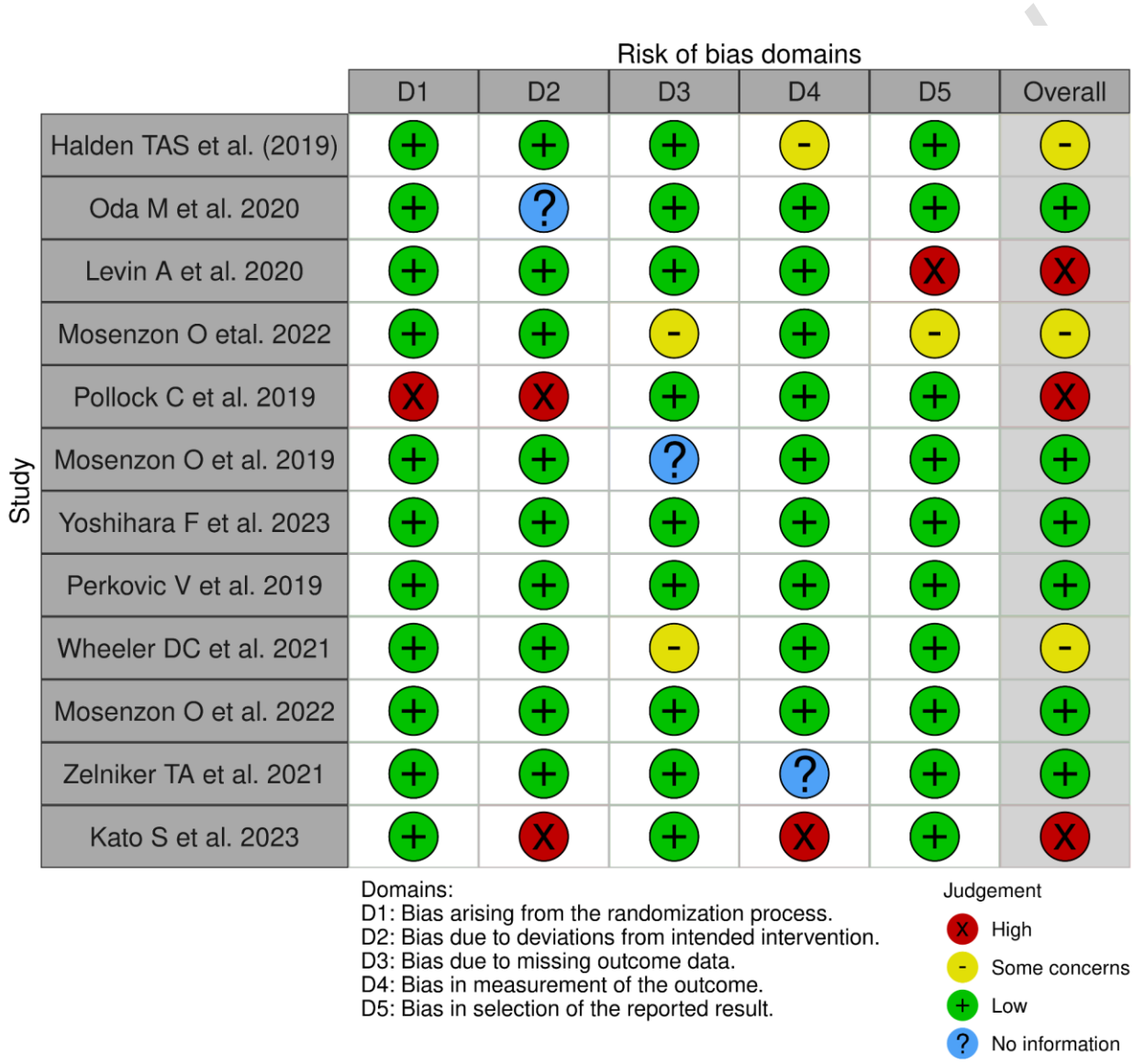

Figure 2: Evaluation of the Bias Risk in the Selected Studies

Forest Plots

Using the generalized inverse variance approach, data from eight different studies were combined to create a forest plot with the primary outcome represented by the hazard ratio (HR). The HR was computed using a random-effects model as well as "log[HR]" and "Standard Error(SE)." The green squares represented the point estimations, and the horizontal axis showed the confidence interval (CI=95%). Lack of influence was shown by the central vertical line. The research used a fixed effects model to show all the data.

