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Review Article

Reno-protective effect of SGLT-2 inhibitors in nondiabetic patients. A comparative review

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ABSTRACT

Pharmaceuticals called sodium-glucose cotransporter-2 (SGLT-2) inhibitors are used to manage diabetes mellitus. They mainly target the enzyme SGLT-2, which is located in the kidney's proximal tubule. Recent research suggests that SGLT-2 inhibitors demonstrate positive effects on kidney health in adult chronic kidney disease (CKD) patients, irrespective of whether they have type 2 diabetes. This study aims to highlight different SGLT-2 inhibitors that have reno-protective effects in non-diabetic patients with different kidney and comorbid disease conditions. It has been demonstrated that dapagliflozin, a particular SGLT-2 inhibitor, reduces early levels of proteinuria in pediatrics with proteinuric CKD. On the other hand, empagliflozin has demonstrated positive effects on kidney health in adult CKD patients, regardless of whether they have type 2 diabetes. Furthermore, canagliflozin has been found to protect against cisplatin-induced acute kidney injury (AKI) in a mouse model. Ertugliflozin administration has been associated with a reduction in the ratio of urinary albumin to creatinine and mitigated a decline in creatinine-based estimated glomerular filtration rate (eGFRCr). In conclusion, in non-diabetic cases, SGLT-2 inhibitors have generally shown promise in maintaining kidney function; dapagliflozin and canagliflozin, in particular, have been demonstrated to have beneficial effects on proteinuria levels and AKI, respectively.

Keywords: *Chronic kidney disease; Empagliflozin; Reno-protective; non-diabetic patients; SGLT-2 inhibitors.*

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1. Introduction

Type 2 diabetes (T2DM) is treated with a new family of oral medications called SGLT-2 inhibitors. Ninety percent of the active renal glucose reabsorption in the S1 segment of the early proximal tubule is attributed to the renal SGLT-2, which is the target of these medications. These inhibitors lower blood glucose levels without the need for insulin by stopping the proximal renal tubules from reabsorbing glucose. According to a recent study, these drugs may have renoprotective benefits since they reduce the degree of albuminuria and moderate the decline in GFR in patients with diabetes-related kidney disease **[1]**.

Large cardiovascular outcome trials (CVOTs) have demonstrated renal protective advantages linked with the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors, as demonstrated by secondary analysis of the combined microvascular outcome **[2-5]**.

Among the therapeutic advantages of SGLT-2 inhibitor medication for the kidney in diabetic patients is the improvement of albuminuria and the mitigation of the rate of renal function deterioration **[6]**. This supports the assumption

that SGLT-2 inhibitors can provide reno-protective benefits in non-diabetic individuals.

2. Methods

The present review included a range of search strategy results and data sources, including literature reviews, systematic reviews, and clinical trials. A search strategy was formulated employing medical subject headings (MeSH) to explore the PubMed scientific databases. The MeSH terms employed encompassed SGLT-2 inhibitors, non-diabetic patients, Reno-protective, Dapagliflozin, Empagliflozin, and Canagliflozin. The inclusion criteria comprised studies published in the English language from 2005 to January 2024, with a particular focus on the most recent literature on the Reno-protective effect of SGLT-2 inhibitors in non-diabetic cases as represented in the article selection flow chart **(Fig. 1)**.

