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Review

# Cardiovascular outcomes of sodium-glucose cotransporter 2 inhibitors: A comprehensive review of clinical and preclinical studies

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ABSTRACT

Diabetes is a leading cause of morbidity and mortality worldwide. Management of diabetes is changing at a rapid pace. Three new classes of antidiabetic drugs including GLP-1 (Glucagon-like peptide 1), DPP-IV (Dipeptidyl peptidase IV) and SGLT2 (Sodium glucose cotransporter 2) inhibitors have been approved in the last few years. Treating diabetes with the antidiabetic drug does not always reduce the cardiovascular complications of diabetes. On the contrary, there was a huge controversy regarding the effect of rosiglitazone on cardiovascular risk reduction a few years ago. Since then, submission of postmarketing cardiovascular outcome study data has been mandated by US FDA and other drug regulatory agencies for newer antidiabetic medications. This is to avoid further premature claims regarding cardiovascular harm or safety of the newer classes. We already have some cardiovascular safety data available on DPP-IV and GLP-1 groups of medications. Dapagliflozin, canagliflozin, and empagliflozin are currently approved SGLT2 inhibitors. We do not have sufficient cardiovascular outcome data available for this novel class. However, this group of drugs, which act by increasing renal glucose excretion, have also shown some non-glycemic benefits including weight reduction, blood pressure control, diuretic action, renal protection, decrease in arterial stiffness and uric acid reduction. Empagliflozin, a new member of SGLT2 class, showed significant cardiovascular morbidity and mortality benefit in recently published EMPA-REG OUTCOME trial. The authors summarize all the published clinical and preclinical cardiovascular outcome data of SGLT2 inhibitors, including recently completed and ongoing major clinical trials in this comprehensive review.



## 1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the common chronic diseases, presently affecting 29.1 million US population. Every year 1.7 million new cases of diabetes are diagnosed among the people aged 20 years or older [1]. T2DM was the seventh leading cause of mortality in the United States in 2010. Cardiovascular mortality is about 1.7 times higher among adults with diabetes than among adults without diabetes [1]. Hospitalization rates for heart attack and stroke were 1.8 and 1.5 times greater respectively among diabetic patients than patients without [2]. Diabetics have an increased incidence of both macro and microvascular complications. Microvascular complications include retinopathy, nephropathy, and neuropathy. Diabetes is also a predominant cause of macrovascular complications such as cardiovascular, peripheral arterial and cerebrovascular disease along with hypertension and dyslipidemia. An imbalance is there between the production of reactive oxygen species (ROS) and antioxidant scavenging of ROS in diabetic patients, resulting in endothelial injury and dysfunction [3]. This creates a proinflammatory environment leading to foam cell formation of macrophages and widespread atherosclerosis with macrovascular complications. Proper glycemic control can prevent microvascular complications as evidenced by several studies previously [4–6]. It is imperative to have a drug that would also address the macrovascular complication, the most significant cause of mortality in diabetic patients.

### 1.1. Why cardiovascular outcomes data is important for antidiabetic drugs?

The National Cholesterol Education Program report from the United States labeled T2DM as coronary heart disease (CHD) equivalent [7]. Diabetic patients without previous myocardial infarction have the same risk of myocardial infarction and cardiac mortality as nondiabetic patients with previous myocardial infarction [7].

Treating diabetes with the antidiabetic drug does not always reduce the cardiovascular complications of diabetes. On the contrary, there was a huge controversy regarding the effect of rosiglitazone on cardiovascular

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risk reduction a few years ago. Nissen and Wolski presented meta-analysis data from 42 randomized trials with rosiglitazone in 2007 [8]. They showed odds ratio for myocardial infarction was 1.43 in the rosiglitazone group (statistically significant) vs. control group. The odds ratio for cardiovascular mortality in the rosiglitazone group, as compared with the control group, was 1.64 (95% CI, 0.98 to 2.74; P = 0.06). As an aftermath of this paper, American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended against using rosiglitazone in 2008 [9]. FDA issued a restriction against using rosiglitazone in 2010. However, FDA removed the restrictions for prescribing rosiglitazone after analyzing RECORD trial data in 2013. The new data demonstrated no significant increase in cardiovascular events with rosiglitazone compared to other standard T2DM medications, including metformin and sulfonylurea [10,11].

Since the rosiglitazone controversy, FDA made post-marketing surveillance mandatory to avoid further premature claims regarding cardiovascular harm or safety of newer antidiabetic drugs. The quest for the antidiabetic drug with improved cardiovascular outcome is ongoing. In recent years, three new antidiabetic classes were introduced for the management of DM, including GLP-1, DPP-4 and SGLT2 inhibitors. We already have some cardiovascular safety data available for other two classes i.e. DPP-IV and GLP-1. SAVOR-TIMI 53(for Saxagliptin) and EXAMINE trial (for Alogliptin) showed that DPP-4 inhibitors did not increase the risk of a major adverse cardiac event compared with placebo [12,13]. ELIXA GLP-1 agonist trial (for Lixisenatide) showed that there was no significant difference in the rate of hospitalization for heart failure in comparison to placebo therapy [14]. A retrospective analysis of Exenatide showed a significant (20%) decreased the risk of CVD and CVD-related hospitalizations in patients with type 2 diabetes mellitus [15].