1. Albumin(urinary) Creatinine Ratio (UACR)

1.1 Dapagliflozin

The current study was mainly concerned with the comparison of UACR. For individuals receiving dapagliflozin, the baseline UACR was 270 gm/mm3 in all tests. Four trials across all investigated the relative UACR between a placebo and a dapagliflozin dose of 10 mg. Interestingly, dapagliflozin use was positively correlated with lower UACR levels in all four investigations. The dapagliflozin group benefited from the cumulative effect size across all inquiries, with a combined effect showing HR= 0.66 [95% CI (0.54, 0.82)]. The data showed heterogeneity, as indicated by Chi2=8.64, df=3, and I^2=65%. Z-score for the overall effect test was 3.82 [p = 0.0001]. Examining individual effect sizes, HR values were reported to be 0.59, CI=95%, [0.39, 0.89], 0.52, CI=95% [0.34, 0.80], 0.41, CI=95% [0.22, 0.76], and 0.97, CI=95% [0.69, 1.39] for Mosenzon et al. (2019) [24], Mosenzon O et al. 2022 [22], Pollock C et al. 2019 [23], and Wheeler DC et al. 2021 [27], respectively. The assessment determined that dapagliflozin effectively decreased the urinary albumin-to-creatinine ratio (UACR) in qualifying patients across every group. (Figure 3)

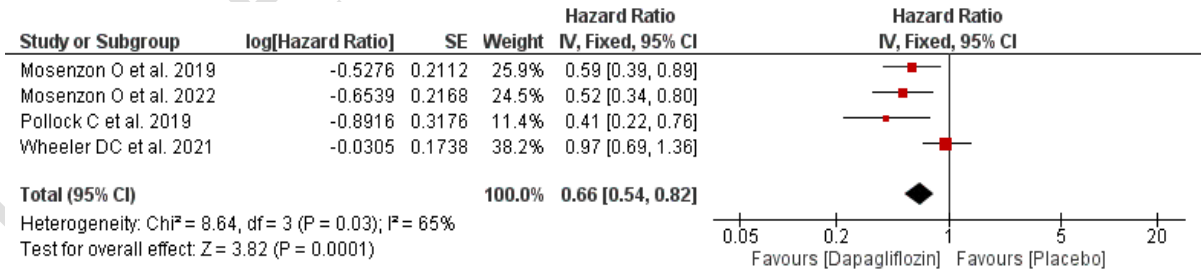

Figure 3: UACR decreases with Dapagliflozin; forest plot of all mean values [22][23][24][27]

1.2 Empagliflozin

Three studies were conducted to find the effectiveness of Empagliflozin, an SGLT2 inhibitor, in reducing the mean UACR among eligible participants. In these studies, participants were administered comparable doses of empagliflozin and a placebo over a period of 24 weeks. It's

worth noting that dichotomous data were utilized for analysis, and the results were interpreted using the Mantel-Haenszel test. A favorable association between the medicine and the primary endpoint was demonstrated by each of the three investigations, which together accounted for one hundred percent of the total. Taking into account the overall effect size of all the studies, the odds ratio (OR) was found to be 0.77, with a confidence range spanning from 0.69 to 0.87 for the 95% confidence level. On the other hand, there was a significant amount of heterogeneity, as demonstrated by a Chi-square value of 10.81 coupled with two degrees of freedom and an I-squared value of 82%. Based on the Z-score of 4.31 (p-value < 0.0001), it was determined that the predicted effect size was statistically significant. Despite the overall favorable trend towards the experimental (Empagliflozin) group, one out of the three studies did not show a significant effect individually, although its mean OR values still leaned towards the experimental group. For this study by Halden TAS et al. 2019, the individual effect sizes were found to be HR= 0.97, CI=95% [0.64,1.47], and HR was found to be 0.65, CI=95% [0.56, 0.76], and 0.97, CI=95% [0.79, 1.18][19], for Levin A et al. 2020 [21], Zelniker TA et al. 2021 [29], respectively. At a 24-week subsequent follow-up, it was established that empagliflozin prominent decreased UACR when comparing to placebo. (Figure 4)

