



Short Communication

Sodium-glucose Co-transporter-2 inhibitors (SGLT2I): A class of drugs with promising cardiorenal protective effects beyond glycemic control

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ABSTRACT

Diabetes Mellitus is always associated with both microvascular and macrovascular complications. Cardiovascular and renal complications are the leading cause of morbidity and mortality in these populations. Sodium-glucose co-transporter 2 inhibitors are a new class of antidiabetic drugs. These drugs have shown promising cardiovascular and renal protective mechanisms and resulted in decreased mortality and hospitalization. The benefits of these drugs are expected to expand to non-diabetic patients and provide improved cardiovascular and renal outcomes. In this brief review, we outline the potential cardiorenal benefits of these drugs and their future implication to improve glycemic, cardiovascular, and renal outcomes.

1. Introduction

Diabetes mellitus (DM) is a common metabolic disorder defined by chronic hyperglycemia that affects around 10% of the world's population and its prevalence is expected to rise over the next few years [1]. DM has always been associated with both microvascular and macrovascular complications [2]. Tight glycemic control with older antidiabetic agents such as metformin, thiazolidinediones (TZD), sulfonylureas (SU), meglitinides, and dipeptidyl peptidase inhibitors (DPP4i), has been associated with reductions in microvascular complications, but no significant effect on macrovascular disease has been observed [3–5]. Glucagon peptide-1 receptor agonists (GLP1-RA) and sodium-glucose co-transporter 2 inhibitors (SGLT2i), on the other hand, have shown cardioprotective and renoprotective benefits, besides decreasing cardiovascular outcomes [5,6]. Currently, four oral SGLT2i drugs are approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the management of Type-2 Diabetes Mellitus (T2DM): Canagliflozin (Cana), Dapagliflozin (Dapa), Empagliflozin (Empa) and Ertugliflozin (Ertu) [7]. All new anti-diabetic drugs must demonstrate effective glycemic control before they can be approved for marketing. Glycated hemoglobin (HbA1c) levels, as well as fasting plasma glucose (FPG) and postprandial glucose (PPG) levels, are

often used to evaluate glycemic control. The SGLT2i have completed a series of double-blind placebo-controlled clinical trials that assess and evaluate the glycemic impact when added to either treatment-naïve patients or patients treated with metformin, SU, TZD, DPP4i, GLP1-RA, or basal insulin as monotherapy [6,8]. In all clinical trials and others studies conducted, SGLT2i have shown promising effects including but not limited to cardiorenal protective activities. This makes it among the most important trends in diabetic pharmacotherapy. This brief article aims at illuminating the promising cardiovascular and renal benefits of SGLT2i and its future implication.

2. Cardiovascular benefits of SGLT2I

Cardiovascular events are among the most frequent and significant consequences in diabetic individuals. According to epidemiological data, the mortality rate from cardiovascular events in diabetic individuals is almost 3 times greater than in nondiabetics [9]. Numerous clinical studies have shown that SGLT2i possesses a protective role on the cardiovascular system and may dramatically reduce the risk of developing cardiovascular disease. The landmark EMPA-REG OUTCOMES trial revealed that the incidence of major adverse cardiovascular events (MACE) was drastically decreased. Empagliflozin was shown to

Abbreviations: DM, Diabetes mellitus; T2DM, Type-2 Diabetes Mellitus; TZD, Thiazolidinediones; SU, sulfonylureas; GLP1-RA, Glucagon peptide-1 receptor agonists; SGLT2i, sodium-glucose co-transporter 2 inhibitors; MACE, Major adverse cardiovascular events.

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be superior to placebo for improving glycemic control and lowering cardiovascular events, including death, in T2DM patients with established cardiovascular diseases [10]. Later, the CANVAS trial [11] and the DECLARE-TIMI58 [12] trial showed similar results confirming the reduction in cardiovascular events. Interestingly, the DAPA-HF study [13] showed that Dapagliflozin greatly reduces cardiovascular mortality and hospitalization for heart failure in individuals with reduced ejection fraction. Most importantly, these benefits were seen both in the presence and absence of diabetes and were associated with heart failure therapy [14]. In 2021, the EMPEROR Preserved trial [15] further confirmed the extension of the cardiovascular benefits of these drugs from HFpEF to patients without T2DM. This further expands the target population of these drugs.

3. Renal benefits of SGLT2i

T2DM patients are at a high risk of developing diabetic nephropathy. “The sodium in the glomerular filtrate that is inhibited from reabsorption by SGLT2i’s acts on the Macula Densa in the renal tubules, which decreases the release of renin from the juxtaglomerular cells” [16]. This tubule-glomerular feedback causes the afferent glomerular arterioles to constrict and the efferent arterioles to dilate. In turn, these modifications diminish intraglomerular pressure and hyperfiltration, the latter is responsible for glomerular fibrosis, diabetic renal failure, and eventually end-stage renal disease [17]. The previously cited trials [10,13,15] and another two trials [18,19] have shown that SGLT2i demonstrated significant renal protection in patients with T2DM and end-stage kidney disease [16]. The 2021 ADA guidelines recommend SGLT2i to the regimen of T2DM with renal disease to reduce the risk of renal failure, MACE, and heart failure hospitalization [20].

4. Conclusion

Given the cardiovascular and renal protective properties of SGLT2i, these drugs are bound to revolutionize the management of T2DM and significantly reduce the complications associated with it. Keeping in mind that those benefits are independent of glycemic control, the target population of these drugs will largely expand including non-diabetic patients. Even though the current real-world data and meta-analysis suggest potential benefits of these drugs for non-diabetic patients, further studies are required to enrich this debate.

5. Future prospects

To date, SGLT2i have shown bright prospects and are expected to become clinical first-line drugs for T2DM. Even though promising cardiorenal benefits for these drugs have been established, further studies on the mechanisms behind these properties are needed in the future to explore the possibility of extending the benefits of these drugs to non-diabetic patients. Extensive studies in this regard are likely to revolutionize the way T2DM is managed and will substantially improve cardiovascular, renal, and glycemic outcomes.

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