Comparison of Dapagliflozin and Empagliflozin in Reduction of Proteinuria – A Comprehensive Review

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Abstract

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have represented a game-changer class of therapeutics in treating both diabetic and non-diabetic chronic kidney disease (CKD). This review seeks to describe a comparative assessment of the anti-proteinuric and kidney protective efficacy of dapagliflozin and empagliflozin. Both agents have shown promise in preventing proteinuria, delaying CKD progression, and lowering cardiovascular risks in recent clinical trials[1,2]. The pharmacological mechanisms, clinical evidence, safety profiles and future implications of dapagliflozin and empagliflozin for proteinuria. Discussed moreover, here highlight patient selection, cost-effectiveness, and real-life use of these agents. The wider use of SGLT2 inhibitors in many populations represents a major advance in nephrology and provides a new opportunity for patients with CKD.

Introduction

Chronic kidney disease (CKD) is characterized by the presence of proteinuria, which is also a predictor for several adverse renal and cardiovascular events[1]. It is strongly linked with progression of CKD as well as risk of mortality. Persistent proteinuria indicates underlying glomerular injury and is an important marker for disease progression. Moreover, conventional approaches including renin-angiotensin system (RAS) inhibitors only limited to slow down disease progression have led the search for alternative therapeutic options[3]. The development of SGLT2 inhibitors has opened new therapeutic avenues that have arisen in the management of proteinuria. Two of the most prominent SGLT2 inhibitors, dapagliflozin and empagliflozin,

exhibit favorable effects in terms of lowering proteinuria and delaying the progression of CKD [2,3]. Although improving glycemic control was the original goal of this medicine, it can also lower glycosylated haemoglobin (HbA1c) by around 0.5–0.8%[4], Clinical trials revealed a number of other advantages, such as reductions of weight, blood pressure, the rate of heart failure hospitalization, and cardiovascular death[5,6]. Additionally, patients using SGLT2 inhibitors need to have a specific degree of kidney function because the kidneys are essential to this medication's method of action[7]. Furthermore, following a specific follow-up time, SGLT2 inhibitor users—especially those with CKD—showed a significant decrease in their urine protein creatinine ratios (UPCR) as compared to placebo users[8,9]. This review focuses on the comparative effectiveness, mechanisms of action, and clinical outcomes of these agents, as well as the newly updated role of SGLT2 inhibitors in practice guidelines for the management of CKD.

Mechanism of Action of SGLT2 Inhibitors

SGLT2 inhibitors prevent glucose reabsorption in the proximal tubules of the kidneys, resulting in glucosuria, natriuresis, and osmotic diuresis. In addition to glycemic control, this mechanism provides favorable hemodynamic and anti-inflammatory effects that contribute to renal protection[1]. Recent studies have reported an additional class of actions of SGLT2 inhibitors involving reduced intraglomerular pressure, oxidative injury, and inflammation that support their renoprotective actions[3].In addition, these agents improve endothelial function and attenuate tubulointerstitial fibrosis, 2 major contributors to the progression of CKD[10]. Regardless of prior therapy, SGLT2i clinical studies show hemoglobin A1c reductions of 0.6% to 1.0% compared to placebo[11,12]. Lowering the glucose cellular flow might help protect the kidneys. Increased glycolysis has been connected to the build-up of hypoxia-induced factor 1α (HIF1α), the inhibition of sirtuin 3, and alterations associated with kidney fibrosis and the

epithelial-mesenchymal transition[13,14]. Moreover, SGLT2 inhibitors are also believed to exert direct effects on renal tubular cells, including decreasing both hypoxia-and fibrosis-induced injuries, both of which are shared features in the pathology of CKD. All these mechanisms provide a multifaceted approach for CKD management[2].

