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Review

Unveiling renoprotection: A comprehensive review of SGLT2 inhibitors, with emphasis on empagliflozin in the treatment of chronic kidney disease

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Abstract: Chronic kidney disease (CKD) affects 10%–13% of the global population, necessitating innovative treatments. Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, shows promise by reducing glycated hemoglobin and benefiting kidney and cardiovascular health. By spotlighting renoprotective mechanisms like glucose control and anti-inflammatory effects, insights from trials such as EMPA-REG OUTCOME unveil decreased kidney disease progression, improved eGFR, and reduced albuminuria with empagliflozin. Safety profiles and comparisons: Evaluating safety profiles, potential adverse events, and comparisons with other SGLT2 inhibitors provides a nuanced perspective on the therapeutic potential of empagliflozin. The review emphasizes the importance of diverse CKD population studies, continuous safety monitoring, and exploring SGLT2 inhibitors in specific demographics. In summary, empagliflozin emerges as a versatile therapeutic option in the SGLT2 inhibitor class for CKD, reshaping disease management. Final thoughts: Ongoing research and vigilant monitoring are crucial for maximizing the potential of SGLT2 inhibitors, especially empagliflozin, to enhance patient well-being in CKD.

Keywords: chronic kidney disease; SGLT2 inhibitors; empagliflozin; clinical trials; safety profile

1. Introduction

Chronic kidney disease (CKD) poses a substantial global health challenge, necessitating innovative therapeutic approaches [1]. With a prevalence of 10%–13% in the population, CKD is a progressive and irreversible condition linked to an elevated risk of cardiovascular complications and mortality. Symptoms manifest in advanced stages, leading to conservative measures for early cases and resorting to replacement therapies such as dialysis or transplantation for more severe instances [2–5]. Globally, it is estimated that nearly 700 million individuals are living with CKD [6]. Beyond primary kidney ailments, prevalent chronic conditions like hypertension and diabetes also contribute to kidney damage, further exacerbating the overall burden of CKD [7].

Over the past two decades, the only agents demonstrating a decline in the risk of CKD progression in both diabetes and non-diabetes patients were angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [8,9]. However, neither class of drugs has shown a reduced risk of all-cause mortality in CKD patients. Additionally, evidence supporting their use in CKD patients without type 2 diabetes mellitus (T2DM) is relatively scarce [10–12].

Various interventions are currently available to impede the progressive decline of renal function and potentially prevent the onset of cardiovascular disease (CVD). These interventions encompass low-protein diets [13], correction of calcium-phosphate disorders [14,15], management of anemia [16,17], control of blood pressure

[18], and proteinuria, along with support for smoking cessation [19]. Emerging therapeutic approaches involve the use of lipid-lowering agents, anti-inflammatory drugs, and antioxidant agents [20].

For individuals with diabetic kidney disease exhibiting elevated levels of albuminuria, extensive placebo-controlled trials have demonstrated that inhibitors of the renin-angiotensin system (RAS) [21–23], SGLT2 inhibitors [24,25], and the non-steroidal mineralocorticoid receptor antagonist finerenone [26,27] have all decreased the risk of progressing to kidney failure.

Recently, SGLT2 inhibitors have shown efficacy in reducing glycated hemoglobin levels and eliciting positive impacts on kidney and cardiovascular outcomes in extensive clinical trials involving individuals diagnosed with type 2 diabetes [28–30]. In three comprehensive clinical outcome trials focusing on participants with T2DM, it was noted that SGLT2 inhibitors, namely empagliflozin, dapagliflozin, and canagliflozin, led to a decrease in heart failure occurrences. Furthermore, these inhibitors demonstrated favorable effects on kidney function, as indicated by lower hazard ratios associated with a significant decline in estimated glomerular filtration rate (eGFR). It's crucial to highlight that these trials were primarily designed to evaluate cardiovascular safety, resulting in the enrollment of participants with an elevated cardiovascular risk [28–30,31].

In a trial involving the SGLT2 inhibitor dapagliflozin, a pre-planned subgroup analysis that focused on patients with CKD and a urinary albumin-to-creatinine ratio (ACR) of at least 200 mg/g revealed that the kidney benefits extended to patients without diabetes. However, limited information is available regarding patients with an eGFR below 30 mL per minute per 1.73 m^2 and how these benefits might vary across the broader spectrum of CKD patients [32,33].