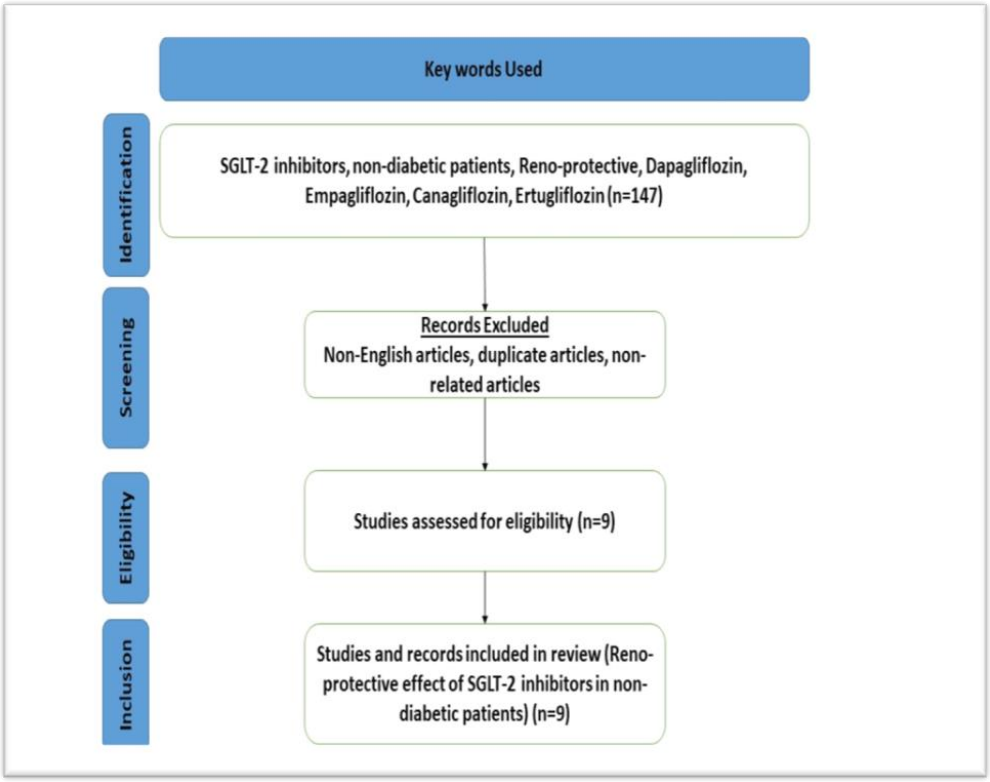

Fig. 1. Articles selection flow chart

3. Results and Discussion

3.1. Chronic Kidney Disease

Chronic kidney disease (CKD) is a medical disorder marked by ongoing changes to the structure or function of the kidneys, or both, with potential consequences to an individual's overall health. Imaging methods may be used to monitor various conditions such as cancers, atrophy, abnormalities, and cysts. On the other hand, edema, growth retardation in children, changes in urine production or quality, and hypertension can all be signs of renal malfunction. Increased blood urea nitrogen, cystatin C, or creatinine levels are commonly used to detect these alterations. Regardless of the underlying injury or illness, renal fibrosis is among the most common pathological signs of CKD **[7-9]**.

The prevalence of CKD in all stages ranges from 7 to 12% worldwide. Adults with CKD G3–G5 have varying prevalence rates around the world; figures have been reported as 1.7% in China, 3.1% in Canada, 5.8% in Australia, and 6.7% in the US. Europe-wide, the prevalence varies; it is 2.3% in Germany, 2.4% in Finland, 4.0% in Spain, and 5.2% in England **[9]**.

The fluctuation in these numerical values is a matter that warrants additional investigation and could potentially be ascribed to various factors (e.g., certain studies may employ a singular time juncture, thereby not satisfying the criteria for CKD); thus, it remains uncertain whether the prevalence has been overestimated or underestimated **[10]**.

3.1.1. Classification

The most accurate measure of overall renal function is thought to be the glomerular filtration rate or GFR. It quantifies the total volume of fluid that is filtered by all the functional nephrons in a specific unit of time **[11]**.

Chronic kidney disease (CKD) is categorized based on the eGFR **(Table 1)**, ranging from stage 1 to 5. Stage 1 signifies an eGFR greater than 90 mL/min, coupled with other renal abnormalities such as proteinuria. In stage 2, the eGFR falls within the range of 60-89 mL/min, while stage 3 corresponds to an eGFR of 30-59 mL/min. Stage 4 is characterized by an eGFR of 15-29 mL/min, and finally, stage 5 indicates an eGFR below 15 mL/min **[12]**.

