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SGLT-2 INHIBITORS – AN ANTIDIABETIC WITH CARDIOPROTECTIVE EFFECTS

Diabetology

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ABSTRACT

Today, global healthcare possesses a tremendous burden due to the increasing prevalence of Type 2 diabetes mellitus (T2DM) that has reached pandemic proportions. The chronic disease of T2DM causes macrovascular and/or microvascular pathologic changes, resulting in increased risk for the development of myocardial infarction, heart failure, stroke, renal failure, and reduced survival. This chronic condition also presents significant interactions between T2DM, heart failure, and renal dysfunction, forming vicious circles, and the interruption of these circles represents important therapeutic goals.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), a new drug class of oral antidiabetic drugs (OADs), approved for the treatment of diabetes, have been shown to exert a favorable metabolic profile help in a significant reduction in the atherosclerotic events, hospitalization for heart failure, cardiovascular and total mortality, and progression of chronic kidney disease.

This minireview will provide a valuable tool for understanding the vicious circle and demonstrating the expanding role of SGLT2 inhibitors critical for cardiologists, diabetologists, nephrologists, and primary care physicians familiar with this drug class.

KEYWORDS

INTRODUCTION

In the 21st century, chronic diseases like Type 2 diabetes mellitus (T2DM), heart failure (HF), and diabetic kidney disease (DKD) have emerged as one of the major pandemics affecting global healthcare.[1] These three conditions co-exist, and the association of T2DM with these two complications creates a vicious cycle worsening the prognosis.

T2DM appears to be the significant risk factor for the development of HF, and it is associated with a 2 to 4 times greater risk of the development of cardiovascular disease (CVD), which is responsible for about two-thirds of all deaths in patients with T2DM[1]. As early as 1974 (Framingham study), it was observed that diabetes is associated with a 2X increase in the risk of heart failure in men and a 5x increase in the risk of heart failure in women. Also, about 3.3% of type 2 diabetic subjects develop HF each year. Additionally, elderly diabetic patients have a 1.3-fold greater risk of developing HF than nondiabetic subjects, and a 1% rise in HbA1c is associated with a 15% increased risk of HF in elderly diabetic patients.[2-4] When the sub-population is considered, diabetes is 3-fold more common in the Southeast Asian population than white patients with HF, despite younger age and less obesity, and more strongly associated with poor outcomes in Asian patients than white patients.[5]

A strong association of kidney disease, defined by increased urine albumin excretion and/or impaired GFR, is established with an increased risk of all-cause and cardiovascular mortality in diabetic and general populations. The Third National Health and Nutrition Examination Survey (NHANES III) data showed that among persons with diabetes, 42.3% had kidney disease, as defined by albuminuria, impaired GFR, or both. In comparison, 9.4% of people without diabetes had kidney disease. Ten-year cumulative all-cause mortality was 19.1% among people with diabetes compared with 8.6% among people without diabetes. Among people with diabetes and no kidney disease, the standardized mortality was 11.5% & 31.1% in patients with both comorbidities. Several studies suggest that patients with diabetes are heterogeneous with respect to their risk of all-cause and cardiovascular mortality and that kidney disease powerfully identifies a subset of people with increased health risk.[6]

A newer class of oral anti-diabetic drugs (OAD) known as Sodium-glucose cotransporter 2 (SGLT2) inhibitors entered the global market initially for the use in people with type 2 diabetes (T2D), and Canagliflozin was the first molecule to get approved by U.S. Food and Drug Administration (FDA) in 2013. This class of drugs acts in the proximal nephron to reduce glucose reabsorption, leading to glycosuria and modest reductions in blood sugar levels.[7]

Beyond glycemic control, there are several other beneficial effects of SGLT2 inhibitors - (1) Excretion of sodium in the urine causes osmotic diuresis and thus leads to a reduction in blood pressure. (2) Weight loss is promoted by reducing endogenous glycerol-derived hepatic gluconeogenesis from visceral adipose tissue. (3) One of the renoprotective effects of this class of drugs leads to albuminuria, reducing the intraglomerular pressure, thereby preventing the subsequent tubular cell injury.[8] The cumulative effects of all these pleiotropic benefits lead to a reduction in cardiovascular events and an additional preserved kidney function. As per the latest American Diabetes Association (ADA - 2021) guidelines, this class of drugs is recommended as supplement treatment in patients with T2D and with high risk or established CVD, established CKD, or heart failure (HF) independent of the patients' hemoglobin A1C (HbA1C) values.[9]

This minireview focusses on the connecting dots of the vicious circle with T2DM and its major complications; Congestive Heart Failure (CHF) and Diabetic Kidney Disease (DKD). It also focuses on the role of SGLT2 inhibitors in the management of blood glucose and beyond blood glucose management.