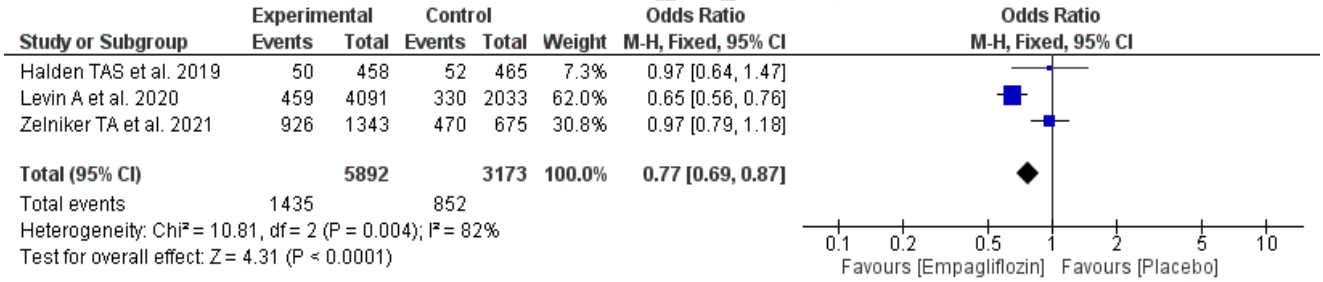

Figure 4: Forest plot for mean UACR reductions with Empagliflozin [19][21][29]

1.3 Canagliflozin

The relative efficacy of the SGLT2 inhibitor canagliflozin has been the subject of a few research, which has decreased the statistical precision of our analysis. Hazard Ratios (HR) for the outcome under examination were only available from two studies. The combined effect size was determined to be HR=0.77 with a 95% confidence interval of (0.71, 0.83). Analysis revealed moderate heterogeneity with a Chi-squared value of 2.19, a degree of freedom 1, and an I-squared value of 54%. The overall effect test yielded a Z-score of 6.20 (p-value < 0.00001). Individual effects were observed at HR=0.79, CI=95% [0.72, 0.87] and HR=0.67, CI=95% [0.71, 0.83], for Oda M et al. 2020 [20], Perkovic V et al. 2019 [26], respectively. (Figure 5)

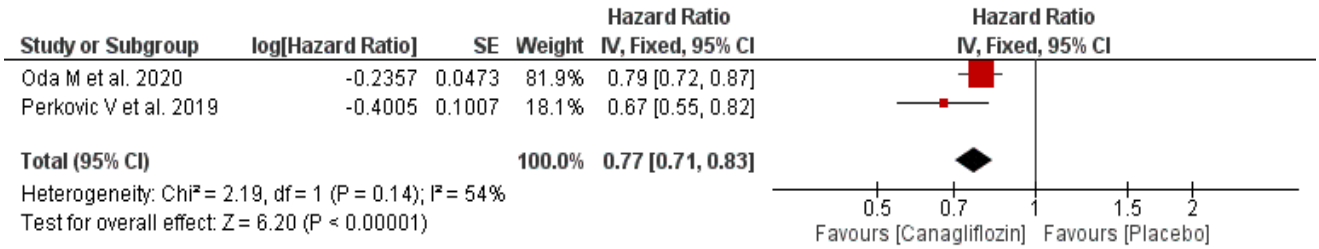

Figure 5: Forest plot using canagliflozin for mean UACR [20][26]

