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Antiarrhythmic Effect of SGLT 2 Inhibitors

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Abstract:

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are gaining ground as standard therapy for heart failure with a class-I recommendation in the recently updated heart failure guidelines from the European Society of Cardiology. Different gliflozins have shown impressive beneficial effects in patients with and without diabetes mellitus type 2, especially in reducing the rates for hospitalization for heart failure, yet little is known on their antiarrhythmic properties. Atrial and ventricular arrhythmias were reported by clinical outcome trials with SGLT2 inhibitors as adverse events, and SGLT2 inhibitors seemed to reduce the rate of arrhythmias compared to placebo treatment in those trials. Mechanistical links are mainly unrevealed, since hardly any experiments investigated their impact on arrhythmias. Prospective trials are currently ongoing, but no results have been published so far. Arrhythmias are common in the heart failure population, therefore the understanding of possible interactions with SGLT2 inhibitors is crucial.

Keywords: Antiarrhythmia, SGLT 2 inhibitors, cardiovascular.

Introduction:

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) (including dapagliflozin, empagliflozin, sotagliflozin, and canagliflozin, among others) are novel oral hypoglycaemic agents with both cardiovascular and renal benefits that can significantly reduce hospitalization due to heart failure, decrease cardiovascular death, protect renal function, and improve insulin resistance **(1, 2).**

Recent clinical studies have shown that SGLT2is have anti-arrhythmic effects also **(3, 4),** and experimental studies have shown that SGLT2is may indirectly or directly affect the onset of arrhythmias via alleviation of myocardium oxidative stress and inflammatory response, improvement of cardiomyopathy and endothelial dysfunction, promotion of cardiomyocyte energy and lipid metabolism, maintenance of cellular ion homeostasis, amelioration of electrophysiological remodeling, improvement of heart failure, inhibition of cardiac sympathetic hyperinnervation and autonomic imbalance, and reduction of body weight, with these combined mechanisms contributing to the suppression of arrhythmias **(5, 6).**

In this review, we summarize the recent clinical evidence, studies on laboratory animals, and related research on the antiarrhythmic effects of SGLT2is, to further explore its underlying mechanisms, safety, and prospects for clinical applications.

Clinical evidence of the antiarrhythmic effects of SGLT2is on atrial arrhythmia.The DECLARE-TIMI 58 trial subgroup analysis in type 2 diabetes mellitus (T2DM) patients suggested that dapagliflozin reduced the risk of atrial fibrillation/atrial flutter (AF) events by 19% (HR: 0.81, 95% CI: 0.68– 0.95, p = 0.009) **(3).** A meta-

analysis showed that SGLT2is significantly reduced AF-related adverse events by 19.33% (RR: 0.83, 95% CI: 0.71– 0.96, p = 0.01) **(4).**

Another systematic review and meta-analysis indicated that SGLT2is was associated with a reduced risk of developing AF (RR: 0.82, 95% CI 0.70– 0.96); however, there was no significant difference in reductions in the incidence of atrial flutter (RR: 0.83, 95% CI 0.58– 1.17), and the occurrence of cardiac arrest (RR: 0.83, 95% CI 0.61– 1.14) was not significantly different **(5).**

More recently, an analysis of the large FDA adverse event reporting system reported that diabetic patients treated with SGLT2is had a lower incidence of AF, which was highly indicated by its antiarrhythmic effect **(6).** However, although these were real-world data, the selected study patients were diagnosed with T2DM or cardiovascular diseases, which would expect a higher prevalence of AF **(1),** and it remains poorly understood if a potential beneficial SGLT2is effect on AF might be due to improving heart failure, or whether it was the result of a direct effect in the myocardium **(2).**

Direct mechanisms by which SGLT2is mediates anti-arrhythmic effects the effect of SGLT2is on the myocardium oxidative stress and inflammatory response. Chronic systemic inflammation, oxidative stress, and fibrosis were closely linked, and these played a key role in the pathogenesis of arrhythmia occurrence **(5).**

Treatment with antioxidants was shown to reduce cardiac pro-inflammatory and fibrotic markers **(1, 6).** A study reported that empagliflozin significantly reduced cardiomyocyte hypertrophy and interstitial fibrosis, indicating that empagliflozin reduced cardiovascular oxidative stress and inflammation **(2).**

The effect of SGLT2is on the cardiomyocytes and myocardial remodeling:

Myocardial fibrosis was an integral part of cardiac remodeling, which led to a decline in cardiac function, even heart failure. Myocardium with abnormally activated fibroblasts secretes extracellular matrix proteins, resulting in impaired ventricular function and contractile dysfunction, promoting cardiac fibrosis, and causing arrhythmias eventually **(5, 7)** showed that dapagliflozin significantly inhibited cardiac fibrosis in post-myocardial infarction rat models.