Table 1. Various phases of CKD

Stage	**1**	**2**	**3**	**4**	**5**
Description	Kidney damage with either normal or high GFR	Kidney damage with mild reduction in GFR	Moderate reduction in GFR	Severe reduction in GFR	Kidney failure
GFR mL/min/1.73 m^2	≥ 90	60 - 89	30 - 59	15 - 29	<15 (or dialysis)
Related terms	Proteinuria, albuminuria, hematuria	Proteinuria, albuminuria, hematuria	Chronic and early renal insufficiency	Chronic and late renal insufficiency, pre-ESRD	Renal failure, uremia, ESRD

Note: ESRD, end-stage renal disease; GFR, glomerular filtration rate.

3.1.2. Epidemiology

The deficiency of research carried out in local communities, the absence of consistent methods for evaluating kidney function, and the use of non-standardized or non-calibrated approaches all lead to an inadequate comprehension of the epidemiology of CKD in low- and middle-income nations. Nevertheless, in areas where evaluations have been carried out, such as sub-Saharan Africa, some Latin American nations (including Mexico), and Southeast Asia, the prevalence of CKD seems to correspond with estimations between 10% and 16%. The majority of prevalence statistics that are now accessible, as stated in the first CKD categorization scheme that was published in 2002, only take into consideration albuminuria based on measurements of GFR **[13, 14]**.

3.1.3. Pathophysiology

Kidney fibrosis gradually appears as a result of chronic and continuous insults resulting from progressive and chronic nephropathies, in contrast to AKI, where the healing process results in a complete functional recovery of the kidneys. This detrimental process affects the three

divisions of the renal organ: the glomeruli, tubules, interstitium, and arteries. From a histological standpoint, it presents vascular sclerosis, tubulointerstitial fibrosis, and glomerulosclerosis **[15]**.

The intricate and overlapping sequence of events that contribute to the formation of scar tissue and fibrosis is a multifaceted and multi-stage phenomenon. It includes the infiltration of impaired kidneys with inflammatory cells recruited from other tissues, the triggering, multiplication, and loss of constitutional renal cells (via programmed cell death, tissue death, degeneration of mesangial cells, and depletion of podocytes), the activation and proliferation of cells that produce extracellular matrix (such as myofibroblasts and fibroblasts), and the deposition of extracellular matrix that replaces the normal structure **[15]**.

The following factors may speed up the course of chronic kidney disease (CKD) **(Fig. 2)**: hypertrophy of the glomerulus, systemic and intraglomerular hypertension, changes in prostanoid metabolism, and the kidney's production of calcium phosphate **[15]**.