2. **Average Reduction in GFR**

The study's second primary focus was on estimating reductions in GFR (glomerular filtration rate). Dapagliflozin was the only drug for which data on eGFR values were available, and the estimation points were all set at 24 weeks across all sample sizes. According to what was said before, the average eGFRs of all patients fell within the range of 30 to 60 ml/min/1.7 m^2. There was no difference in sample sizes between the control and intervention groups. At the 24-week point, results on eGFR decreases were presented from four investigations. The dosage schedules used by the intervention and placebo groups were comparable. It was found that the total effect size was HR= 0.67 [95% CI (0.60, 0.75). It was found that the heterogeneity was I2= 22%, df=3, and Chi^2= 3.87. A p-value of less than 0.0001 was obtained for Z=7.19 in the overall effect test.

The individual effect sizes were as follows: for Mosenzon O et al. 2019 [24], Mosenzon O et al. 2022 [22], Wheeler DC et al. 2021 [27], and Yoshihra F et al. 2023 [25], HR was found to be 0.54, CI=95% [0.40, 0.73], 0.73 [95% CI (0.63, 0.85)], 0.64 [95% CI (0.52, 0.79)], and 0.56 [95% CI (0.32, 0.98)], respectively. One hundred and forty percent of the four studies showed a significant positive connection between the variables under investigation. As a result, it was concluded that dapagliflozin is an effective way to lower eGFR values in people who have a low to moderate risk of developing DKD. (Figure 6)

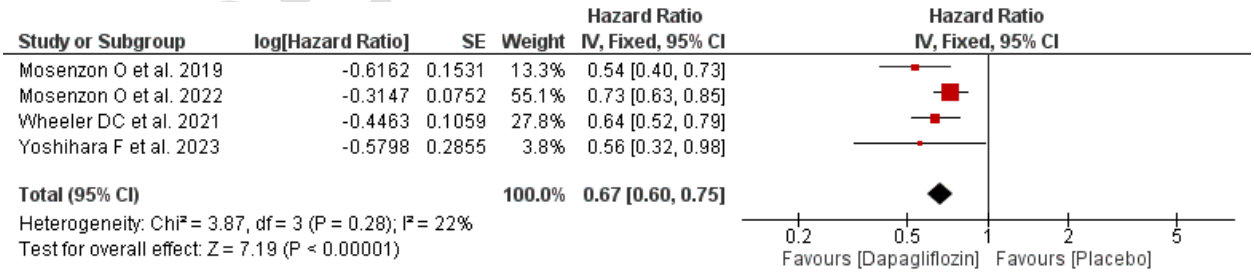

Figure 6: Forest plot for the mean reduction in eGFR assessed with Dapagliflozin [22][24][25][27]

3. **Hematocrit**

A relatively decrease in kidney function, which occurs frequently as a consequence of chronic renal disease linked to either type I or type II diabetes, is directly correlated with a decrease in hematocrit levels. SGLT2 inhibitors have been observed to lead to a notable increase in

hematocrit levels, typically by around 10%. Data from three studies focused on dapagliflozin revealed consistent improvements in hematocrit levels across all studied populations, as indicated by the graphical representation. All three studies demonstrated enhanced hematocrit indices. After combining the data, the effect size that was obtained was HR=0.42 with a 95% confidence interval ranging from 0.19 to 0.93. In the analysis, there was very little heterogeneity, as indicated by Chi2=0.00, df=2, and I2=0%. The Z-score obtained from the test for the overall effect was 17.20, with a p-value of less than 0.00001. For the research conducted by Halden TAS et al. in 2019, the individual effect sizes were calculated as follows: HR=0.42 [95% CI (0.38, 0.46)], 0.41 [95% CI (0.15, 1.12)], and 0.42 [95% CI (0.19, 0.93)] [19], Mosenzon O et al. 2019 [24], Pollock C et al. 2019 [23], respectively. The examination determined that dapagliflozin significantly impacts the secondary endpoint (Hematocrit), thus further solidifying its nephroprotective efficacy in diabetic kidney disease. (Figure 7)

