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THE EFFECTS OF SGLT2 INHIBITORS ON CELLULAR SENESCENCE

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Annotation: SGLT2 inhibitors have been shown to lower the risk of heart failure (HF) in people with diabetes, improving outcomes for HF patients across all levels of left ventricular ejection fraction (LVEF). This is achieved by reducing HF exacerbations and the risk of cardiovascular death. However, there is still uncertainty regarding the mechanisms responsible for these benefits beyond the inhibition of the sodium-glucose cotransporter 2 (SGLT2). Limited studies have explored the effects of SGLT2 inhibitors on cardiac remodeling through imaging and specific biomarkers, particularly in HF patients, with existing findings being inconclusive and primarily focused on those with diabetes and reduced LVEF. Importantly, there is a lack of data examining how SGLT2 inhibitors influence cardiac geometry, function, and biomarkers in the context of HF, regardless of LVEF.

Adverse remodeling of the myocardium, especially in the left ventricle, is a critical factor in the progression of HF, which is typically classified based on LVEF. However, other aspects, such as the left atrium's role, are often overlooked. The left atrium significantly impacts cardiac function, especially concerning left ventricular filling during the diastolic phase. Dysfunction of the atrium can directly contribute to pulmonary congestion. Atrial remodeling occurs in HF irrespective of the extent of left ventricular systolic dysfunction and can be identified in both preserved and reduced LVEF cases. The morphology of the left atrium has been linked to the risk of developing HF in high-risk individuals and has been associated with increased rates of hospitalization and mortality among HF patients. Consequently, atrial health has become an essential focus in recent European Society of Cardiology (ESC) guidelines for HF. This study aims to examine the effect of SGLT2 inhibitors on cardiac remodeling parameters, with a specific focus on left atrial remodeling, in patients with HF, independent of their LVEF status.

Key words: Atrial remodeling, cardiac remodeling, SGLT2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a recent class of antidiabetic drugs that target SGLT2 located in the renal proximal tubules. SGLT2 is responsible for around 80–90% of renal glucose reab sorption, and SGLT2 inhibitors reduce blood glucose levels by suppressing renal glucose reabsorption[5]. Beyond their anti-diabetic effect, SGLT2 inhibitors have shown beneficial effects on major adverse cardiovascular events and improve doutcomes in chronic kidney disease. The EMPA-REG OUTCOME trial reported a reduction in major cardiovascular disease events in empagliflozin-treated type 2 diabetic patients. In addition, the risk of hospitalisation for heart failure was 35% lower in patients treated with empagliflozin11,12. Moreover, empagliflozin showed improved cognitive impairmentinolder frail patients with type 2 diabetes and heart failure with preserved ejection fraction (HFpEF)[4]. Similarly, the CANVAS and DECLARE-TIMI clinical trials demonstrated that canagliflozin and dapagliflozin reduced the risk of cardiovascular death or hospitalisation for heart failure in individuals with type 2 diabetes and cardiovascular disease, respectively[4]. The DELIVER trial suggests that the improvements due to dapaglifozin are increased the greater degree of frailty[6]. In patients with chronic kidney disease, regardless of their diabetes status, SGLT2 inhibitors (i.e. dapagliflozin)

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reduce the risk of death due to renal or cardiovascular causes[3].Thebeneficial effects of SGLT2 inhibitors are likely to be inde pendent of glycemic control, and the mechanisms behind these effects have been extensively debated[2].

Introduced as a new class of drugs for the treatment of type 2 diabetes, SGLT2 inhibitors (e.g., dapagliflozin, canagliflozin, empagliflozin) inhibit the reabsorption of glucose in the kidney, leading to glycosuria. In addition to their blood glucose lowering effect, several clinical trials have shown the advantages of SGLT2 inhibitors on renal and cardiovascular out comes, with and without diabetes. On the other hand, it is important to be aware of their potential adverse effects. Increased glucosuria may lead to urinary tract and genital infections[5]. Moreover, hypotension50 and hypovolemia risk could be observed as a consequence of natriuretic and blood-pressure lowering effects. A risk of ketoacidosis was also reported in some cases. Despite the absence of robust evidence indicating an increased risk of hypoglycaemia[3], it is acknowledged that the concomitant administration of insulin secretagogues potentially contributes to the occurrence of hypoglycemia[5]. Nevertheless, the recent attention on repositioning SGLT-2 inhibitors as senotherapeutic agents targeting aging is noteworthy. The anti-aging effects of SGLT2 inhibitors have been attributed to multiple mechanisms. These include the reduction of inflammation, free radicals, and oxidative stress; regulation of mitochondrial function and autophagy; modulation of nutrient-sensing pathways such as mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuins (SIRT); suppression of senescent cell burden; and extension of lifespan. SGLT2 inhibitors have been suggested to mimic calorie restriction by increasing AMPKandSIRT1,while decreasing mTOR and insulin/IGF1 (insulin-like growth factor 1) signalling, which may potentially affect longevity62. Furthermore, increasing evidence points to the benefits of SGLT2inhibitors through mTOR, AMPKandSIRT1pathwaysindifferent tissues and cells, such as kidney63, cardiac microvascular endothelial cells[7], and cardiomyocytes. In this review, we focus on the effects of SGLT2 inhibitors in various models of senescence and their mechanism of action. Summarises the studies that show anti-senescence effects of SGLT2 inhibitors.

