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SGLT2 INHIBITORS: TRANSFORMING CARDIOVASCULAR AND RENAL CARE

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ABSTRACT

In recent years, SGLT2 inhibitors have revolutionized the landscape of diabetes management, heart failure treatment, and renal care. Originating from the isolation of phlorizin in the 19th century, these inhibitors have evolved into powerful agents targeting the SGLT2 protein, thereby inducing glucosuria and offering significant cardiovascular and renal benefits. Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin have emerged as key players in this therapeutic landscape, demonstrating efficacy in reducing cardiovascular events, slowing chronic kidney disease progression, and improving heart failure outcomes. Despite their remarkable potential, barriers to prescribing SGLT2 inhibitors persist, including cost and prescriber reluctance. This comprehensive review explores the clinical impact of SGLT2 inhibitors, their mechanisms of action, and recommendations for successful implementation, highlighting their transformative role in modern cardiovascular and renal care.

KEYWORDS: Phlorizin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin.

INTRODUCTION

Over the last years, SGLT2 inhibitors have undergone a remarkable evolution, transitioning from a novel hypoglycemic agent to a powerful therapy for type 2 diabetes, and heart failure, and now, an exciting prospect for chronic kidney disease, regardless of diabetes status.[1] In the 19th century, French scientists isolated phlorizin from apple tree bark, initially employing it to combat malaria. Later, its role in inhibiting glucose reabsorption in the kidneys was uncovered. This discovery paved the way for developing SGLT2 inhibitors, which target the SGLT2 protein responsible for glucose and sodium cotransport in the kidneys. By blocking glucose reabsorption, these medications induce glucosuria. Originally designed for diabetes management, clinical trials now reveal their potential in safeguarding kidney and heart health, extending benefits to individuals without diabetes.[2] SGLT2 inhibitors offer significant cardiovascular and renal benefits beyond glucose control, impacting patients with type 2 diabetes, heart failure regardless of ejection fraction, and chronic kidney disease. SGLT2 inhibitors are revolutionizing cardiovascular and renal care in the 21st century, emerging as game-changing medications in the field.[3] SGLT2 inhibitors are recognized for their organ-protective effects, particularly in cardiovascular and renal care. These medications induce diuresis and natriuresis, enhancing hemodynamic function and contributing to cardiorenal protection. One leading hypothesis suggests that SGLT2 inhibitors restore tubuloglomerular feedback via adenosine-dependent mechanisms, mitigating intraglomerular pressure and glomerular injury. Beyond glucose control, these agents may reduce oxidative stress and inflammation, alleviating proximal tubular cell workload and tissue damage. Recent studies demonstrate their potential to decrease oxidative stress and preglomerular vasoconstriction, further underscoring their multifaceted benefits.[2] Barriers to prescribing SGLT2 inhibitors, including high costs, limited insurance coverage, and reluctance among prescribers due to perceived adverse effects and unfamiliarity, persist despite updated clinical guidelines, particularly in older patients. Overcoming these hurdles requires improved access, education for prescribers, and adherence to established initiation guidelines to ensure broader utilization of these efficacious and protective treatments.[3] SGLT2 inhibitors Canagliflozin Dapagliflozin, Empagliflozin, and Ertugliflozin act on the SGLT-2 proteins located in the renal proximal convoluted tubules reducing glucose reabsorption in the kidneys and promoting its excretion in urine. Sotagliflozin uniquely inhibits both SGLT2 and

SGLT1, offering benefits in both type 1 and type 2 diabetes. Clinical trials demonstrate its efficacy in improving glycemic control, reducing weight, and lowering blood pressure when used alone or with other diabetes treatments.

CANAGLIFLOZIN

In the CREDENCE trial, Canagliflozin, an SGLT2 inhibitor, significantly reduced the risk of kidney failure and cardiovascular events by 30% over a median follow-up of 2.62 years in patients with type 2 diabetes and albuminuric chronic kidney disease. It notably lowered the incidence of end-stage kidney disease, cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure, indicating long-term benefits in managing both kidney disease and cardiovascular risk.[4] Canagliflozin treatment also decelerated the increase in elevated heart and kidney stress biomarkers such as NT-proBNP, high-sensitivity cardiac troponin T, growth differentiation factor-15, and IGFBP7 over time, correlating strongly with future cardiac and renal events, thus enhancing outcome prediction.[5] Additionally, a post-hoc analysis showed that Canagliflozin increased hemoglobin and hematocrit levels while reducing the risk of anemia-related outcomes, suggesting a potential role in managing anemia in this patient population.[6] In the CANVAS Program, Canagliflozin demonstrated remarkable cardiovascular protection, reducing events by 14%, offering hope for patients with type 2 diabetes and heightened cardiovascular risk. Though renal outcomes remained uncertain, Canagliflozin exhibited promising signs of slowing albuminuria progression and decreasing the necessity for renal replacement therapy. However, concerns arose regarding an elevated risk of toe or metatarsal amputation.[7] Nevertheless, Canagliflozin showcased a significant reduction in the risk of sustained kidney function loss, along with a slower decline in eGFR and decreased albuminuria, indicating its potential as a kidney-protective therapy in this population.[8] An analysis of three randomized controlled trials highlights Canagliflozin's efficacy in reducing cardiovascular and kidney events in type 2 diabetes patients, irrespective of disease duration. Notably, it not only slows the progression of albuminuria but also triggers regression, even within the initial five years of diagnosis. These results underscore the importance of early initiation of SGLT2 inhibitor therapy for effective management of type 2 diabetes, offering consistent benefits for heart and kidney health, and potentially leading to improved patient outcomes.[9]

