

# Sodium-Glucose Co-Transporter 2 Inhibitors; One Shot, Two Gains

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**Abstract:** - Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are the newest category of antidiabetic drugs that inhibits sodium-glucose co-transporter 2 in the proximal convoluted tubule and thus prevent reabsorption of glucose that leads to glycosuria. Apart from their hypoglycemic actions they also plays a major role in improving cardiac functions<sup>[1]</sup>. There is an extreme association between diabetes and the onset of cardiovascular diseases. Among people with diabetes cardiovascular diseases are one of the major causes of death. Compared to those who are non-diabetic adults with the history of diabetic ones have high prevalence rate of cardiovascular diseases<sup>[2]</sup>. In this context, SGLT2 inhibitors are vital for the reduction of cardiovascular diseases in diabetic as well as non-diabetic patients. There are mainly four SGLT2 inhibitors available in the market which are dapagliflozin, canagliflozin, empagliflozin and ertugliflozin. The key mechanisms involving their cardioprotective actions are improving cardiac cell metabolism and ventricular loading conditions, inhibiting the exchange of Na<sup>+</sup>/H<sup>+</sup> in the myocardial cells, alteration in the production of adipokines and cytokines, reducing the extend of cardiac cells necrosis and cardiac fibrosis<sup>[1]</sup>. Urogenital infections, decrease in glomerular filtration rate, reduction in uric acid levels, postural hypotension, dizziness, bladder and breast cancer are some of the postulated adverse effects associated with SGLT2 inhibitors<sup>[3]</sup>.

## I. INTRODUCTION

The impact of Type 2 diabetes mellitus (T2DM) and heart failure (HF) is great all over the world that cause for a marked reduction in the life expectancy and quality of life. Above all if they are in combined form the scene will get worsen significantly<sup>[4]</sup>. The chance of occurrence of heart failure in T2DM patients is two to five folds and vice versa, heart failure patients are highly prone to develop T2DM. Therefore any of one will trigger the progression of the other. The presence of heart failure will leads to other cardiac conditions like angina, myocardial infarction, hypertension, valvular disease, chronic tachycardia, cardiomyopathies, etc.<sup>[5]</sup> In case of acute coronary syndrome there is an increased risk of atherosclerosis in T2DM patients with lost regenerative functions of myocardial muscles. In the absence of obstructive coronary stenosis T2DM also cause functional variations. T2DM is also responsible for the abnormalities in the responses of vasoactive stimuli which eventually enhance the occurrences of major cardiac adverse events (MACE). T2DM also contributes to the abnormal rhythmic activity of the heart by inducing changes in the propagation of ionic currents leading to both atrial and ventricular arrhythmias<sup>[6]</sup>. In this context SGLT2 inhibitors are inevitable to play down

the harmful cardiac events in diabetic and non-diabetic patients. So many studies have shown that besides their hypoglycemic actions they also assists for improving cardiac functions. To achieve glycemic control they reduce the blood glucose level by glycosuria. Inhibition of SGLT2 is present at the luminal surface of proximal tubule aids this process. When the plasma glucose concentration become above 180-200 mg/dl urinary excretion of glucose takes place. SGLT2 receptor inhibitors like dapagliflozin, canagliflozin, remogliflozin and ertugliflozin makes the renal tubular threshold glucose concentration to 50mg/dl for glycosuria. They also lower the reabsorption of filtered glucose and enhance glycosuria. All these processes reduce plasma glucose levels independent of insulin<sup>[6]</sup>.

## II. NON-HYPOGLYCEMIC ACTIONS OF SGLT2 INHIBITORS

Following are some of the mechanisms of cardio protective actions of SGLT2 inhibitors.

### *Blood pressure*

They results in lowering of blood pressure. The two factors that plays their role here are natriuresis and direct effect of glomerular hemodynamics. Both these actions will leads to a spike in urine output which thus causes reduced plasma volume which eventually create a decline in blood pressure. A study was carried out by Kohan et al. in CKD patients using dapagliflozin which showed a marked improvement in BP. An extra factor that is responsible for BP reduction is weight reduction via reduction of visceral fats. Sympathetic nervous system, RAAS, vasodilators like nitric oxide (NO) also plays an important role in BP reduction<sup>[7]</sup>. From a trial called Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) it showed a reduction in systolic/diastolic blood pressure of 5/2 mm Hg. In type 1 diabetes patients empagliflozin has also contributed to reduce arterial stiffness, which leads to blood pressure-lowering effects as a result of SGLT2 inhibition<sup>[9]</sup>.