Aging causes various structural and functional impairments in the cardio vascular system. With age, senescent cells accumulate in the heart and vasculature, leading to cardiovascular pathologies103.Ithasbeenshownthat removing senescent cells in aged mice, either pharmacologically using senolytics or genetically, improved myocardial dysfunction, led to the for mation of new cardiomyocytes and decreased hypertrophy and fibrosis associated with cardiac aging[8]. With age, the SGLT2 protein levels in cardiomyocytes increase. By inhibiting SGLT2, age-associated defects of the [Ca2+]i-homoeostasis, phospholamban (PLB) phosphorylation, Na+/Ca2+ exchanger (NCX) activity and mitochondrial Ca2+-loading can be restored[4]. Given their benefits on cardiovascular events and all-cause mortality, SGLT2 inhibitors may have anti-aging effects. In support of this, as reported by Katsuumi etal., the administration of canagliflozin toApoE knockout atherosclerotic mice contributed to the reduction of senescent cells and improvement of atherosclerosis[5]. In a study on high glucose induced cardiac stromal cell senescence, empagliflozin treatment reversed the increase in SA-β-gal-positive cells and Phospho-p38, as well as the decrease in pAkt protein expression[8]. High glucose conditions disrupt the PI3K/Akt/eNOS pathway, leading to activation of mitogenic and pro inflammatory factors, therefore these findings highlight a possible link between downregulation of the PI3K/Akt pathway and senescence induction[3]. In another study

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investigating the cardiovascular effects of empagliflozin treatment in obese and lean control ZSF1 rats, the expression levels of senescence markers p53, p21 and p16 and SGLT1 and SGLT2 proteinexpressionwereincreasedintheinneraorticcurvature,comparedto the outer curvature in control lean rats, which was prevented by empagliflozin treatment[9]. In a murine diabetic cardiomyopathy model, treatment with empagliflozin attenuated apoptosis, fibrosis, autophagy, senescence and cardiac dysfunction. Furthermore, empagliflozin treatment inhibited hyperactivation of autophagy through the AMPK/GSK3β signalling pathway[4]. A recent study has also revealed that increased senescence markers (p53, p21, γ-H2AX, SASP and SA-β-Gal activity) in STZ and high fat diet (HFD)-induced type 2 diabetic mouse model and high glucose and palmitic acid-exposed AC16 cardiomyocyte cells were reversed by empa gliflozin. The researchers have proposed a novel mechanism for the drug, suggesting that the amelioration of senescence was related to the Theincreased expression of SASP proteins and senescence markers by cardiotoxic chemotherapeutic drugs like doxorubicin[1] indicates a possible correlation between senescence, heart disease and cancer treatment. Dox orubicin, which increases the expression of p16Ink4a, p53/p21Cip1/Waf1 and SA β-Gal activity in cardiomyocytes, has been linked to the development of cardiomyopathy. A study proposing that doxorubicin-induced cardio toxicity is associated with cardiomyocyte senescence, additionally noted beneficial effects on doxorubicin-induced cardiac dysfunction upon seno lytic navitoclax treatment[8]. In a study investigating the effects of dapagli f lozin on doxorubicin-induced cardiotoxicity, rats were given dapagliflozin for 6 weeks, followed by doxorubicin for 4 weeks. The group treated with doxorubicin exhibited a decrease in systolic function parameters, which were normalised by dapagliflozin pre-treatment. Additionally, in vitro studies demonstrated that dapagliflozin treatment reduced doxorubicin induced apoptosis and normalised STAT3 expression in cardiomyocytes. Notably, the cardioprotective effect of dapagliflozin, suppressing doxorubicin-induced ROS and apoptosis, was shown to decrease when STAT3 was knocked down in cardiomyocytes[5].This suggests that the cardioprotective effects of dapagliflozin are mediated by STAT3.

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