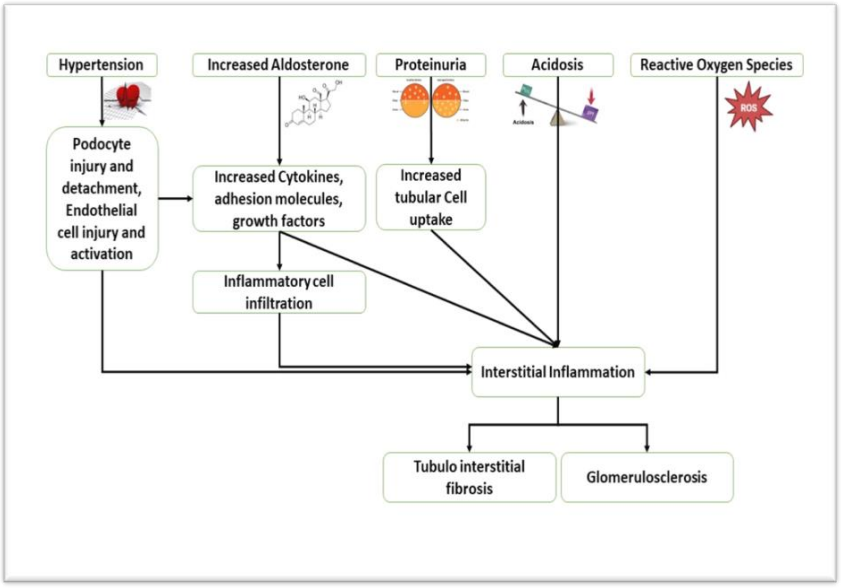

Fig. 2. Mechanisms underlying chronic kidney disease progression

3.1.4. Proteinuria

Proteinuria, the presence of excess protein in the urine, is a significant marker and consequence of chronic kidney disease (CKD). It occurs when the kidneys' filtering units, known as glomeruli, are damaged, allowing proteins such as albumin to leak into the urine **[16]**. In the early stages of CKD, proteinuria may be mild and asymptomatic. However, as kidney function declines, the amount of protein in the urine increases, leading to more severe health issues **[17]**.

One of the primary consequences of proteinuria in CKD is the exacerbation of kidney damage. The presence of protein in the urine indicates that the kidneys' filtering capacity is compromised. This can lead to a vicious cycle where the loss of proteins further damages the kidneys, increasing proteinuria and accelerating CKD progression **[18]**. Proteinuria also can lead to edema (swelling) due to the loss of proteins that help regulate fluid balance in the body **[19]**. Another significant consequence of proteinuria is its impact on cardiovascular health. Patients with

CKD and proteinuria are at a higher risk of cardiovascular diseases, including heart attacks and strokes **[20]**.

3.2. SGLT-2 inhibitors

SGLT-2 inhibitors, a class of pharmacotherapeutic medications, are used to treat diabetes mellitus. These agents exert their primary effect by selectively targeting SGLT-2, an enzyme localized within the proximal tubular epithelium of the kidneys. The main way that SGLT-2 inhibitors work is by slowing down the kidneys' ability to reabsorb salt and glucose **[21]**.

These specific drugs have garnered considerable attention due to their observed nephroprotective effects and their ability to decrease the occurrence of cardiovascular events, as demonstrated in several large-scale clinical trials **[22, 23]**. Indeed, SGLT-2 inhibitors were found to enhance GFR and lower mortality in a large-scale clinical study involving 4,304 CKD patients who were not diabetics **[24]**. Similarly, a second clinical study with 6,609 individuals with chronic kidney disease found that using empagliflozin medication was related to a decreased risk of renal disease progression **[25]**.

These findings are in line with previous post hoc analyses of clinical trials that found no connection between blood glucose levels, hemoglobin A1c (HbA1c), and the SGLT-2 inhibitors' nephroprotective benefits **[26]**. SGLT-2 inhibitors have also been demonstrated to improve renal oxygenation, lower glomerular hypertension, and hyperfiltration, and trigger anti-inflammatory and antifibrotic pathways **[27]**.

3.2.1. Renoprotective Mechanisms

Recent research has presented many explanations for the reno-protective benefit of SGLT-2 inhibitors in those with diabetes. Enhanced glomerular hyperfiltration, decreased renal oxygen consumption and inflammatory response, and improved cell energy metabolism are some of these processes. The indirect mechanism of SGLT-2 inhibitors' reno-protective benefits includes lowering blood pressure, uric acid, insulin, and insulin levels examined in a recent study. Other effects included encouraging weight reduction, increasing glucagon levels, and enhancing diuresis **(Fig. 3) [28, 29]**.