SGLT2 inhibitors being the newest drug class, we do not have sufficient cardiovascular outcome data.

### 1.2. SGLT 2 inhibitors

Dapagliflozin, canagliflozin, and empagliflozin are currently approved SGLT2 inhibitors. The first drug in the class, canagliflozin (Invokana, Johnson & Johnson) was approved by USFDA in March 2013. This was followed by approval of dapagliflozin (Farxiga, AstraZeneca) and empagliflozin (Jardiance, BoehringerIngelheim Pharmaceuticals) in January 2014 and August 2014 respectively [16]. All three drugs can be given once daily oral dosing. Studies have shown that SGLT2 inhibitors are useful in the significant reduction of HbA1c both as a single agent or combination therapy [17–19].

Beyond glucose lowering, these drugs also modify other non-glycemic cardiovascular risk factors. Emerging evidence suggests that SGLT-2 inhibitors help to reduce blood pressure, arterial stiffness, body weight, visceral adiposity, albuminuria, serum uric acid level and oxidative stress. They are associated with a small increase in HDL and LDL with a decrease in triglyceride level [20].

### 1.3. Mechanism of antidiabetic action of SGLT2

SGLTs transport glucose from the tubular lumen into the tubular epithelial cells. Two SGLT isoforms have been identified: SGLT2, which is expressed on the brush border of epithelial cells of proximal renal tubules (mainly in S1 and S2 segments) and SGLT1, which is expressed primarily in the small intestine, the S3 segment of the proximal tubule of the kidney, and myocardium (Fig. 1) [21]. Normally the kidneys filter of about 160–180 g of glucose each day. More than 99% of this glucose is reabsorbed in the proximal tubule. With rising concentration of glucose in the glomerular filtrate reabsorption of glucose also increases until the transport maximum for glucose is reached. In the background of diabetes filtration as well as reabsorption of glucose increase up to two to threefold. SGLT2 inhibitors lower the threshold for glucose excretion. It increases the urinary glucose excretion at a given plasma concentration (Fig. 2). The glucose excretion curve is shifted towards left after using this drug. But it is to be kept in mind that SGLT2 inhibitors can inhibit only 30–50% glucose reabsorption in healthy individuals. Compensation of glucose reabsorption by SGLT1 receptors or limited amount of SGLT2 inhibitors in the proximal tubule may play a role for this restricted action [22].

They increase urinary glucose excretion and subsequent plasma glucose-lowering effect in an insulin-independent manner with a low risk of hypoglycemia. An increase in urinary glucose excretion helps to reduce body weight in diabetic patients by causing negative energy balance [23].

### 1.4. Non-cardiovascular adverse events associated with SGLT2 inhibitors

SGLT2 inhibitors are associated with both male and female genital mycotic infections, increased urine volume, urinary tract infections. Hypotension is a common adverse effect, particularly among older patients and should be avoided in patients with severe renal impairment, end-stage renal disease, or patient on dialysis. There are additional

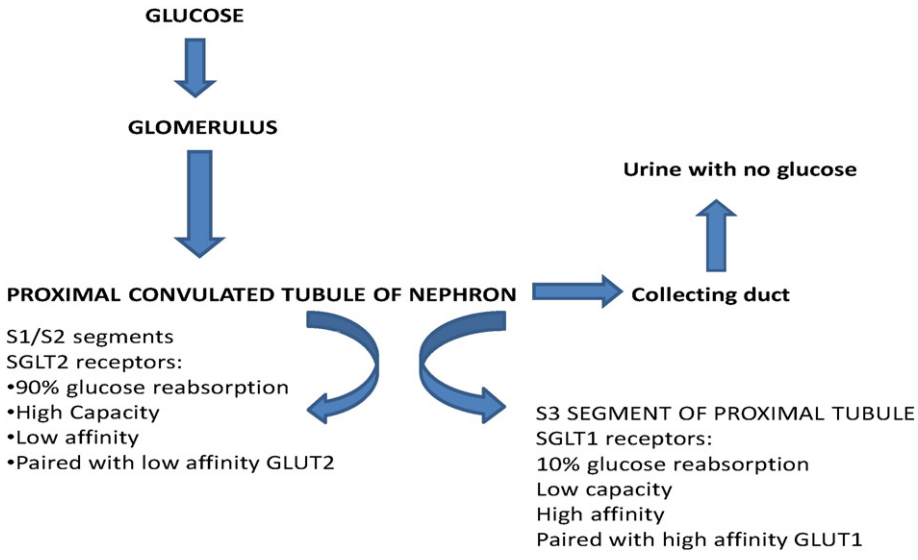


**Fig 1.** Schematic diagram showing glucose absorption in nephron.