The canagliflozin study demonstrated a noteworthy reduction in the combined occurrence of sustained doubling of serum creatinine, end-stage kidney disease, and death from renal causes. Additionally, participants treated with canagliflozin exhibited a slower decline in eGFR and a decreased urinary albumin-to-creatinine ratio (UACR). These results indicate a potential protective effect of canagliflozin on kidney health in individuals with type 2 diabetes, underscoring its role in mitigating adverse renal outcomes [34].

A clinical trial involving 6609 patients with chronic kidney disease demonstrated that the use of empagliflozin therapy was associated with a reduced risk of kidney disease progression [35]. Among all SGLT2 inhibitors, empagliflozin stands out as the first to demonstrate a statistically significant decrease in all-cause hospitalizations for individuals with CKD [36]. This review aims to comprehensively explore and assess the evolving role of empagliflozin and other SGLT2 inhibitors in reshaping the treatment paradigm for CKD. It goes beyond their evolving roles to scrutinize related factors such as emerging research findings, renoprotective actions, safety profiles, and a comparative analysis of empagliflozin with other SGLT2 inhibitors in CKD patients.

2. Methodology

In conducting this comprehensive review on SGLT2 inhibitors, with a particular focus on empagliflozin in treating chronic kidney disease, a rigorous methodology was

followed. A systematic literature search spanned various electronic databases, such as PubMed, MEDLINE, and Cochrane Library, using a combination of keywords and controlled vocabulary related to SGLT2 inhibitors, empagliflozin, and chronic kidney disease. Clear inclusion and exclusion criteria were established, emphasizing studies investigating the renoprotective effects of SGLT2 inhibitors, with exclusion criteria for studies with unrelated outcomes or insufficient data. Data extraction was conducted systematically, covering study design, patient characteristics, interventions, and outcomes related to renoprotection. Findings were synthesized qualitatively, emphasizing the renoprotective effects of SGLT2 inhibitors, especially empagliflozin. A comparative analysis with other SGLT2 inhibitors was performed to explore differences in efficacy, safety profiles, and renoprotective actions. A flowchart illustrating the paper selection process were provided for clarity and replicability (**Figure 1**).

