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Research Article

Effects of Sglt2 Inhibitors on The Heart

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Introduction:

Cardiovascular disease and type 2 diabetes are prevalent throughout the world and represent a real public health problem. The prevalence of T2DM ranges from 6.9% to 10.2% in developed countries and more than 7% in developing countries.

It causes 17.5 million deaths annually, or approximately 31% of all deaths worldwide. Increasing evidence suggests a strong association between T2DM and cardiovascular disease.

T2DM is considered a major risk factor for cardiovascular morbidity and mortality, contributing to both microvascular complications (nephropathy, retinopathy, neuropathy) and macrovascular complications.

SGLT2 inhibitors are initially oral antidiabetic agents. They block the cotransport of sodium and glucose in the proximal tubule, inducing blood glucose and natriuresis. This action reduces renal reabsorption of glucose and induces hyperglycemia. The metabolic effects of SGLT2 inhibitors are significant reductions in blood glucose and glycated hemoglobin (HbA1c) and weight loss associated with induced glycosuria, which corresponds to a caloric loss of approximately 300 kcal per day.

Clinical studies with the different molecules in this therapeutic class - empagliflozin, dapagliflozin and canagliflozin - show that SGLT2 inhibitors induce a mean reduction in HbA1c of 0.5-1.0%, a mean weight reduction of 2 kg and a 2-4 mmHg reduction in systolic blood pressure, with a low risk of hypoglycemia [1].

SGLT2 inhibitors also have beneficial cardiovascular effects, mainly by reducing heart failure. Indeed, this effect has been clearly demonstrated in the EMPA-REG OUTCOME study with empagliflozin [2], in the CANVAS study with canagliflozin [3] and more recently in the DECLARE study with dapagliflozin [4]. In the EMPA-REG OUTCOME study, a 14% reduction in major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) ($p = 0.04$) and a 35% reduction in hospitalization for heart failure ($p = 0.002$) were observed with empagliflozin.

In the CANVAS study, a 14% reduction in major cardiovascular events ($p = 0.02$) and a 33% reduction in hospitalization for heart failure were reported with canagliflozin [2], [3]. In the DECLARE study, in which 60% of patients were in primary prevention, dapagliflozin reduced hospitalization for heart failure by 27% [4]. The CVD-REAL real-life study confirmed this benefit, with a 39% reduction in hospitalizations for heart failure, observed with all molecules in the class [5].

Note that the cardiovascular effects of SGLT2 inhibitors appear very early, so the effects of HbA1c and weight reduction observed with this class of therapy can be excluded. Furthermore, cardiovascular effects have also been observed in diabetic patients with significant reductions in glomerular filtration rate, where the metabolic effects of SGLT2 inhibitors are limited.

Therefore, this suggests that the direct cardiovascular effects of SGLT2 inhibitors are likely responsible for the reduction in heart failure. The exact mechanism underlying the improvement in myocardial function by SGLT2 inhibitors remains unclear. However, we can make some hypotheses.

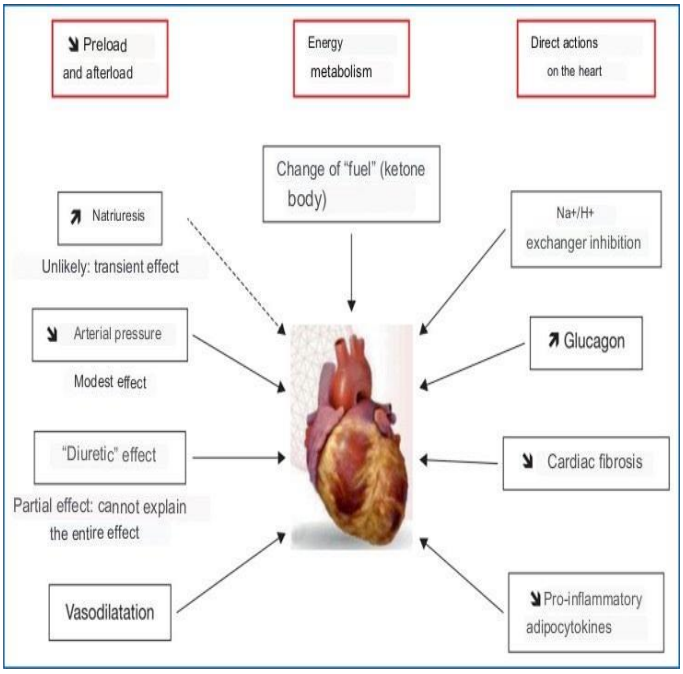


Figure 1. Main mechanisms thought to explain the cardiovascular benefit of SGLT2 inhibitors