Clinical Evidence of Dapagliflozin in Proteinuria Reduction

In the DAPA-CKD trial, dapagliflozin was shown to markedly decrease proteinuria and ameliorate CKD progression among both diabetic and non-diabetic individuals[1]. Another retrospective study also found that compared to treatment with enalapril, dapagliflozin treatment was associated with reduction in albuminuria, reduction in inflammatory markers, and improvement of renal function. Further analyses have underscored that dapagliflozin is consistently effective across the spectrum of CKD, with especially pronounced advantages in patients with high baseline albuminuria[3]. Additionally, the effects of dapagliflozin to improve cardiovascular outcomes and reduce heart failure hospitalizations also make it attractive in management of patients with CKD[15]. The legacy data of long-term follow-up have established that dapagliflozin not only preserves renal function but also lowers the risk of end stage kidney , establishing it as a cornerstone of contemporary nephrology practice. when dapagliflozin is combined with RAAS blocking as part of normal therapy as opposed to a placebo. When compared to a placebo, dapagliflozin decreased the corresponding risk of dying from any cause by 31% and the absolute risk reduction by 5.3% during a median of 2.4 years[1]. Dapagliflozin dramatically reduced the risk for mortality from all causes by 32% and the risks for the renal and cardiovascular outcomes by 29% and 17%, respectively[16]. Food has no effect on the pharmacokinetics of dapagliflozin. Dapagliflozin has a 78% absolute oral bioavailability following a dosage of 10 mg. Dapagliflozin has a mean steady-state volumetric distribution of 118 L and is about 91% protein bound. It has an average half-life of 12.9 hours. The liver

primarily uses CYP to convert dapagliflozin into its inactive metabolite, dapagliflozin 3-O-glucuronide. 75% of a dosage is recovered in the urine, and 21% is in the feces, indicating that the medication plus its metabolites are primarily eliminated in the urine[17].

Clinical Evidence of Empagliflozin in Proteinuria Reduction

The EMPA-KIDNEY trial demonstrated that empagliflozin reduced CKD progression and the progression of proteinuria in a broad range of patients, including patients without diabetes[2]. Improvements were obtained for empagliflozin particularly among patients with high baseline albuminuria but also benefited patients with only minimal albuminuria, demonstrating wider applicability[10]. Further analyses from most recent observational studies have confirmed the consistent benefit of empagliflozin in broad ranges of patients. Similarly, empagliflozin has been shown to also decrease cardiovascular mortality and hospitalizations for heart failure in CKD patients[18]. A recent meta-analysis suggested that cardioprotective and renoprotective effects of empagliflozin may extend to patients with preserved eGFR, which challenges the previous paradigm of albuminuria-centric treatment initiation[2]. In a study involving individuals with poorly managed type 1 diabetes mellitus, empagliflozin treatment for eight weeks reduced the flow of renal plasma and attenuated excessive filtration in conjunction with elevated urine adenosine, indicating that the hemodynamic alterations were caused by tubuloglomerular feedback activation[19,20,21]. Empagliflozin 25 mg was found to improve macroalbuminuria at the starting point to microscopic albumin or microalbuminuria instead of no albuminuria in more patients with advanced CKD than those who received a control group 32.6% n = 14 in empagliflozin 25 milligrams vs. 8.6 percent n = 3 in the control group, along with 27.5 percent n = 14 in empagliflozin 25 milligrams vs. 21.4% n = 15 in the control group[22].

Comparative Efficacy

Head-to-head comparisons indicate that dapagliflozin and empagliflozin lower proteinuria and delay CKD progression. Empagliflozin, on the other hand, seems to confer greater relative reductions in proteinuria in patients with low albuminuria, and dapagliflozin appears to be equally beneficial in multiple patient populations[1,2]. Differences in pharmacokinetics, patient selection by age and metabolic status, and variation in trial design may account for the subtle differences between the two agents. Compared with individuals receiving DPP4i (control group), patients administered with SGLT2i showed a considerably decreased risk of atherosclerosis incidents, HHF, and renal events. Additionally, the GFR level indicated a significant improvement in renal protection[23]. There is a synergy between both agents when used in combination with standard-of-care therapy, such as RAS inhibitors, underlining their combined utility in a holistic approach to CKD treatment[3]. Further studies directly comparing the two agents in diverse patient populations are warranted to optimize individualized treatment strategies.