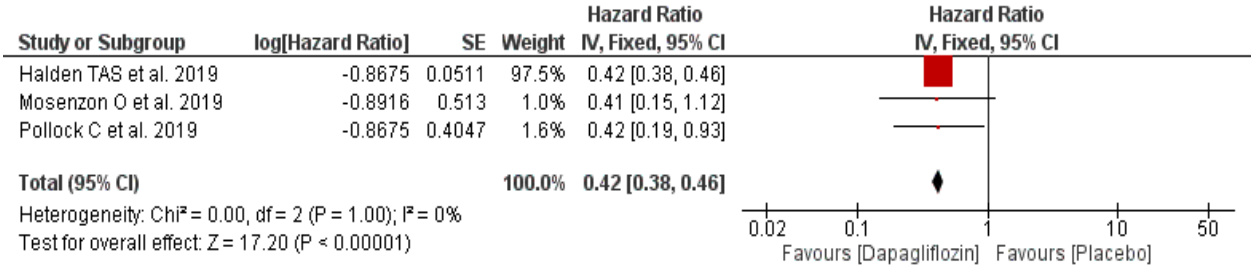

Figure 7: Forest plot for average Increase in Hematocrit with Dapagliflozin [19][23][24]

Discussion

When it comes to patients who have known risk factors for developing complex diabetic nephropathy, SGLT2 inhibitors offer a positive outlook. This article takes a comprehensive look at the role that SGLT2 inhibitors play in slowing down the progression of diabetic kidney disease (DKD). When chronic renal disease and diabetes are present at the same time, there is an unavoidable chain of events that leads to a steady decline in kidney function [31]. The existing data clearly demonstrates the significant contribution of SGLT2 in safeguarding against potential deterioration in kidney function. Recent studies have shown that the majority of SGLT-2 receptors are situated in the proximal tubule, where they supervise the reabsorption of sodium ions and glucose. One possible mechanism by which SGLT-2 inhibitors prevent the renal tubules from reabsorb Na+ is by binding competitively to glucose [32]. Enhancing the TGF pathway's function leads to better relaxation of the outflow in small arteries, consequently reducing intraglomerular pressure and alleviating glomerular hyperfiltration [33]. Preserving kidney function and reducing the progression of nephropathy are both greatly aided by these consequences. The use of SGLT2 inhibitors is not without its limitations, though. Most people whose diabetes is progressing to type 1 or type 2 and who are nearing end-stage renal disease (ESRD) benefit from these inhibitors [34]. However, SGLT2 inhibitors should not be used by anyone with the following conditions: chronic kidney disease (CKD) stage 3 or 3b, a history of

diabetic ketoacidosis (DKA), a predisposition to urinary tract infections (UTIs), or amputations of limbs caused by diabetic neuropathy. It is recommended that these individuals not use pharmacological therapy based on SGLT2 inhibitors. Because kidney function continues to decline with time, those with an estimated glomerular filtration rate (eGFR) below 60, 30, or 25% ml/min/1.7 m2 should see a nephrologist for guidance on whether to renew their prescription or adjust the dosage. Medication replacement that is both effective and safe can significantly reduce mortality rates in these cases [35].

The latest meta-analysis has presented findings on the urinary albumin-to-creatinine ratio (UACR) outcomes across all medications within the SGLT2 inhibitor class, namely Dapagliflozin, Empagliflozin, and Canagliflozin. Conducting a thorough comparative assessment is crucial to identifying the most suitable drug for commencing pharmacotherapy in all patients. With an HR= 0.66 [95% CI (0.54, 0.82)], dapagliflozin was found to have the most significant impact in the most current study. That's a 0.0001 p-value. Empagliflozin also showed a significant impact size with an odds ratio of 0.77 (95% CI: 0.69 to 0.87) and a p-value less than 0.001, whilst canagliflozin showed an effect with a hazard ratio of 0.77 (95% CI: 0.71 to 0.83). The p-value is less than 0.00001.