Diabetes, Heart Failure, And Renal Dysfunction – Trio Of The Vicious Circle

The three chronic conditions; Type 2 Diabetes (T2D), Chronic Heart Failure (CHF), and Diabetic Kidney Disease (DKD), generally coexist, and each factor worsens the prognosis of the remaining two, establishing a series of the vicious cycle (Fig.1) Elaborating it in detail, T2DM is a potent risk factor for developing HF, causing a 2 - 4 times higher risk of the development of cardiovascular disease (CVD), resulting in two-thirds of all deaths in patients with T2DM. [1,9,10]

Connecting the dots, HF also plays a pivotal role in the development of T2DM, as advanced HF is linked with the development of insulin resistance and consecutively T2DM. [1,9,10]

The long-standing T2DM leading to one of the most prevalent microvascular complications, Diabetic Kidney Disease (DKD), is the primary cause of associ

Hence, the connection of failing heart and the failing kidney resulting in the lower cardiac output and an elevated renal venous pressure reduces renal blood flow, and also in HF, the upregulation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) leads to the constriction of afferent glomerular arterioles further reducing the glomerular filtration.[1,11]

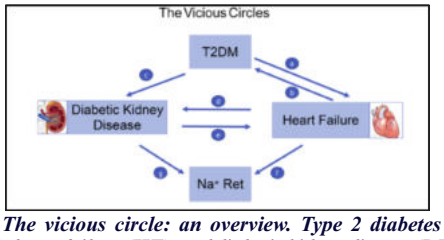

Fig.1 - ***The vicious circle: an overview. Type 2 diabetes mellitus (T2DM), heart failure (HF), and diabetic kidney disease (DKD).***

T2DM is a major risk factor for HF (a) and for DKD ©. HF can cause or intensify the severity of T2DM (b). Both T2DM (c) and HF (d) and can cause DKD. DKD can intensify HF (e). Both HF (f) and DKD (g) can cause sodium retention (Na+ ret), pulmonary congestion, dyspnea and edema. (Adapted from Braunwald E. 2019)[1]

Role Of Sglt2 Inhibitors – In The Management Of The Trio (t2dm, Chf, And Dkd)

Usually, the glucose homeostasis is maintained by an equilibrium of three organs, the glucose entering the bloodstream from intestinal absorption, hepatic glucose production, and the uptake and metabolism of glucose by peripheral tissues.

The role of the kidney is crucial, too, in maintaining homeostasis by filtration and reabsorption of the glucose. The high-capacity sodium-glucose-linked transporter 2 (SGLT2) located in the convoluted segment of the proximal renal tubule is responsible for approximately 90% of the reabsorption of filtered glucose. Rest 10% gets reabsorbed by the SGLT1 transporter located in the descending proximal tubule.[13]

Each day approximately 180g of glucose is filtered by the kidneys, and the SGLT2 transporters reabsorb the same. However, the capacity of these SGLT2 transporters is limited, and when blood glucose levels exceed above the threshold, glucose starts appearing in the urine. In the case of T2DM, the kidney's glucose handling gets altered; renal gluconeogenesis and renal glucose uptake both are increased in the post-absorptive and postprandial states, and renal glucose reabsorption is increased, and thus specific SGLT2 inhibitors are being developed as a novel means of controlling hyperglycemia in T2DM.[13]

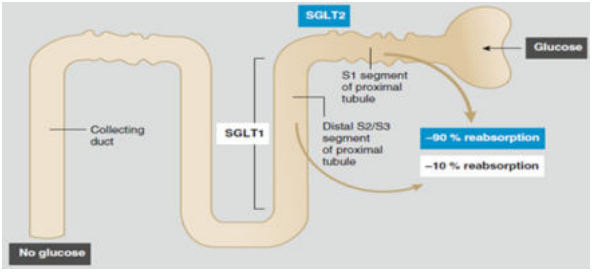

Fig. 2 - Role of SGLT Receptors in Glucose Reabsorption

As described earlier, the pathophysiology of renal disease in HF is a complex mechanism, as HF can result in CKD through increased venous pressure and low cardiac output, resulting in renal hypoperfusion, inflammation, and sympathetic activation. And on the other hand, kidney dysfunction worsens the prognosis of HF by increased sodium and fluid retention, accelerated atherosclerosis, inflammation, anemia, uremic toxins, and neurohormonal activation. The vicious circles of T2DM, CHF, and CKD is often difficult to predict, making its management challenging. [15]

The unique presumed cardio-metabolic-renal effects of SGLT2 inhibitors is being exerted via multifactorial ways summarized in Table 1.