DAPAGLIFLOZIN

In the DAPA-CKD trial, dapagliflozin demonstrated significant efficacy in reducing adverse kidney and cardiovascular outcomes among patients with chronic kidney disease (CKD), regardless of their diabetes status. Notably, it substantially decreased the risk of declined estimated glomerular filtration rate (eGFR), end-stage kidney disease, or renal/cardiovascular death, along with lowering the risk of death from cardiovascular causes or hospitalization for heart failure.[10] These benefits extended to stage 4 CKD patients with albuminuria, affirming dapagliflozin's role as a viable treatment option in this population.[11] In the DIAMOND trial, dapagliflozin was investigated in non-diabetic patients with proteinuric kidney disease. While it did not significantly alter proteinuria, it induced a reversible decline in measured glomerular filtration rate (mGFR) and reduced body weight.[12] In the DECLARE TIMI-58 trial involving participants with type 2 diabetes, dapagliflozin didn't increase major adverse cardiovascular events but showed a lower rate of cardiovascular death or hospitalization for heart failure, with fewer heart failure hospitalizations. Additionally, it reduced renal events but had higher risks of diabetic ketoacidosis and genital infections.[13] In the DAPA-HF trial with 4744 patients having heart failure and reduced ejection fraction, dapagliflozin significantly decreased the risk of worsening heart failure or cardiovascular death over 18.2 months, regardless of diabetes status. Adverse events related to volume depletion, renal dysfunction, and hypoglycemia were similar between groups, highlighting its safety and potential as a heart failure treatment beyond glucose control.[14] Furthermore, in the DELIVER trial focusing on patients with LVEF ≤40%, dapagliflozin effectively reduced heart failure hospitalizations and cardiovascular death over 2.3 years, with consistent benefits across LVEF subgroups. Adverse event rates were comparable between dapagliflozin and placebo groups, suggesting its broader application in managing heart failure, even in patients with mildly reduced or preserved ejection fraction.[15]

EMPAGLIFLOZIN

In the EMPA-KIDNEY trial, empagliflozin showcased its prowess in mitigating chronic kidney disease (CKD) progression and reducing cardiovascular risk in at-risk patients. Over a median follow-up of 2 years, it significantly decreased the combined risk of kidney disease progression or cardiovascular death compared to placebo, with consistent benefits across different patient subgroups. Although hospitalization rates were lowered, there were no significant differences in heart failure hospitalization, cardiovascular death, or all-cause mortality between the treatment and placebo groups. Importantly, the rates of serious adverse events were similar between the two, highlighting empagliflozin's safety profile. These findings illuminate empagliflozin's potential to revolutionize CKD management and cardiovascular risk reduction.[16] In the EMPA-REG OUTCOME trial, empagliflozin showed significant reductions in cardiovascular death, nonfatal myocardial infarction, or stroke in type 2 diabetes patients at high cardiovascular risk. It also lowered rates of cardiovascular death, heart failure hospitalization, and all-cause mortality. However, it increases the risk of genital infections.[17] Empagliflozin demonstrated a 25% reduction in cardiovascular death or heart failure hospitalization risk in HFrEF patients in the EMPEROR-Reduced study, regardless of medication or diabetes

status. This improvement was primarily driven by a 31% decrease in heart failure hospitalizations, potentially linked to renal benefits indicated by a slower decline in estimated GFR.[18] Similarly, in the EMPEROR-Preserved study with preserved ejection fraction patients, empagliflozin yielded a 21% lower risk of combined cardiovascular death or heart failure hospitalization, mainly due to a significant 29% reduction in heart failure hospitalizations. These results highlight empagliflozin's consistent effectiveness across diverse patient populations, offering promising advancements in heart failure management.[19]

