KUŁAK, Klaudia, CHAMERA-CYREK, Katarzyna, JANIK, Izabela, KUŚMIERSKA, Martyna, KOMAN, Anna, PLISZKA, Marzena, GADŻAŁA, Katarzyna, PALACZ, Karolina, SZTYBÓR, Izabela and PRZYGODZKA, Sabina. SGLT-2 inhibitors in heart failure: a literature review on mechanisms, efficacy and safety. Quality in Sport. 2024;15:52083. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.15.52083
https://apcz.umk.pl/QS/article/view/52083

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 01.06.2024. Revised: 20.06.2024. Accepted: 01.07.2024. Published: 05.07.2024.

SGLT-2 inhibitors in heart failure: a literature review on mechanisms, efficacy and safety

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ABSTRACT:

Introduction: Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors), known as flozins, are a recent class of medications gaining recognition for their effectiveness in diabetes, cardiovascular health, and heart failure management. The objective of this study is to examine and integrate recent literature concerning the mechanisms, effectiveness, and safety of SGLT2 inhibitors in managing heart failure.

Material and Methods of Research: A literature review focused on keywords related to the topic was performed using databases such as PubMed and Google Scholar.

Results: SGLT-2 inhibitors, initially developed for type 2 diabetes, significantly benefit heart failure (HF) with reduced, mildly reduced, and preserved ejection fractions by improving various cardiac outcomes. These drugs lower glucose levels and promote osmotic diuresis,

natriuresis, and favorable metabolic effects, reducing cardiac preload and afterload. Consequently, SGLT-2 inhibitors are now pivotal in HF treatment, enhancing cardiac efficiency and reducing HF-related hospitalizations and mortality.

Conclusion: SGLT-2 inhibitors substantially decrease cardiovascular risk and hospitalizations for heart failure in patients with or without type 2 diabetes, making them crucial in HF management. Consequently, SGLT-2 inhibitors should be considered first-line therapy for heart failure, regardless of concurrent medications, due to their efficacy and comprehensive benefits in managing this condition.

Keywords: SGLT2 inhibitors, flozins, heart failure

I. Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors), commonly referred to as flozins, represent a relatively recent class of medications. Since their introduction, these drugs have rapidly gained significant recognition and acceptance within the medical community, particularly among specialists such as diabetologists, cardiologists, and nephrologists. Their effectiveness in managing various conditions related to diabetes and cardiovascular health has made them an essential tool in contemporary medical practice [1,2]. Furthermore, a growing number of studies are being undertaken to explore the mechanisms of action of SGLT2 inhibitors in heart failure.

Heart Failure (HF) is a complex and life-threatening syndrome marked by considerable morbidity and mortality rates. Since being identified as an emerging epidemic in 1997, heart failure has continued to pose a significant clinical and public health challenge. Patients with HF often experience severely diminished functional capacity and quality of life, which can significantly impact their daily activities. Additionally, the financial burden associated with HF is substantial, encompassing both direct medical costs and indirect costs related to lost productivity and caregiving. This syndrome affects over 64 million individuals globally, underscoring its widespread prevalence and the critical need for effective management strategies [3,4].

It is essential to note that guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) now incorporates four classes of medications, one of which is sodium-glucose cotransporter-2 inhibitors (SGLT2i) [5].

II. Purpose of the study

The aim of this study is to review and synthesize current literature on the mechanisms, efficacy, and safety of SGLT2 inhibitors in the treatment of heart failure. By doing so, it seeks to provide a detailed and comprehensive understanding of their therapeutic potential, clinical benefits, and associated risks. This analysis will thereby inform clinical practice, aid healthcare professionals in making evidence-based decisions, and guide future research directions to further explore and optimize the use of SGLT2 inhibitors in heart failure management.