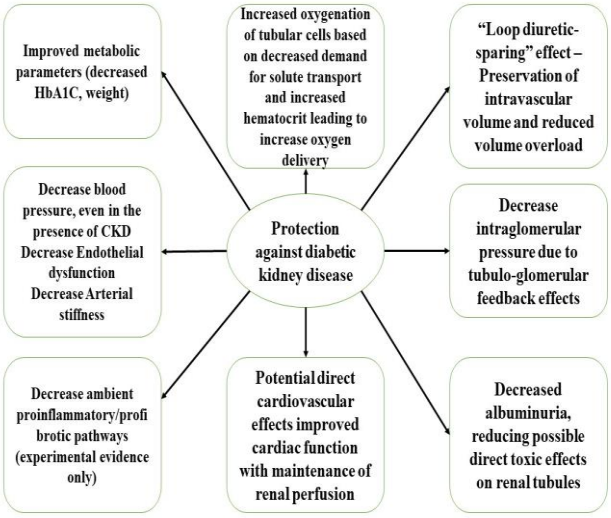

Fig. 3. Proposed mechanisms underlying renal protection with sodium-glucose cotransporter-2 inhibition

SGLT-2 inhibitors have been shown to postpone the onset of end-stage renal failure in non-diabetic instances of nephropathy by lowering the rate of single nephron glomerular filtration (SNGFR) and preventing hyperfiltration. Keep in mind that stopping SGLT-2 inhibitors returns SNGFR to its pre-starting SGLT-2 inhibitor level **[30]**.

Adding to the discussed reno-protective effects of SGLT2 inhibitors, they were also found to lower the risk of major adverse cardiovascular events and reduce all-cause and cardiovascular mortality. This demonstrates how these medications can be used for purposes other than treating diabetes **[31]**.

3.2.2. Uses of SGLT-2 inhibitors

The main purpose of SGLT-2 inhibitors is to treat T2DM in adult patients. It can be taken either alone or in addition to other antidiabetic medications. Furthermore, regardless of a person's diabetes status, SGLT-2 inhibitors such as dapagliflozin are authorized for the treatment of CKD for those who are at risk of their disease progressing **[32]**.

3.2.3. Side Effects

The most often reported side effects related to d SGLT-2 inhibitors are nasopharyngitis (common cold), urinary tract infections (UTIs), and genital mycotic infections (yeast infections). Other potential side effects include volume depletion (dehydration), hypoglycemia (low blood sugar), ketosis (breakdown of fat for energy), diabetic ketoacidosis (a severe complication of diabetes), bone fractures, and bladder cancer **[33]**.

3.3. Dapagliflozin

3.3.1. Clinical Efficacy

Studies have indicated that dapagliflozin is effective in lowering blood sugar levels for those with T2DM. Additionally, it has been noted to have other benefits such as a decrease in blood pressure and weight loss **[34]**. Additionally, dapagliflozin has demonstrated the potential to lower the risk of cardiovascular death, heart failure-related hospitalization, and kidney failure in those with CKD **[35]**.

3.3.2. The impact of dapagliflozin on proteinuria in non-diabetic individuals with chronic kidney disease

Conversely, a prospective case series, based on observation without intervention, was initiated among six patients diagnosed with Alport syndrome (AS) or focal segmental glomerulosclerosis (FSGS). With a once-daily dosage of either 10 mg dapagliflozin (n= 3) or 10 mg empagliflozin (n= 3), the patients gave their agreement for off-label therapy. The patients responded favorably to the combination of the renin-angiotensin-aldosterone system (RAAS)-blockade with either empagliflozin or dapagliflozin, and it helped reverse the initial fall in eGFR and albuminuria. This suggests that treating inherited podocytopathies by correcting the glomerular filtration barrier's hemodynamic excess via SGLT-2-mediated mechanisms has a lot of potential **[36]**.

Enrolling participants in an open-label, randomized clinical trial with an age range of 18 to 80 years was done. These patients had already taken their ACE inhibitor or angiotensin receptor blocker to the fullest extent allowed, and their eGFR ranged from 25 to 45 mL/min/1.73 m^2, while their albuminuria levels were between 150 and 2000 mg/g. For a period of four weeks, the individuals were randomized to receive a daily dosage of either dapagliflozin (10 mg) or finerenone (20 mg). Following this first stage, both medications were given in combination for a further four weeks. The results demonstrated that when finerenone was given either alone or in conjunction with dapagliflozin, the urine albumin-to-creatinine ratio (UACR) was

decreased by 24% and 34%, respectively. Similar to this, dapagliflozin treatment alone or in conjunction with finerenone caused an 8% and 10% drop in UACR, respectively **[37]**.