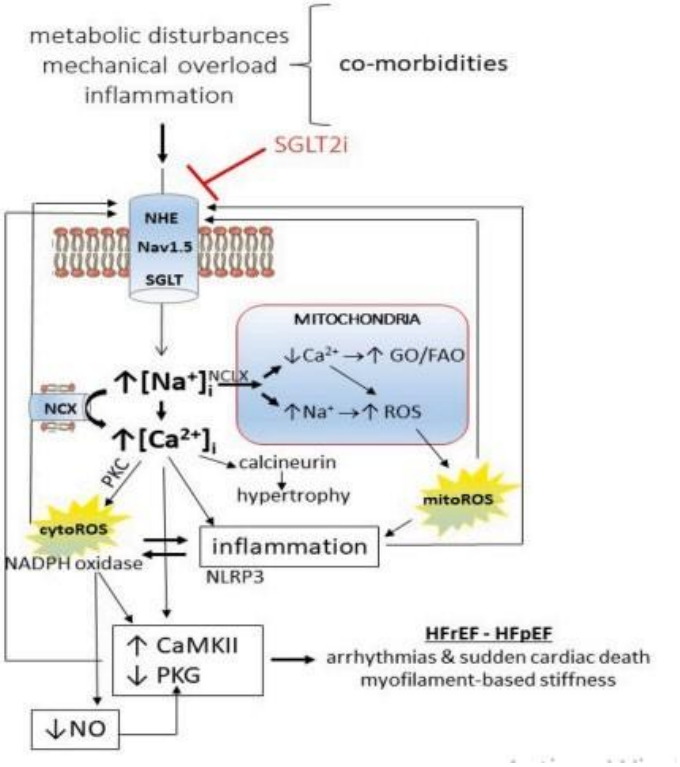
Decrease in preload and postload with the SGLT2 inhibitors

1.Direct effect on the heart muscle

It is important to note that the SGLT2 transporter is not present in cardiomyocytes. However, SGLT2 inhibitors may directly affect the heart through other mechanisms.

- Direct effects on Na+/H+ exchangers: Heart failure is characterized by an increase in sodium (Na+) and calcium (Ca++) in the cytoplasm of cardiomyocytes and a parallel decrease in Ca++ in the mitochondria. In vitro, increasing glucose concentration from 5.5 mmol/L to 11 mmol/L significantly increases Na+ and Ca++ in the cytoplasm of cardiomyocytes [17].

Empagliflozin has been shown to significantly reduce cytosolic Na+ and Ca++ concentrations and increase mitochondrial Ca++ [17]. This increase in sodium can cause some fatal arrhythmias. According to the DAPA-HF study, the addition of these SGLT2 inhibitors significantly reduced these arrhythmias.



- Glucagon increase: SGLT2 inhibitors increase glucagon production and plasma levels, resulting in beneficial effects on the cardiovascular system. Glucagon has been shown to have positive inotropic and inotropic effects [18]. This effect is rapid and independent of the sympathetic nervous system. Glucagon receptors are present on cardiac muscle cells. Its activation by glucagon promotes myocardial contractility primarily through an increase in cyclic adenosine monophosphate (cAMP) and a consequent increase in calcium current [19].

Glucagon also promotes glucose uptake by cardiomyocytes through activation of phosphoinositide 3-kinase and has antiarrhythmic effects [20]. These effects of glucagon may explain the reduction in heart failure and sudden death (due to antiarrhythmic effects) observed in the EMPA-REG OUTCOME study.

- Reducing cardiac fibrosis: Cardiac fibrosis is considered an important pathophysiological factor in the development of heart failure. Several studies have shown antifibrotic effects of SGLT2 inhibitors (Figure 4).