III. Materials and methodology

The literature was gathered through searches on PubMed and Google Scholar, supplemented by references from the initially retrieved articles. The search included various combinations of terms related to SGLT2 inhibitors and heart failure. Only studies published after 2017 were included in the review, ensuring the analysis focuses exclusively on the most recent and relevant knowledge available.

IV. Description of the state of knowledge

SGLT-2 inhibitors role in heart failure

SGLT-2 inhibitors, initially developed for managing type 2 diabetes, have demonstrated significant benefits in treating heart failure (HF) with reduced (HFrEF) mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF). These medications, including dapagliflozin, empagliflozin, and canagliflozin, have become a pivotal addition to heart failure therapy due to their ability to improve various cardiac outcomes. Heart failure (HF) is a complex clinical syndrome resulting from either functional or structural abnormalities in the ventricles' ability to fill or eject blood, resulting in a variety of symptoms. Heart failure can be categorized based on the left ventricular ejection fraction (LVEF) into four groups. Heart failure with reduced ejection fraction (HFrEF) occurs when the left ventricular ejection fraction (LVEF) is 40% or lower. Heart failure with improved ejection fraction (HFimpEF) is characterized by a previous left ventricular ejection fraction (LVEF) of 40% or lower, followed by an increase in

LVEF to above 40% during follow-up. Heart failure with mildly reduced ejection fraction (HFmrEF) is diagnosed when the left ventricular ejection fraction (LVEF) falls within the range of 41% to 49%. Heart failure with preserved ejection fraction (HFpEF) is identified when the left ventricular ejection fraction (LVEF) is equal to or greater than 50%.

Mechanisms of action

Cardiac metabolism involves a complex network of numerous pathways responsible for providing a constant supply of ATP to the continually active contractile apparatus. Disruptions in these pathways are linked to myocardial dysfunction. The latest antidiabetic drugs, SGLT2 inhibitors, have been shown to decrease cardiovascular mortality and heart failure hospitalizations. Although the mechanisms behind these benefits are not yet fully understood, these drugs may be crucial in restoring energy efficiency to the damaged heart [6].

SGLT-2 inhibitors work by promoting glycosuria, which leads to osmotic diuresis and natriuresis. This helps in reducing plasma volume and cardiac preload and afterload. Additionally, these drugs have been shown to have beneficial effects on myocardial metabolism, inflammation, and fibrosis, contributing to their positive impact on heart failure [6, 7, 8].

Prospective randomized trials have shown that sodium-glucose cotransporter type 2 (SGLT2) inhibitors offer benefits for various cardiovascular and renal risk factors, including HbA1c, blood pressure, body weight, renal hyperfiltration, and cardiorenal outcomes. These inhibitors may enhance adipose tissue function and reduce serum levels of leptin, TNF-α, and IL-6, while increasing adiponectin. Although data on high-sensitivity C-reactive protein and other inflammatory markers in humans are limited, animal studies have reported reductions in cytokine and chemokine levels, along with protective effects against the progression of atherosclerotic lesions. The underlying mechanisms behind this anti-inflammatory effect are varied and may include weight loss, reduced inflammation in adipose tissue, a slight increase in ketone bodies, lower uric acid levels, and reduced oxidative stress [9].

These beneficial effects seem attributable to the significant reduction of intracellular sodium levels, well-known to exert a cardioprotective role in the prevention of oxidative stress and consequent cardiomyocyte death. From a molecular perspective, patients' exposure to gliflozins' treatment mimics nutrient and oxygen deprivation, with consequent autophagy stimulation. This allows to maintain the cellular homeostasis through different degradative pathways. Moreover SGLT-2 inhibitors act as consequent glucose lowering, erythropoiesis enhancing and ketogenesis stimulating factors [10].