### *Systolic and diastolic cardiac functions*

Many studies have shown that the use of SGLT2 inhibitors are responsible for improvement in patients with myocardial infarction. The reduced intravascular volume induced by diuresis and natriuresis, decreased preload and afterload due to improvement in atrial elasticity both will lessens the myocardial strain and lower the risk of heart failure and its

due mortality. In some animal studies it was found that the heart failure was happened due to the increased cytoplasmic levels of Na and Ca. In these animals SGLT2 inhibitors blocks the exchange of Na cardiomyocytes that in turn shoot up the mitochondrial Ca levels and decrease the cytoplasmic Na and Ca levels. These variations in the electrolyte concentrations are typically due to existence of chronic hyperglycemia<sup>[7]</sup>.

#### *Effect on arterial stiffness*

T2DM is one of the major responsible factor for increasing arterial stiffness. Studies have shown that SGLT2 inhibitors have caused for a considerable reduction in mortality rate due to cardiovascular events. This is enabled mainly through the mechanisms like natriuresis and effect on arterial stiffness. Some are there studies based on the effect of dapagliflozin hydrochlorothiazide on arterial stiffness and renal resistive index. It was performed by monitoring urinary glucose, sodium, isoprostanes, pulse wave velocity and flow-mediated dilation. The result was both the drugs exerted an equal amount of diuresis as well as antihypertensive effects. This describes the positive influence of SGLT2 inhibitors on arterial stiffness and endothelial dysfunction<sup>[7]</sup>.

#### *Cardiac inflammation*

One among the triggers for diabetic cardiomyopathy is cardiac inflammation. SGLT2 inhibitors can directly reduce the cardiac inflammation. 10 weeks Empagliflozin treatment have caused a significant reduction in cardiac interstitial microphage infiltration. This was shown in the genetic prediabetes/metabolic syndrome rat model. Another reports by Lee et al. pointed a marked improvement in cardiac inflammation among the Wistar rats in the acute phase of myocardial infarction that are treated by dapagliflozin up to 2 days. The mechanism left behind that was dapagliflozin reduced inflammatory cytokines mRNA levels like IL-1 $\beta$  and IL-6 and enhanced anti-inflammatory cytokine mRNA levels including IL-10, and also caused an increase in the phenotype macrophage ratio of M2/M1. As M1 is a proinflammatory phenotype and M2 is an anti-inflammatory one, these findings put forward that dapagliflozin induce macrophage polarization towards anti-inflammatory phenotype. Other study has described the direct mechanism of SGLT-2 inhibitors on cardiac inflammation reduction which is mediated the reduction of cardiac nucleotide binding oligomerization domain-like receptor 3 (NLRP3) inflammasome. The NLRP3 inflammasome is an interleukin-1 $\beta$  family cytokine-activating multi-protein signaling complex upregulated in the heart and that is linked with cardiac inflammation in T2DM, which is a key aid that is responsible for subsequent diabetic cardiomyopathy.

#### *Improvement in cardiac mitochondrial function*

The pathological progression of diabetic cardiac myopathy may leads to mitochondrial dysfunction. As mitochondria are the power house of cell, they are very important for energy

production. Studies have shown that SGLT2 inhibitors plays a key role in the attenuation of mitochondrial dysfunction. In a genetic diabetes mouse model, empagliflozin was found to repair the structural abnormalities inter-myofibrillar of mitochondria like defects in the appearance of sarcomeres, lowered electron density of matrix, cristae loss and mitochondrial fragmentation. Some studies in insulin resistant rats exposed that a 4 week treatment with dapagliflozin has shown an increase in the production of mitochondrial reactive oxygen species. There was an increase in the protein expressions of peroxisome proliferator-activated receptor gamma coactivator1-alpha (PGC1- $\alpha$ ) and carnitine palmitoyl transferase 1 (CPT1) after dapagliflozin treatment. These proteins are essential ones that regulate oxidation of cardiac mitochondrial fatty acid, which in turn is a key factor for mitochondrial biogenesis. Another notable incident was the increased expression of complex I of the electron transport chain. These all events suggest that dapagliflozin can restore the reduced cardiac metabolism during cardiac injury<sup>[8]</sup>.