The combined use of finer one and dapagliflozin not only reduced albuminuria but also proved to be safe. Additionally, the observed effect of the combination therapy was found to be at least as potent as the predicted additive effect of each drug on its own, suggesting a synergistic influence on albuminuria **[37]**.

3.3.3. Dapagliflozin's impact on the rate at which kidney function decreases in those with chronic renal disease

In a clinical research study using a randomized controlled design, individuals with CKD aged 18 and older were eligible to participate, regardless of their diabetes status. The eGFR of the subjects ranged from 25 to 75 mL/min per 1.73 m^2, and their UACR varied from 200 to 5000 mg/g. In addition to their regular medication, the patients were randomly assigned to receive either a placebo or oral dapagliflozin (10 mg/day). Patients with T2DM, higher HbA1c levels, and greater UACR experienced the most significant differences in the average eGFR slope between those treated with dapagliflozin and those receiving a placebo **[38]**.

3.3.4. Efficacy and Safety of Dapagliflozin in Children with Inherited Proteinuric Kidney Disease

Proteinuria is considered a significant contributing factor to the advancement of CKD. In pediatric nephrotic syndrome, approximately 5% to 10% display resistance to steroid treatment and other immunosuppressive therapies. Roughly one-third of these cases can be linked to monogenic disorders. The fundamental strategy for addressing proteinuric CKD revolves around the use of blockers that target the renin-angiotensin-aldosterone system. However, these agents often prove ineffective in achieving a satisfactory reduction of proteinuria **[39]**.

The clinical findings from a study involving a cohort of 8 individuals aged 6 to 18 years indicated that dapagliflozin resulted in an average reduction of initial proteinuria levels by 33.3% after 4 weeks and 22.6% after 12 weeks in the subgroup of pediatric patients diagnosed with proteinuric CKD **[39]**.

3.3.5. Cost-Effectiveness of Dapagliflozin for Non-diabetic chronic kidney disease

In the United States, CKD affects approximately one in seven adults, imposing a considerable economic burden with an annual cost of $100 billion. The introduction of dapagliflozin in conjunction with standard care has demonstrated an extension of life expectancy by an additional two years. Furthermore, this intervention has led to an increase in discounted quality-adjusted life years (QALYs) from 6.75 to 8.06. It is noteworthy that the total incidence of kidney failure needing KRT dropped from 17.4% to 11.0% when dapagliflozin was released. Furthermore, the average duration of KRT has significantly dropped across the cohort's lifetime, from 0.77 years to 0.43 years **[40]**.

For individuals experiencing non-diabetic CKD, dapagliflozin has shown effectiveness in improving life expectancy, slowing down CKD progression, reducing the number of patients requiring kidney replacement therapy, and shortening the duration of time spent on kidney replacement therapy. The utilization of dapagliflozin aligns with established conventional criteria for cost-effectiveness **[40]**.

3.4. Empagliflozin

3.4.1. Clinical benefits

The administration of empagliflozin resulted in advantageous outcomes with the main

measures of effectiveness in both CKD and non-CKD patients. The benefits and safety of empagliflozin generally held throughout a wide range of renal function, even at baseline eGFR of 20 ml/min/1.73 m^2 **[41]**.

Empagliflozin has demonstrated effectiveness in improving cardiorenal outcomes and reducing the risk of heart failure hospitalization in patients with diabetes **[42]**.

3.4.2. Empagliflozin's impact on proteinuria and the development of kidney function in those with non-diabetic glomerulonephritis

Empagliflozin exhibits a beneficial impact on the improvement of proteinuria in individuals diagnosed with glomerulonephritis. Additionally, compared to a placebo, empagliflozin tends to safeguard kidney function in patients with glomerulonephritis **[43]**.