A healthy heart requires a substantial amount of energy to maintain normal contractile function, utilizing several substrates, including glucose and free fatty acids (FFAs). Over 95% of ATP is generated by mitochondrial oxidative phosphorylation, with glycolysis providing a lesser contribution. Under stressful conditions such as heart failure (HF), glucose utilization by the heart muscle is impaired, shifting the metabolism primarily to FFA consumption, which is less efficient due to increased oxygen demand by the myocardium. This shift can lead to lipotoxicity caused by higher production of reactive oxygen species (ROS) and impaired calcium absorption from the sarcoplasmic reticulum, potentially resulting in diastolic dysfunction [10, 11].

Ketone bodies offer an alternative substrate that can improve cardiac metabolic efficiency. Studies on both humans and animal models have demonstrated that beta-hydroxybutyrate (β-OHB) can enhance cardiac function and metabolism, promoting reverse ventricular remodeling and improving cardiac output and diastolic function [10, 12, 13]. Additionally, ketone bodies exert an anti-inflammatory effect by suppressing the activation of the NLRP3 inflammasome [10].

SGLT2 inhibitors (SGLT2i) have intrinsic metabolic mechanisms that may lead to euglycemic ketoacidosis. SGLT2 inhibition stimulates lipolysis, increasing FFAs, which contributes to ketogenesis. This process also increases sodium ion concentrations in the renal tubule fluid, leading to reduced urinary excretion of negatively charged ketones. Furthermore, increased glucagon levels, resulting from reduced insulin secretion or activity of pancreatic alpha cells expressing SGLT2, also contribute to ketogenesis. These metabolic changes potentially improve cardiac efficiency, thus preventing HF [14]. By lowering plasma glucose levels, SGLT2i trigger an increase in circulating ketones [15]. SGLT2i are also suggested to promote the breakdown of branched-chain amino acids (BCAAs) as an alternative fuel source [16]. Maintaining sodium and calcium homeostasis in the myocardium is crucial for efficient excitation–contraction coupling, but this balance is disrupted in HF. Increased intracellular sodium levels in myocytes enhance the activity of the Na+/Ca2+ exchanger, raising calcium levels in the sarcoplasmic reticulum. While this mechanism improves cardiac contractility and function, it also raises the risk of arrhythmia and oxidative stress due to reduced mitochondrial calcium levels. Thus, elevated sodium and myocardial calcium levels can contribute to cardiovascular death and HF [17]. Empagliflozin has been shown to lower cardiac intracellular Na+ and Ca2+ while increasing mitochondrial Ca2+ by inhibiting NHE1 [18]. This NHE1 inhibition appears to be a class effect of SGLT2i, as demonstrated by studies on Dapagliflozin and Canagliflozin [19]. Although SGLT2 receptors are not expressed in the heart, the inhibition

of NHE1 and subsequent reduction in cardiac cytosolic Na+ suggest a potential class effect of SGLT2i in addressing HF [20]. NHE1 and NHE3 inhibition could thus be a therapeutic strategy to prevent cardiac remodeling and HF, despite mixed results from studies with NHE1 inhibitors [10]. SGLT2i also reduce serum uric acid (UA) levels, an important independent risk factor for HF. Hyperuricemia is associated with HF with preserved ejection fraction (HFpEF) in hypertensive individuals and is a predictor of HFpEF incidence through various mechanisms [21].

Adipokines, such as Leptin are implicated in various cardiovascular diseases related to obesity, while adiponectin appears to have a cardioprotective role. Altered leptin metabolism and structure lead to epicardial fat accumulation, playing a crucial role in HF development due to cardiac fibrosis and inflammation, contributing to ventricular remodeling. SGLT2 inhibition reduces serum leptin and increases adiponectin levels, likely providing cardioprotection [22]. Canagliflozin has been shown to reduce serum leptin levels compared to glimepiride, along with a reduction in the pro-inflammatory cytokine IL-6, though TNF-α levels were unaffected [23]. Dapagliflozin has been reported to reduce ectopic epicardial fat, TNF-α, and PAI-1, suggesting a possible role for SGLT2i in various mechanisms involved in cardiovascular inflammation [24].