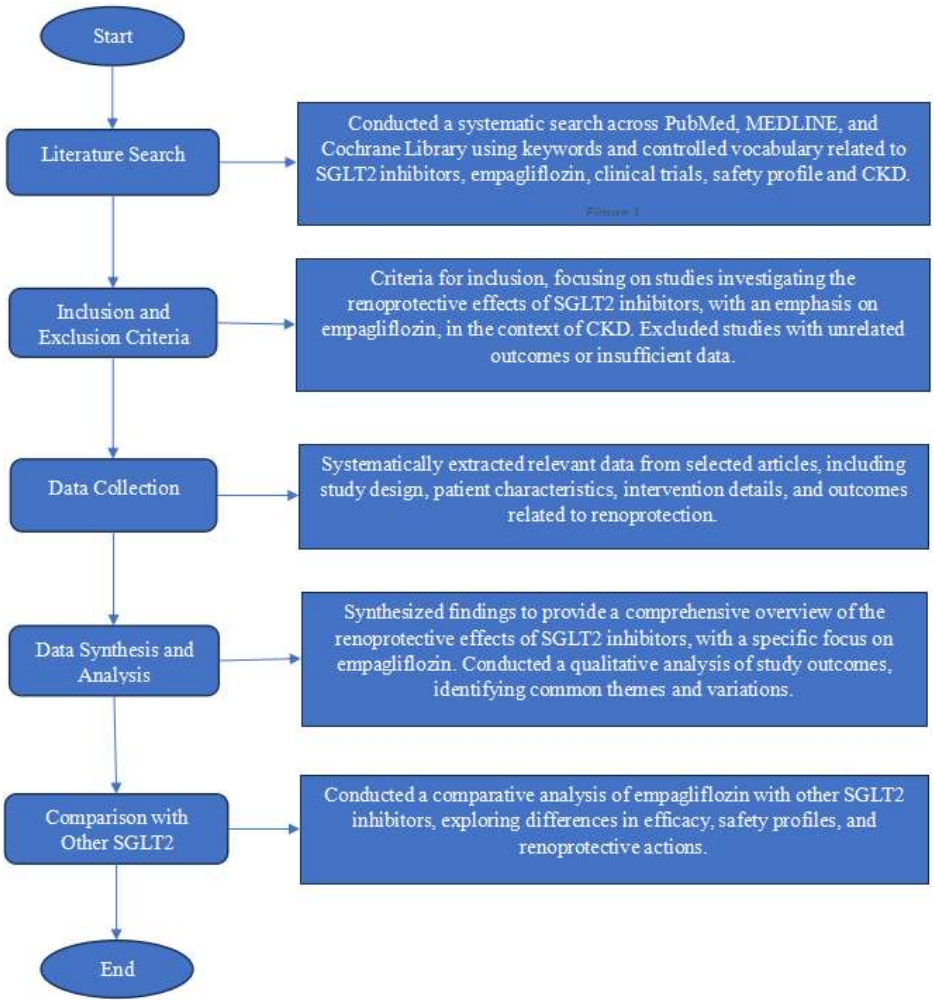

Figure 1. Flowchart for review methodology.

3. Renoprotective actions of SGLT2 inhibitors and empagliflozin

SGLT2 inhibitors constitute a recent class of antihyperglycemic medications approved for treating T2DM [37]. These drugs operate by hindering glucose reabsorption in the early proximal tubule of the kidneys, leading to increased glucose excretion in the urine and an overall reduction in body glucose load [38]. A pivotal

mechanism involves tubuloglomerular feedback, where SGLT2 inhibitors induce heightened sodium passage along the nephron. Macula cells sense this sodium and respond through adenosine to constrict afferent glomerular arterioles, thereby safeguarding glomeruli by reducing intraglomerular pressure [39].

Early clinical trials of SGLT2 inhibitors demonstrate a 0.5%–1.0% reduction in glycated hemoglobin levels without inducing hypoglycemic events [40]. This effect is attributed to the drugs lowering the glucose reabsorption threshold at the tubular level, maintaining values above 75 mg/dL, well beyond the threshold for symptomatic hypoglycemia [41]. The resulting decrease in blood glucose levels and improved insulin resistance contribute to a long-term reduction in microvascular complications. Additionally, the increased production of ketone bodies, driven by a higher glucagon/insulin ratio, may enhance energy utilization and mitochondrial function [42].

In individuals with CKD, a phenomenon of single-nephron hyperfiltration occurs, unrelated to diabetes but associated with adaptive responses to the gradual reduction in the number of functional units [43]. Consequently, even with normal blood glucose levels, this state leads to increased filtration and reabsorption of a higher glycemic load per individual nephron [44]. In such circumstances, the inhibition of SGLT channels produces effects that go beyond mere glycosuria. Apart from influencing intrarenal hemodynamic changes, SGLT2 inhibitors also exert direct anti-inflammatory and antifibrotic nephroprotective effects. Specifically, SGLT2 inhibitors inhibit the production of reactive oxygen species, thereby reducing glomerulosclerosis and tubulo-interstitial fibrosis [45–47].

Empagliflozin, belonging to the SGLT2 inhibitor class, functions through a mechanism akin to other drugs in this category. Predetermined exploratory analyses of the annual rate of change in the eGFR, a well-acknowledged indicator of kidney disease progression, revealed that empagliflozin slowed the long-term decline in eGFR in patients with a baseline urinary albumin-to-creatinine ratio of less than 300 (including those with a urinary albumin-to-creatinine ratio of <30) [35,48].

4. Clinical evidence

Drawing insights from pivotal clinical trials, notably the EMPA-REG OUTCOME study [49], this study consolidates the most recent evidence substantiating the renoprotective benefits of empagliflozin. The findings underscore significant reductions in the risk of kidney disease progression, notable enhancements in eGFR, and substantial decreases in albuminuria. Empagliflozin has also demonstrated efficacy in mitigating the onset and progression of CKD among individuals diagnosed with type 2 diabetes and a population of people with CKD at risk of kidney disease progression [50,51]. Collectively, these outcomes contribute to the expanding body of evidence advocating for the utilization of SGLT2 inhibitors, such as empagliflozin, as a promising therapeutic strategy in the context of CKD.