The effect of SGLT2is on the myocardium endothelial cells and endothelial dysfunction

A dysfunctional endothelium was defined as an imbalance between its integrity and function, which is associated with a diminished vasodilatory capacity, inflammation, and prothrombosis. Additionally, SGLT2is had a positive effect on the suppression of arrhythmia occurrence by improving endothelial dysfunction **(6).**

The effect of SGLT2is on myocardial metabolic alteration

Under physiological conditions, myocardial energy is mainly supplied by mitochondrial oxidative metabolism and glucose metabolism. When myocardial energy metabolism changes, it can promote arrhythmogenesis **(3, 5).** A study revealed that empagliflozin treatment, by reducing triglyceride accumulation, significantly reduced myocardial and liver steatosis. It was not clear, however, whether the observed empagliflozin effect on cardiac triglyceride accumulation was tissue-specific **(2, 4).** A possible explanation for SGLT2is inhibition-mediated cardioprotection was ketone body formation **(6).** Through stabilization of membrane potential, ketones increased mitochondrial biogenesis and exerted anti-arrhythmic effects **(5).**

The effect of SGLT2is on ion homeostasis in cardiomyocytes

Myocardial Ca2+ and Na+ homeostasis are essential for cardiac signal transduction, heart rhythm regulation, and cardiac myocyte energy production **(1, 5).** Therefore, it is critical to study the molecular mechanisms involving Ca2+ and Na+ homeostasis to better understand the mechanism of arrhythmia occurrence.

The effect of SGLT2is on related ion channel proteins/receptors

Research has implied that diminished SERCA2a activity and leaky RyR increased diastolic [Ca2+] in the failing heart, and the aberrant expression of ion channel proteins, which is the major trigger of the occurrence of arrhythmia. Notably, SGLT2is may affect Ca2+ handling, Na+ balance, and mitochondrial ROS release through ion channel proteins, which may have an antiarrhythmic effect **(3, 6).**

Indirect mechanisms by which SGLT2is exerts anti-arrhythmic effects

SGLT2is reduces the ventricular pressure load and volume load

Increasing blood pressure or myocardial oxygen consumption by any means may induce atrial or ventricular arrhythmias both experimentally and in patients. Conversely, a decrease in blood pressure or cardiac load (i.e., preload, afterload) may eliminate arrhythmias due to its causes. SGLT2is mainly acts on SGLT2 receptors in renal proximal tubular epithelial cells, inhibiting Na+ and glucose reabsorption, significantly increasing urine output, reducing cardiac preload and myocardial oxygen consumption, and lowering blood pressure **(3).**

SGLT2is improves heart failure

Multiple trials have demonstrated the effect of SGLT2is to reduce overall mortality, particularly in patients with heart failure **(2, 6).** As mentioned above, SGLT2is might reduce volume overload and improve cardiac function in heart failure patients **(1).** Researchers have reported that empagliflozin reduces blood pressure, arterial stiffness, and vascular resistance, improving the cardiac output of heart failure patients **(5).** Thus, the initial finding and the largest mechanism for the cardiac benefit of SGLT2is was its ameliorative effect on heart failure, which may also be its indirect anti-arrhythmic mechanism.

SGLT2is reduces body weight

Weight gain and obesity are closely related to arrhythmogenesis, and weight reduction is an essential component of arrhythmia intervention. SGLT2is achieve a negative energy balance through diuresis, Na+ excretion, and glucose excretion, leading to weight loss. In obese rats, empagliflozin not only reduces body weight but also improves endothelial function and cardiac remodeling **(5).** Clinical studies have shown that SGLT2is significantly reduced body weight and suppressed obesity compared to placebo, which can result in a 2– 3 kg weight loss, mainly by promoting osmotic diuresis leading to volume loss **(4).**

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