In a rat myocardial infarction model, dapagliflozin was shown to reduce collagen synthesis by inhibiting myofibroblast differentiation and increasing M2 macrophage activity [21]. In vitro, empagliflozin reduces transforming growth factor-β1 (TGF-β1)-induced fibroblast activation and reduces the expression of key fibrotic enzymes (e.g. collagen type 1, connective tissue growth factor) [14].

2. Natriuretic effect:

SGLT2 inhibitors that block the SGLT2 transporter induce transient natriuresis. This is mainly observed during the first few weeks of treatment. This alone does not explain the beneficial cardiac effects of this class of treatments, as other phenomena also play a role in improving cardiac performance [6].

✓ **Decrease in blood pressure:**

SGLT2 inhibitors have been shown to reduce systolic blood pressure by an average of 4 mmHg, which may contribute to the observed cardiovascular effects. However, a meta-analysis of studies on systolic blood pressure reduction in diabetic patients found that a reduction in the risk of major cardiovascular events was only observed for blood pressure reductions of >10 mmHg, and no significant reduction in cardiovascular mortality was observed. There wasn't. Therefore, the small reduction in systolic blood pressure achieved by SGLT2 inhibitors is likely to have only a partial effect and does not account for the entire cardiovascular benefit.

✓ **Diuretic" effect of SGLT2 inhibitors:**

Osmotic diuresis has been observed with SGLT2 inhibitors, which may explain the beneficial cardiovascular effect.

This "diuretic" effect is likely to partially explain the cardiovascular benefit of SGLT2 inhibitors, as indicated by data from the EMPA-REG OUTCOME study showing that part of the cardiovascular effects of empagli-flozin is associated with inducedhemoconcentration [7].

However, it should be noted that the various prospective studies with diuretics have never demonstrated a significant reduction in cardiovascular mortality [8]. This suggests that the overall cardiovascular effects observed with SGLT2 inhibitors cannot be explained by this simple "diuretic" effect of SGLT2 inhibitors.

However, the reduction in interstitial volume under SGLT2 inhibitors is greater than the reduction in plasma volume, as demonstrated by a study comparing dapagliflozin with a loop diuretic [9]. This more specific reduction in interstitial edema appears to be a potential advantage, particularly in patients with heart failure.

✓ **Vasodilation:**

Diabetic patients are known to suffer from arteriosclerosis, which causes the diabetes-related increase in blood pressure and causes actual cardiovascular complications.

Some data suggest that SGLT2 inhibitors induce vasodilation. In fact, empagliflozin has been shown to reduce arteriosclerosis in hypertensive diabetic patients [10]. In patients with type 2 diabetes, dapagliflozin has been shown to increase endothelium-dependent vasodilation independent of its effect

on blood pressure [11].

This vasodilation is expected to reduce afterload and improve cardiac function. Empagliflozin may modulate the renin-angiotensin system by promoting the production of angiotensin 2 fragments (particularly angiotensin 1-7), which promotes vasodilation and induces the activation of MAS receptors or angiotensin type 2 receptors.

The positive effects are achieved through activation of the body (AT2R). Affects the heart muscle [12].

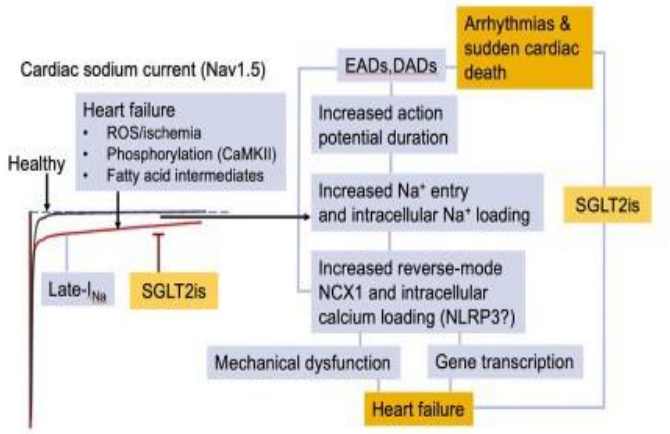


Fig. 2. Proposed mechanisms for the induction of late-I_{Na} in HF and how the development of HF and arrhythmias may be suppressed by SGLT2i-mediated late-I_{Na} inhibition. ROS, reactive oxygen species; EADs; early after-depolarizations, DADs; delayed afterdepolarizations, CaMKII; calcium/ calmodulin-dependent protein kinase II.