#### *Diuresis*

During EMPAREG OUTCOME the reduction in heart failure hospitalizations was observed due to the potential diuretic action of empagliflozin. There are some differences in the action of SGLT2 inhibitors compared to loop and thiazide diuretics that are: 1) SGLT2 inhibitors are not showing any reflex sympathetic nervous system activation (i.e., no net increase in heart rate though the blood pressure lowers), 2) The point of action SGLT2 inhibitors are on the proximal tubule whereas thiazide diuretics have action on distal tubule (i.e., proximal to the macula densa) and results in increased urinary sodium and chloride delivery to the juxtaglomerular apparatus and 3) SGLT2 inhibitors have a prominent positive effect on blood glucose and uric acid, on the other hand thiazide and loop diuretics induce hyperglycemia and hyperuricemia. It was suggested that these effects provided by SGLT2 inhibition can restore tubuloglomerular feedback that would result in afferent arteriolar vasoconstriction as well as reduced glomerular filtration (i.e., decreased hyperfiltration) by lowering intraglomerular pressure. SGLT2 inhibitor treatment would also exert an effect on other neurohormonal factors like local RAAS inhibition which is mainly because of the enhanced delivery of sodium and chloride to the macula densa. Eventually all these effects would leads to reduced levels of aldosterone and decreased sympathetic nerve activity. They either or both lower the risk of cardiovascular death and heart failure<sup>[9]</sup>.

#### *Effect on RAAS*

Before the EMPA-REG OUTCOME there were some studies defining the increased action of SGLT2 inhibitors on RAAS. This can be concluded as a compensatory response to volume contraction, natriuresis, and lowered blood pressure. However, there is a consistent effect with afferent vasoconstriction than the efferent vasodilation that is related

with RAAS inhibition. Moreover, as a result of empagliflozin treatment reduced arterial stiffness can be found in those ones with withT1DM which is unrelated with RAAS activity. According to EMPA-REG OUTCOME, it clearly describes the activation of empagliflozin is mediated by non-classic RAAS pathways. During the empagliflozin treatment it causes the activation of RAAS as a result of reduced intravascular volume and blood pressure. This leads to the stimulation of type 1 angiotensin II receptor, which is the pathological centre of cardiovascular diseases. However, in EMPA-REG OUTCOME trial, 81% of patients received angiotensin-converting enzyme inhibitors or type 1 angiotensin II receptor blockers. The addictive cardio protective actions performed by empagliflozin effects by the activation of the type 2 angiotensin II receptor pathway and angiotensin 1-7 activation, these events causes the responses like vasodilation, anti-inflammatory effects, and positive inotropic effects<sup>[9]</sup>.

#### *Adverse effects of SGLT2 inhibitors*

Urogenital infections, decrease in glomerular filtration rate, reduction in uric acid levels, postural hypotension, dizziness, bladder and breast cancer are some of the postulated adverse effects associated with SGLT2 inhibitors<sup>[3]</sup>. Canagliflozin is reported with doubled risk of lower limb amputation in the CANVAS program. In the EMPA-REG OUTCOME trial empagliflozin was associated with peripheral artery disease. An initial decrease in glomerular filtration was also observed. There was an increased risk of fractures with 12 weeks canagliflozin treatment in CANVAS program. FDA have warned over the occurrence of diabetic ketoacidosis although it is rarely associated with SGLT2 treatment. In order to avoid the worsening of renal function SGLT2s should be used with caution or discontinued if there is hypovolemia. Since SGLT2 inhibitors can enhance the glucose concentration in the urine they can precipitate urogenital infections which may be complicated by urosepsis and pyelonephritis. There are also some postulated concerns on bladder cancer, but it is not yet confirmed at the present<sup>[10]</sup>. Although SGLT2 inhibitors are predominant in their renal protective actions some randomized controlled trials shown acute kidney injury for a less extend<sup>[11]</sup>.

### III. CONCLUSION

Though SGLT2 are well known for their hypoglycemic action they are also contributing inevitably to the cardio protective actions and thus reduce risk of hospitalizations. Blood pressure lowering, effects on RAAS, diuretic actions, etc. are the mechanisms that are found to have support cardiac actions. Despite of diabetic patients SGLT2 inhibitors are also playing a crucial role in improving cardiac functions in non-diabetic ones too. Therefore SGLT2 inhibitors exert a positive effects on cardiac function as well as cardiac structure and hence makes favorable cardiovascular outcomes.

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