Conditions	Effects
SGLT2i and heart failure	1. Osmotic diuresis and natriuresis reduce cardiac overload. a. Greater reductions of interstitial fluid compared with other diuretic agents
	2. Direct cardiac effects
	3. Reduction of sympathetic nervous system overdrive
	4. Possible improvement in myocardial efficiency
	5. Improved oxygen delivery through stimulation of renal EPO secretion
	6. Reduction in inflammation (by activation of adenosine monophosphate-activated protein kinase)
	7. Reduction of oxidative stress (improving mitochondrial function)
	8. Metabolic: lowering of HbA1c, blood pressure, body weight, vascular stiffness
SGLT2i and atherosclerosis	1. Reduction in inflammation
	2. Reduction in epicardial fat and noxious signals including leptin and RAAS
	3. Reduction in oxidative stress
	4. Improved endothelial function
	5. Cardioprotective effects by shifting circulating vascular progenitor cell toward M2 polarization
	6. Reduction in uric acid
	7. Metabolic: lowering of HbA1c
SGLT2i and progression of kidney disease	1. Metabolic: lowering of HbA1c, and body weight (link to HF)
	2. Reduction in blood pressure and vascular stiffness
	3. Restoration of the tubuloglomerular feedback
	4. Reduction in workload regarding ATP production
	5. Anti-inflammatory and antifibrotic effects, reduction in oxidative stress
	6. Reduction in uric acid
Interaction between heart and kidney	1. Prevention of progress of disease in one organ may prevent deterioration of the other

EPO = erythropoietin; HbA1c = glycated hemoglobin A1c; HF = heart failure; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium glucose cotransporter inhibitor.
Adapted from Zelniker, T. A., & Braunwald, E. (2020)[16]

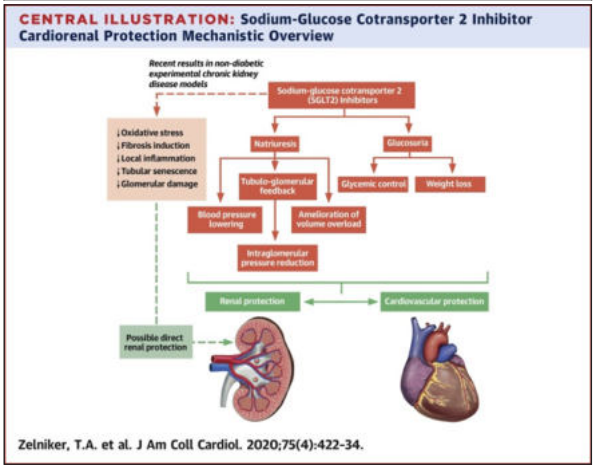

Fig. 3 - Sodium-Glucose Cotransporter 2 Inhibitor and Cardiorenal Protection - Mechanistic Overview (Adapted from Zelniker, T. A., & Braunwald, E. (2020))[16]

SGLT2 INHIBITORS – DATA FROM THE REAL-WORLD

In a real-world setting, a meta-analysis evaluating data from EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 showed that the decrease in the composite of cardiovascular death or heart failure hospitalization did not statistically differ among patients with (HR, 0.71; 95%CI, 0.61–0.84) or without (HR, 0.79; 95%CI, 0.71–0.88) history of heart failure at baseline (P for interaction = 0.51). The major trials and outcomes are summarized in Table 2.

Table 2 - Landmark clinical trials of sodium-glucose cotransporter 2 inhibitors (Adapted from Naito, R., & Kasai, T. (2021))[17]

Ref.	Population (n)	Age, yr (mean)	Intervention	Follow-up period (median)	Patients with a history of HF	Patients with a history of CVD	Main results
EMPA-REG	T2DM (7028)	63.1	Empagliflozin	3.1 yr	10.1%	100%	CV death or HF (HR, 0.66; 95%CI, 0.55–0.79) HF (HR, 0.65; 95%CI, 0.50–0.85) CV death (HR, 0.62; 95%CI, 0.49–0.77)

CANVAS	T2DM (9734)	63.3	Canagliflozin	2.4 yr	14.4%	65.6%	CV death or HF (HR, 0.78; 95%CI, 0.67–0.91) HF (HR, 0.67; 95%CI, 0.52–0.87) CV death (HR, 0.87 95%CI, 0.72–1.06)
DECLARET IMI 58	T2DM (17160)	63.9	Dapagliflozin	4.2 yr	10.0%	40.6%	CV death or HF (HR, 0.83; 95%CI, 0.73–0.95) HF (HR, 0.73; 95%CI, 0.61–0.88) CV death (HR, 0.98; 95%CI, 0.82–1.17)
VERTIS-CV	T2DM (8246)	64.4	Ertugliflozin	3.5 yr (mean)	23.7%	71.4%	CV death or HF (HR, 0.88; 95%CI, 0.75–1.03) HF (HR, 0.70; 95%CI, 0.54–0.90) CV death (HR, 0.92; 95%CI, 0.77–1.11)

Numbers are % of patients with coronary artery disease. T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; HF: Heart failure; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval.

Summary

The chronic conditions, T2DM, HF, and CKD, are closely intertwined, representing the vicious circles that warrant immediate management to reduce the global healthcare burden. The newer class of oral antidiabetic drugs (OADs), Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially approved for glucose-lowering, has shown pleiotropic benefits exerting metabolic and direct cardioprotective and nephroprotective effects reducing the overall burden.

These cardio-metabolic-renal effects of SGLT2i are multifactorial, and several large-scale clinical trials have demonstrated impressive reductions in clinical end-points, including mortality and morbidity. This class of drugs represents an essential tool for T2DM management beyond glycemic control to cardiologists, diabetologists, nephrologists, and primary care physicians.

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