3. Effects of SGLT2 inhibitors on myocardial energy metabolism

Treatment with SGLT2 inhibitors results in increased glucagon and decreased insulinemia, which together with a decreased available glucose pool (secondary to diabetes) causes increased lipolysis and thus ketogenesis.

In patients with type 2 diabetes, an increase in β-hydroxybutyrate has been shown during treatment with SGLT2 inhibitors, with a concomitant decrease in glucose oxidation [13].

In a porcine model, empagliflozin increases myocardial ketone consumption by decreasing glucose consumption after experimental myocardial infarction [14].

In this metabolic situation, it has been suggested that the myocardium preferentially selects beta-hydroxybutyrate as an energy source, which has the property of producing energy with less oxygen consumption than fatty acids or glucose [15].

The bioenergetic interest of ketone bodies was reinforced by studies in healthy subjects showing that a 390-minute infusion of hydroxybutyrate was associated with a 50% decrease in myocardial glucose uptake and a 75% increase in myocardial blood flow. confirmed [16].

However, this intriguing "fuel metabolism" hypothesis favoring ketone bodies has not yet been fully test.

4. Effect on adipocytokines:

Epicardial adipose tissue is thought to promote heart failure through the production of pro-inflammatory cytokines that act directly on the myocardium [22].

A tomographic study of 40 coronary type 2 diabetic patients showed a significant reduction in epicardial fat after 6 months of treatment with dapagliflozin [23]. In this study, decreased epicardial fat was correlated with decreased plasma levels of tumor necrosis factor alpha (TNF-α).

Some data suggest that SGLT2 inhibitors restore the balance between pro- and anti-inflammatory cytokines that is more favorable to the myocardium. For example, 52 weeks of treatment with canagliflozin significantly reduced plasma interleukin-6 (IL-6) levels and reduced adiponectin, independent of changes in body weight, lipids, and HbA1c, compared to sulfonamides. increased [24]

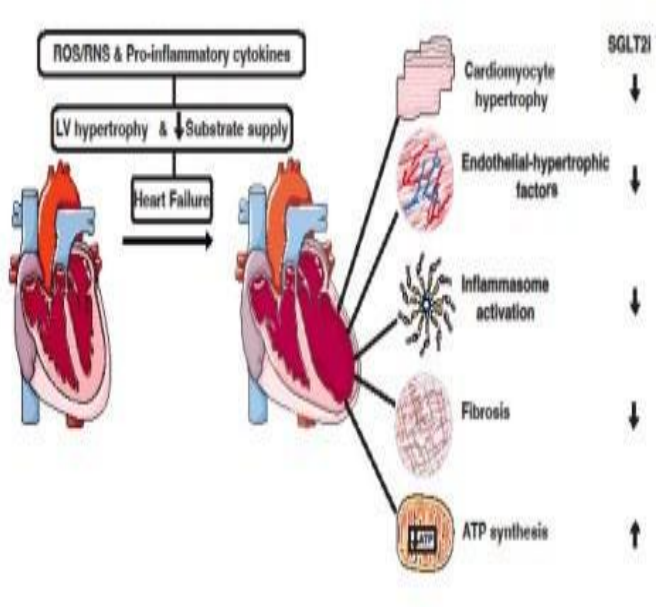


FIG : 4 Effect on adipocytokines

Conclusion:

In particular, her SGLT2 inhibitors, new anti-diabetic drugs, have proven effective in reducing the risk of heart failure. The observed early reduction in heart failure hospitalizations suggests that cardiovascular benefits are not associated with reductions in hyperglycemia and that other mechanisms are involved.

The exact reason why myocardial function improves under SGLT2 inhibitors remains unclear, but levels are elevated under SGLT2 inhibitors, indicating that cardiac myocytes use ketone bodies, which have high bioenergetic power, as their preferred energy substrate. level has increased. The positive inotropic hormone glucagon under SGLT2 inhibitors and possible direct effects on the myocardium (inhibition of the Na+/H+ exchanger, reduction of inflammation and myocardial fibrosis)

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