5. Safety profile

SGLT2 inhibitors, used to lower glucose in diabetes, present various adverse events. Hypoglycemia risk isn’t heightened when used alone due to their mechanism,

but it may increase when combined with other glucose-lowering agents, especially insulin [52]. Not all initially suspected adverse events, like urinary tract infections (UTIs), have been consistently confirmed [53]. Certainly, in the EMPA-REG clinical trial, the occurrence of these events was more frequent with empagliflozin compared to the placebo [31]. While UTI risk isn't elevated, genital infections [54,55], including serious cases like Fournier's gangrene [56,57], are more common with SGLT2 inhibitors. Diabetic ketoacidosis (DKA), a rare but severe event, has been associated with SGLT2 inhibitors, particularly in type 1 diabetes [53,58–60].

Hypotension, linked to the drug's mechanism, is observed, contributing to the cardiovascular protection seen with these drugs [53]. They demonstrate benefits in reducing cardiovascular risks and mortality [61]. Some controversies surround lower limb amputation and fractures, with differing findings in clinical trials [29,53,62]. Potential interactions with other drugs, like statins, have been reported, emphasizing the need for careful monitoring.

In terms of safety, recent data highlights myotoxicity when combining rosuvastatin and canagliflozin [63]. Adverse events show gender and ethnicity differences, requiring further investigation for a comprehensive understanding [64,65]. Limited data on pediatric use, specifically dapagliflozin, indicate the need for cautious monitoring, especially concerning genital infections, UTIs, hypotension, DKA, and hypoglycemia. Despite a lower risk of lower limb amputation in children with diabetes, ongoing research is essential for a thorough evaluation of efficacy and safety in pediatric populations [66].

6. Empagliflozin in comparison to other SGLT2 inhibitors

When comparing empagliflozin to other SGLT2 inhibitors, various factors such as efficacy, safety profiles, and specific outcomes in diverse patient populations come into play. Empagliflozin, in contrast to its counterparts like canagliflozin and dapagliflozin, has exhibited notable effectiveness in reducing blood glucose levels, showcasing additional cardiovascular benefits beyond glycemic control. This was evidenced in trials such as the EMPA-REG OUTCOME study [49,51], where empagliflozin demonstrated a reduction in cardiovascular events among individuals with type 2 diabetes. In comparison to dapagliflozin, both empagliflozin and dapagliflozin have shown cardiovascular benefits, although the specific outcomes may vary [67]. Additionally, when compared to canagliflozin, empagliflozin has been a subject of research investigating its renal effects, revealing renoprotective properties, as demonstrated in trials like EMPA-KIDNEY [68]. These findings collectively emphasize the multifaceted benefits of empagliflozin, positioning it as a promising therapeutic option within the SGLT2 inhibitor class, particularly in addressing cardiovascular and renal outcomes in individuals with type 2 diabetes.

7. Future directions and challenges

Expanding research to encompass diverse CKD populations, stages, and etiologies is crucial for a comprehensive understanding of SGLT2 inhibitors' efficacy and safety, including those without diabetes. Continuous real-world safety monitoring is essential to fine-tune the nuanced risk-benefit profile. Further exploration of SGLT2

inhibitors' safety and efficacy in specific populations, such as pediatric, elderly, and pregnant individuals, is essential for tailored recommendations. Prioritizing cost-effectiveness and accessibility are critical for broad implementation and fair access. Addressing these challenges is pivotal for the ongoing transformation in CKD management, with SGLT2 inhibitors leading the way in reshaping therapeutic approaches and enhancing patient well-being.

8. Conclusion

In conclusion, this review illuminates the pivotal role of SGLT2 inhibitors, specifically empagliflozin, in the landscape of CKD. Empagliflozin's multifaceted benefits, ranging from glycemic control to cardiovascular and renal outcomes, mark it as a promising therapeutic option. The findings underscore its significant contributions in reducing the risk of kidney disease progression and improving key indicators like eGFR and albuminuria. However, the journey towards renoprotection is accompanied by challenges, emphasizing the need for ongoing research, vigilant monitoring, and addressing accessibility concerns. As we navigate this evolving narrative, SGLT2 inhibitors, and empagliflozin, in particular, emerge as beacons of hope, reshaping the landscape of CKD management and fostering optimism for improved patient well-being.

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