SGLT2i treatment has modest effects on lipid profiles, with decreases in HDL cholesterol and triglycerides and a 20–30% reduction in small dense LDL particles [25].

Mechanisms of hemodynamic protection

Obesity and type 2 diabetes mellitus (T2DM) can lead to heart failure with preserved ejection fraction (HFpEF) by increasing cardiac preload. This increase is due to volume overload resulting from plasma volume expansion. In these patients, insulin resistance (IR) and proinflammatory cytokines released by hypertrophic visceral adipocytes cause arterial stiffness, endothelial dysfunction in arterioles, and a reduction in capillary density both systemically and in the heart, thereby increasing cardiac afterload [26,27]. The direct cardiac effects of SGLT2 inhibitors (SGLT2i) include improvements in preload due to natriuresis and osmotic diuresis, and reductions in afterload through decreased sodium levels and circulating volume. This results in lowered systolic and diastolic blood pressure by 3–5 mmHg and 2–3 mmHg, respectively.

These benefits occur without any increase in heart rate and while reducing arterial stiffness. [28, 29]. Several mechanisms appear to contribute to the blood pressure (BP) reduction induced by SGLT2 inhibitors (SGLT2i). These include decreased sodium reabsorption in the proximal

renal tubule, leading to increased diuresis, improved vascular function through reduced stiffness and vascular resistance, and body weight reduction [30]. The role of SGLT2 inhibitors (SGLT2i) as blood pressure-lowering drugs has been confirmed by two meta-analyses, which showed reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) [31, 32]. SGLT2i have also been found to be more effective at night than during the day, particularly beneficial for high-risk patients with uncontrolled nocturnal hypertension [30]. Additionally, pulse wave velocity (PWV), an index of arterial stiffness, decreased after 48 hours of Dapagliflozin administration in a small cohort of T2DM patients [33]. The beneficial effect of Dapagliflozin on endothelial function has been emphasized in several studies. Other indicators of arterial stiffness, such as central systolic BP and forward and backward pulse wave amplitude, have been positively impacted by both Empagliflozin and Dapagliflozin [34, 35]. Gliflozins induce natriuresis and glucosuria by inhibiting SGLT2 in the proximal renal tubule [36, 37]. Non-reabsorbed glucose and sodium in the tubule trigger osmotic diuresis. As a result, sodium and chloride concentrations decrease in the tubular fluid, which inhibits the NA-K-2Cl cotransporter, preventing sodium reabsorption in the loop of Henle [38]. Consequently, there is a decrease in plasma volume and total body sodium content, leading to changes in cardiac preload conditions, which positively impact the left ventricular Franklin-Starling curve [39]. SGLT2 inhibitors may also influence afterload by impacting both blood pressure and arterial stiffness. Recent research indicates that the rise in hematocrit linked with SGLT2 inhibitors is partly due to hemoconcentration resulting from decreased extracellular fluid volume and enhanced diuresis [39]. Alternatively, treatment with Dapagliflozin resulted in elevated levels of erythropoietin (EPO) and reticulocyte counts, leading to an increase in hematocrit and hemoglobin values. Additionally, the rise in erythropoietin yields beneficial impacts on the mitochondrial function of cardiomyocytes, cell proliferation, inflammation, and angiogenesis. Furthermore, it initiates myocardial protection by augmenting hematocrit, thereby leading to an increased supply of oxygen to the tissues [40].