The analysis indicates that dapagliflozin resulted in the most significant reduction in UACR, followed by canagliflozin and then empagliflozin. Nevertheless, it's important to acknowledge that these outcomes are heavily influenced by various factors such as patient characteristics, treatment adherence, glucose tolerance, and concurrent health conditions. Most investigations have therefore failed to reach a definitive conclusion regarding the comparative evaluation of these medications. One research, by Kato S. et al. 2023 [30], compared varying dosing schedules of Sotagliflozin, an alternative SGLT2 inhibitor, within the relevant patient group. Two distinct dosages of 200mg and 400mg were evaluated. Results indicated that the 200mg dosage reduced UACR by 23.7%, whereas the 400mg dosage resulted in a slightly lower reduction of 18.3%. This suggests a more significant decrease in kidney-related indicators with the lower dosage. Notably, Sotagliflozin is approved for treating Type 1 DM patients.

Early administration of SGLT2 inhibitors to diabetic individuals, particularly those prone to or already experiencing DKD, may mitigate the risk of kidney-related complications [36]. Think about the potential advantages of combining SGLT2 inhibitors with other medications that are already helpful in treating DKD, including ACE inhibitors or ARBs, which are RAAS inhibitors. [37]. Utilizing combination therapy could yield synergistic benefits in mitigating the progression of renal disease. The next logical stride in addressing diabetic kidney disease involves the integration of support through the enhancement of treatment algorithms, the provision of comprehensive education and training for healthcare practitioners, and facilitating access to these medications for eligible patients [38], with or without sequelae.

Strengths

Our study search method yielded a large number of articles, providing a varied viewpoint on the existing literature on SGLT2 inhibitors and their effect on the course of DKD. To raise the bar for study quality and cut down on bias risk, we instituted stringent inclusion criteria. In addition, a meta-analysis was used to combine data quantitatively, which allowed for a comprehensive review of the effectiveness and safety of SGLT2 inhibitors. The described methodological changes enhance the study findings to provide critical information on the proper administration of these drugs in treating DKD.

The limitations of this study include the struggle to identify the most appropriate results and indicators to measure and report. This study tried to describe in possible detail how it was done, including the sample sizes for the multiple analysis that were not conforming to the regular protocols, although different. The study ways and the sample structure and composition of the primary research concerned were mentioned without highlighting the methodological characteristics. Therefore, the use of a small number of primary studies to measure the effectiveness of such a large sample is another limitation. In addition, the contrasting aggregate effect over all sizes, we contrasted all sizes without assessing within-group or sub-group sizes. Many studies show a question within populations that shows that the results of final analyses are different.

Conclusion

To summarize, SGLT2 inhibitors present an attractive option for DKD treatment by substantially and substantially reducing the potential for DKD progression as well as significantly improving the health of the kidney. This treatment not only controls diabetes but also defends the kidney by inhibiting glomerular hyperfiltration, reducing inflammation and fibrosis and keeping renal function. They can be much more effective if started earlier and used together with current medications. The incorporation of SGLT2 inhibitors into medical practice can significantly broaden the treatment's benefits and drug-facilitated lifestyle enhancements in persons suffering from DKD.

Abbreviations

DM - Diabetes Mellitus
DKD - Diabetic kidney disease
T1DM and T2DM - Type 1 or 2 Diabetes Mellitus
SGLT2 - Sodium-Glucose Co-Transporter Inhibitors
eGFR - Estimated Glomerular Filtration Rate
UACR - Urinary Albumin Creatinine Ratio
CKD - Chronic Kidney Disease

DECLARE-TIMI Trial - The Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58

CREDENCE Trial - Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation

HR - Hazard Ratio

DKA - Diabetic Ketoacidosis

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