In a clinical trial, 3730 patients with class II, III, or IV heart failure with an ejection fraction of 40% or less were randomly assigned to receive 10 mg of empagliflozin once a day or a placebo in addition to their regular medication. Over the course of a median of 16 months, the primary end event happened in 462 out of 1867 patients (24.7%) in the placebo group and in 361 out of 1863 cases (19.4%) in the empagliflozin group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; P<0.001). The effect of empagliflozin on the primary outcome was independent of the presence of diabetes in the patient. Hospitalizations for heart failure were less common in the empagliflozin group than in the placebo group (hazard ratio, 0.70; P<0.001) **[44]**.

Individuals receiving empagliflozin had a decreased risk of severe renal consequences, and compared to the placebo group, the estimated glomerular filtration rate decreased at a slower yearly rate (-0.55 vs. -2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001). On the other hand, empagliflozin has been related to more frequent reports of simple genital tract infections **[44]**.

Regardless of diabetes, the effect of SGLT-2 inhibitors on cardiovascular events in patients with HFrEF was evaluated in a pre-specified meta-analysis of two large-scale studies (n= 8474). When SGLT-2 inhibitors were administered, compared to control, there was a statistically significant 13% decrease in all-cause mortality (hazard ratio [HR] 0.87, p= 0.018) and a 14% decrease in cardiovascular death (HR 0.86, p= 0.027). Additionally, SGLT-2 inhibitors led to a 26% decrease in the combined risk of cardiovascular death or first heart failure hospitalization (HR 0.74, p<0.0001) and a 25% reduction in recurrent hospitalizations for heart failure or cardiovascular death (HR 0.75, p<0.0001) **[45]**.

Additionally, there was a significant reduction in the risk of the composite renal endpoint (0.62, p= 0.013). Empagliflozin and dapagliflozin's consistent effects on heart failure hospitalizations in the two separate studies imply that these medications also improve renal outcomes and help lower the risk of cardiovascular and all-cause mortality in HFrEF patients **[45]**.

A controlled phase 3 experiment was undertaken in 241 locations throughout eight countries: China, Japan, Malaysia, Germany, Italy the United Kingdom, Canada, and the United States. To be eligible for inclusion, patients had to fulfill two requirements: they needed to have an eGFR of 20 to less than 45 mL/min per 1.73 m^2 or 45 to < 90 mL/min per 1.73m^2 and a UACR of 200 mg/g or greater at screening. They were randomized to receive 10 mg of oral empagliflozin per day in a 1:1 ratio, or a matching placebo. 6609 individuals were observed for a median of 2.0 years (IQR 1.5–2.4)

after being randomly assigned. According to study data, there was a statistically significant decrease in the incidence of renal disease progression in the empagliflozin group. With a hazard ratio of 0.71, progression happened in 11.6% of those using empagliflozin as opposed to 15.2% in the placebo group. These findings imply that taking empagliflozin in individuals with chronic renal illness may reduce their risk of disease progression **[46]**.

3.5. Canagliflozin

3.5.1. Canagliflozin protective effect against acute kidney injury secondary to cisplatin administration

An assessment was carried out to determine if canagliflozin offers a defense against acute kidney injury (AKI) brought on by cisplatin. This defense depends on adenosine monophosphate-activated protein kinase (AMPK) activation and the subsequent induction of autophagy. It was discovered through experimental research employing the human proximal tubule epithelial cell (HK-2) line that canagliflozin shields renal proximal tubular cells against cisplatin. However, the protective effects of canagliflozin were neutralized by the addition of either chloroquine or dorsomorphin, an AMPK inhibitor. Moreover, canagliflozin demonstrated efficacy in protecting mice against cisplatin-induced AKI in a mouse model of the disease. Nevertheless, the protective effect of canagliflozin disappeared when cisplatin and chloroquine or dorsomorphin were given together. These combined results suggest that canagliflozin's capacity to protect against cisplatin-induced AKI depends critically on the activation of AMPK and autophagy in renal proximal tubular cells **[47]**.