Inhibition of fibrosis and apoptosis

Cardiac damage caused by high blood sugar levels is attributed to elevated levels of reactive oxygen species (ROS), inflammation, and apoptosis. Increased glucose levels lead to the formation of non-enzymatic glycation end products in proteins, lipids, and nucleic acids, resulting in inflammation, apoptosis, and subsequent fibrosis. Enlargement of epicardial fat triggers a shift in the production of adipokines, leading to increased levels of leptin rather than adiponectin. This rise in leptin levels promotes the synthesis of proinflammatory cytokines and,

consequently, stimulates the expression of inducible NOS in cardiomyocytes via the activation of nuclear factor-kappa B (NF-κB) [10]. Research indicates that inhibiting SGLT2 reduces circulating levels of chemokine 2, IL-6, and TNF-α. Consequently, SGLT2 inhibitors may alter inflammatory responses in various cells of both the kidneys and other tissues through diverse molecular pathways. These effects influence oxidative stress, hemodynamics, cytokine production induced by hyperglycemia, activation of the renin-angiotensin-aldosterone system (RAAS), immune system function, and inflammation associated with obesity [41]. Recent research has delved into the molecular mechanisms underlying the progression of HFpEF. Overexpression of inducible nitric oxide synthase (iNOS) results in decreased activity of two proteins: a variant of X-box binding protein 1 (XBP1) and enzyme 1α. Diminished expression of XBP1 suppresses protein response, leading to the accumulation of destabilized proteins in myocardial tissue and heightened cardiomyocyte apoptosis [42]. Schiattarella et al. demonstrated that either a deficiency in iNOS expression or overexpression of XBP1 in HFpEF-afflicted mice improves the phenotype by reducing left ventricular filling pressures and mitigating pulmonary congestion. SGLT2 inhibitors might inhibit iNOS expression and activate eNOS, thereby increasing XBP1s expression and promoting titin phosphorylation in cardiac muscle [43]. Myocardial fibrosis represents a crucial part of the cardiac remodeling, leading to HF. Kang et al. illustrated that Empagliflozin effectively inhibits profibrotic markers, such as type I collagen, α-smooth muscle actin, connective tissue growth factor, and matrix metalloproteinase 2. Additionally, it attenuates transcription growth factor β1 (TGF-β1)-induced fibroblast activation [44]. SGLT2 inhibitors also target AMP-activated protein kinase (AMPK), an enzyme crucial for regulating metabolic balance by promoting catabolism and inhibiting anabolism. AMPK serves as a mediator for various signaling hormones and plays a protective role in mitochondria, reducing inflammation, apoptosis, and fibrosis. In streptozotocin-induced diabetes (STZ) in mice, Empagliflozin has been observed to activate AMPK/Drp1 signaling, thus protecting mitochondria by reducing mitochondrial fusion and oxidative damage. This is accompanied by enhancements in vascular system integrity through the phosphorylation of endothelial nitric oxide synthase (eNOS) and the mitigation of microvascular endothelial lesions in coronary endothelial cells [45]. Ischemia–reperfusion (I/R) and hypoxia/reoxygenation (H/R) in isolated cardiomyocytes, Empagliflozin demonstrated a reduction in the infarcted area and improvement in myocardial contractility. These effects are mediated through the modulation of AMPK signaling pathways [45]. Empagliflozin also affects the TGF-β/Smad pathway, which plays a significant role in regulating tissue fibrosis. It induces the blockade of this pathway, resulting in a subsequent decrease in the fibrotic transformation

of myocardial tissue [46]. Both animal and clinical research have shown a sympathetic inhibitory effect of SGLT2 inhibitors. This effect, besides being linked to the reduction of fibrosis, which is a significant substrate for arrhythmias, indicates the potential role of SGLT2 inhibitors in preventing arrhythmic events [47]. SGLT2 inhibitors induce a reduction in autonomic nervous system (ANS) activity by lowering insulin, leptin, and glucose levels in the blood, thereby improving insulin resistance, hyperinsulinemia, and anemia. These changes collectively contribute to a decrease in carotid body (CB) activation, as well as in the volume of sodium and the levels of protein-bound uremic toxins. Consequently, this inhibits the activation of the organum vasculosum of the lamina terminalis (OVLT) in the region of the third anteroventral ventricle (AV3V) of the hypothalamus [48]. Taken together, these findings suggest a potential effect of SGLT2 inhibitors on reverse cardiac remodeling in patients with heart failure, both with preserved (HFpEF) and reduced (HFrEF) ejection fraction, as well as in non-diabetic patients.