ERTUGLIFLOZIN

A multicenter, double-blind trial investigated the cardiovascular effects of ertugliflozin in patients with type 2 diabetes and atherosclerotic cardiovascular disease. Ertugliflozin, administered at 5 mg or 15 mg once daily, showed noninferiority to placebo for major adverse cardiovascular events. Moreover, while not statistically significant, there was a trend towards superiority in reducing the composite outcome of death from cardiovascular causes or hospitalization for heart failure with ertugliflozin. Importantly, no significant differences were observed in death from cardiovascular or renal causes between treatment groups. However, both doses of ertugliflozin were associated with a slightly higher incidence of amputations than placebo.[20] Additionally, ertugliflozin effectively reduces the risk of hospitalization for heart failure and combined events in patients with type 2 diabetes, advocating its use for heart failure prevention.[21] Ertugliflozin offers insulin-independent glucose control and reduces hypoglycemia risk. Clinical trials demonstrate improvements in A1C, body weight, and blood pressure, with a reduction in heart failure and renal complications, though genital mycotic infections are a notable side effect. Ertugliflozin provides strong cardiorenal protection, making it safe for diabetic patients with cardiorenal complications.[22] In the VERTIS CV trial, the efficacy and safety of ertugliflozin remained consistent across age groups, confirming its cardiorenal benefits in older adults aged 65+ and 75+, thus emphasizing its reliability in this population.[23] Ertugliflozin in VERTIS CV patients lowered insulin initiation probability, delaying it by approximately 1.8 years, and decreased insulin dose needs without raising hypoglycemia risk compared to placebo.[24]

SOTAGLIFLOZIN

Sotagliflozin, targeting both SGLT1 and SGLT2, holds the potential for reducing cardiovascular risks and heart failure hospitalizations in diabetic patients with kidney disease, irrespective of albuminuria levels. However, it does not notably enhance cardiovascular or renal outcomes compared to a placebo and carries significant adverse effects, including increased instances of diarrhea, diabetic ketoacidosis, genital mycotic infections, and volume depletion. Although hypertension incidence was lower, hypotension was more common with sotagliflozin. Further, longer-term studies are necessary to evaluate its efficacy and safety in this patient population comprehensively.[25] Additionally, while sotagliflozin at 400 mg, but not 200 mg, demonstrated a significant reduction in HbA1c after 26 weeks in CKD3 patients, both doses led to decreased UACR in those with at least A2 albuminuria at 26 weeks, although the effects were not sustained at week 52.[26] Initiating sotagliflozin before or shortly after discharge in hospitalized type 2 diabetes patients with worsening heart failure significantly reduces cardiovascular deaths, heart failure-related hospitalizations,[27] and urgent visits at 30 and 90 days post-discharge, emphasizing the importance of early SGLT inhibitor initiation.[28]

Recommendations for successful use of SGLT2 inhibitors

SGLT2i can be prescribed to patients with proteinuric CKD with or without T2DM, having eGFR > 20ml/min/1.73m^2, uACR > 200mg/gm, and heart failure. patients should receive thorough counseling on the potential side effect profile of SGLT2 inhibitors, monitor home blood pressure, volume status, weight, and blood glucose, avoid the keto diet, maintain proper hygiene and foot care when commencing an SGLT2 inhibitor, and watch for hypoglycemia. The use of SGLT2 inhibitors should be avoided in cases of ketoacidosis, lupus nephritis, risk of genital infection, and polycystic kidney disease. Patients should receive a clear “sick-day” advice plan and should be advised to withhold their SGLT2 inhibitors if unwell, hypovolemic, hypotensive, or fasting for any reason.[2]

CONCLUSION

The evolution of SGLT2 inhibitors marks a significant milestone in the treatment landscape of type 2 diabetes, heart failure, and chronic kidney disease. From the pioneering discovery of phlorizin in the 19th century to the development of modern SGLT2 inhibitors targeting renal glucose reabsorption, these medications have demonstrated remarkable efficacy in improving cardiovascular and renal outcomes, transcending their initial role as hypoglycemic agents. The extensive clinical evidence presented for canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin underscores their pivotal role in reshaping cardiovascular and renal care in the 21st century. Moreover, the multifaceted benefits of SGLT2 inhibitors extend beyond glucose control to include organ protection, reduction of cardiovascular events, preventing heart failure hospitalizations regardless of ejection fraction, delaying kidney disease progression, and improving overall patient outcomes. Despite existing barriers to their widespread utilization, including cost concerns and prescriber reluctance, efforts to overcome these hurdles are essential to ensure broader access to these efficacious and protective treatments. Moving forward, continued research and clinical practice will further elucidate the optimal use of SGLT2 inhibitors and refine guidelines for their prescription. By addressing safety concerns, enhancing patient education,

and expanding access, SGLT2 inhibitors hold promise as game-changing medications that can significantly improve outcomes for patients with type 2 diabetes, heart failure, and chronic kidney disease. As we embrace the era of personalized medicine, SGLT2 inhibitors stand as shining examples of innovation and progress in cardiovascular and renal care.

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