Safety Profile

For both dapagliflozin and empagliflozin, safety was acceptable overall with genital infections, urinary tract infections, and volume depletion being the most consistently reported side effects,24 Adverse event rates were generally low and presumably similar across studies[1]. Recent meta-analyses suggest SGLT2 inhibitors appear to possibly present a marginally increased risk for diabetic ketoacidosis with T1DM,2 however, overall safety is favorable particularly for CKD and T2DM patients. There did not appear to be a difference between dapagliflozin and empagliflozin on the risk of combined coronary and ischemic events when comparing the two SGLT2i groups and the control group[25]. There will be additional future long-term safety data, and post-marketing safety studies to help address the safety of SGLT2

inhibitors and their risk benefit balance. Potential practical applications could be strategies to manage volume depletion and infection risk.

Cost-Effectiveness and Real-World Applications

Cost-effectiveness studies have shown dapagliflozin and empagliflozin provides considerable value in the management of CKD when elevated cardiovascular and renal benefit along with cost. The experience of "real-world" population-based data registry studies have replicated the same findings that prescribers were starting the use of SGLT2 inhibitors in a population similar to that of clinical studies[2]. The use of SGLT2 inhibitors has markedly increased their treatment role in daily CKD practice and treatment guidelines. There is increasing evidence that stratifies the early use of SGLT2 inhibitors to achieve added benefits over the long-term particularly in high-risk populations[6]. Further research should focus on creating simulation cost-effectiveness models that can capture population based quality of life indices and health care resource utilization as organizations and even countries move toward value-based health care management models. In India dapagliflozin is 18.3rs a tablet empagliflozin is 48.9rs a tablet.

Discussion

The management of chronic kidney disease (CKD) and in the case of both diabetic and non-diabetic patients, has been completely altered with the introduction of SGLT2 inhibitors, which include dapaglifloxin and empaglifloxin. The already mentioned SGLT2 inhibitors have demonstrated appeal due to their remarkable renoprotection potential, as depicted in this review, and had benefit on proteinuria reduction, CKD trajectory, and cardiovascular benefits. Drug trials such as DAPA-CKD and EMPA-KIDNEY have provided widespread validated benefits, and adapt these medications as a cornerstone of care across nephrology and

cardiometabolic disease. Despite sharing common mechanisms of action, dapaglifloxin continues to further diverge from empaglifloxin as a medical therapy. Particularly in terms of cardiovascular risk stratification we continue to note that empaglifloxin's beneficial effect may be superior from an individual perspective in patients with lower baseline proteinuria activity, and dapaglifloxin may be superior for patients at a greater range of baseline albuminuria or impaired kidney function. These differences may continue to evolve with the varying dosing practices, patient populations, and pharmacokinetics. Furthermore, the positive evidence of empaglifloxin use on hemodynamic control by means of tubuloglomerular feedback could be another possible explanation of superiority in certain groups.

Conclusion

In conclusion, dapagliflozin & empagliflozin are now mainstays for proteinuria and chronic kidney disease (CKD), not just for their glucose-lowering effects, but for their renal, cardiac and other benefits. Both drugs provide similarly high levels of efficacy and an acceptable toll of side effects, but dapagliflozin is a less expensive option in resource-limited settings. The benefits of head-to-head comparisons are largely overlapping, and will differ only in particular subpopulations which should be the subject of further research.

It has been a significant advance in nephrology that SGLT2 inhibitors are now being more widely used in CKD treatment regimens. In order to promote and use them in various populations, we need to focus future research on cost-effectiveness modelling, long-term, real-world studies, and personalized treatment algorithms. Overall, more widespread use of these medications has the potential to greatly reduce the global mortality, morbidity, and health care expenditure related to CKD.

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