3.6. Ertugliflozin

A clinical trial that focused on assessing the efficacy and safety of ertugliflozin, found that this medication was able to decrease the likelihood of encountering the composite exploratory endpoint, which includes a sustained 40% decrease in baseline eGFRCr, the need for chronic renal replacement therapy, and mortality attributed to renal causes **[48]**. In addition, administration of ertugliflozin correlated with a reduction in the ratio of urinary albumin to creatinine and mitigated the decline in eGFRCr **[49]**.

In a different clinical trial, individuals were randomized to receive a placebo or ertugliflozin at a dose of 5 or 15 mg/d. Plasma samples were taken for biomarker analysis at three distinct intervals during the trial: baseline, 26 weeks, and 52 weeks. The results showed that independent of the participants' initial kidney function state, ertugliflozin treatment led to a persistent lowering of the tubular damage marker kidney injury molecule-1 (KIM-1) in people with T2DM and stage 3 CKD **[50] (Table 2)**.

Conclusion

SGLT-2 inhibitors, such as empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin, have shown promising results in improving renal function in individuals with CKD, both diabetic and non-diabetic. These inhibitors have been linked to a drop in the total number of renal failure cases that need KRT as well as a shorter KRT duration. In summary, SGLT-2 inhibitors have shown significant promise in improving renal outcomes and reducing the need for kidney replacement therapy in chronic kidney disease (CKD) patients. These medications are effective in decreasing albuminuria and preserving renal function.

Table 2. Summary of renoprotective effects of different SGLT-2 inhibitors

Therapy	Number of subjects	Disease conditions	Clinical outcomes	Ref
Dapagliflozin or Empagliflozin	6	Alport syndrome (AS) / Focal segmental glomerulosclerosis (FSGS)	Decline in eGFR Reduction of albuminuria	**[36]**
Dapagliflozin alone or + finerenone	20	eGFR between 25 and 45 mL/min/1.73m^2 & albuminuria levels (150 to 2000 mg/g)	dapagliflozin alone or + finer enone resulted in a decrease in albumin-to-creatinine ratio by 8% and 10%	**[37]**
Dapagliflozin	4304	eGFR 25 and 75 mL/min per 1.73m^2 urinary albumin-to-creatinine ratio (UACR) 200-5000 mg/g	Significant decrease in the long-term decline of eGFR in individuals with chronic kidney disease	**[38]**
Dapagliflozin	8	Proteinuric CKD pediatrics	Reduction of initial proteinuria levels by 33.3% after 4 weeks of treatment and 22.6% after 12 weeks	**[39]**
Empagliflozin	3730	Class II, III, or IV heart failure + Ejection fraction of ≤ 40%	Fewer hospitalizations for heart failure. Reduced risk of serious renal outcomes.	**[44]**
Empagliflozin or Dapagliflozin	8474	Heart failure with reduced ejection fraction	13% reduction in all-cause death 14% reduction in cardiovascular death Reduction in the risk of the composite renal endpoint	**[45]**
Empagliflozin	6609	eGFR of 20 to < 45 mL/min per 1.73 m^2, or 45 to < 90 mL/min per 1.73 m^2 + urinary albumin-to-creatinine ratio 200 mg/g or higher	kidney disease progression occurred in 11.6% of patients in the empagliflozin group compared to 15.2% of patients in the placebo group	**[46]**
Canagliflozin	HK-2 cell line	Cisplatin-induced acute kidney injury	canagliflozin protected renal proximal tubular cells from cisplatin-induced acute kidney injury	**[47]**
Ertugliflozin	231	T2DM + stage 3 CKD	Sustained reduction of the tubular injury marker KIM-1	**[50]**

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Publish

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing Interests

The authors declare that no competing interests exist.

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Authors' Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Reem Gamal Hammad. The first draft of the manuscript was written by Reem Gamal Hammad and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

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