Inhibition of autophagy and stress

Autophagy serves as a mechanism for maintaining cellular homeostasis by eliminating potentially harmful substances and recycling cellular components in response to metabolic stress, such as hypoxia [49]. Pathways that induce autophagy include the activation of adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (SIRT1), and hypoxia-inducible factors (HIF-1alpha and HIF-2alpha) [50]. Experimental studies suggest that SGLT2 inhibitors may activate these pathways, leading to the stimulation of autophagy. This lysosomal-mediated degradative pathway plays a crucial role in clearing damaged organelles, thereby reducing inflammasome activation and mitigating cardiomyocyte dysfunction and coronary microvascular injury [51].

Guidelines

The American Diabetes Association (ADA) advises including SGLT-2 inhibitors in the treatment approach for individuals with type 2 diabetes mellitus (T2DM) who have heart failure (HF) or are at a heightened risk of developing HF [52]. Likewise, the latest guidelines from the European Society of Cardiology (ESC) in 2021 [53] and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) in 2022 [54] recommend utilizing SGLT-2 inhibitors (currently dapagliflozin and empagliflozin) to manage chronic, stable heart failure with reduced ejection fraction (HFrEF). These guidelines offer a class 1 recommendation for reducing cardiovascular

death and hospitalizations due to HF, irrespective of the patient's diabetes status. Furthermore, the AHA/ACC/HFSA HF guidelines for 2022 suggest a class 2A recommendation for heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) based on the findings of the EMPEROR-Preserved trial. This recommendation may be upgraded in subsequent guidelines following the publication of the DELIVER trial [55].

Effect of SGLT-2 inhibitors on other systems of the human body

SGLT-2 inhibitors (sodium-glucose co-transporter 2 inhibitors) are a class of drugs primarily used in the treatment of type 2 diabetes mellitus to enhance blood sugar management alongside dietary changes and physical activity. Their mechanism of action is based on blocking the SGLT-2 protein in the kidneys, which is responsible for the reabsorption of glucose from the primary urine into the blood and lowering the renal threshold for glucose. Blocking this transporter leads to increased excretion of glucose in the urine, which in turn lowers blood glucose levels [56]. SGLT-2 inhibitors provide multiple more benefits. The first noteworthy effect is on the urinary tract. Patients with chronic kidney disease (CKD) face elevated risks of declining estimated glomerular filtration rate (eGFR), progression to end-stage kidney disease (ESKD), and heart failure (HF) compared to the general population. Studies have shown that SGLT-2 inhibitors can impact the health of patients through lowering the risk of CKD progression [57]. In chronic kidney disease, the natriuretic and diuretic impact of SGLT-2 inhibition remains intact due to elevated glucose levels at the individual nephron level. This heightened glucose burden arises from increased blood glucose levels and single nephron hyperfiltration in the remaining nephrons. Consequently, it triggers paracellular sodium secretion in the proximal tubule, thus maintaining a natriuretic, kaliuretic, and diuretic effect, despite a decrease in nephron count [58]. In a randomized controlled trial of a diverse group of chronic kidney disease patients susceptible to disease advancement, treatment with empagliflozin resulted in a reduced likelihood of kidney disease progression or cardiovascular-related mortality compared to receiving a placebo [59]. The aforementioned actions of SGLT-2 also have an impact on lowering both systolic and diastolic blood pressure and reducing HbA1c in patients with type 2 diabetes mellitus and hypertension [60]. What is more, we can’t forget that type 2 diabetes is often associated with obesity. SGLT-2 inhibitors have been shown to enhance body composition in individuals with type 2 diabetes mellitus, leading to reductions in body weight, body mass index, waist circumference, visceral fat area, subcutaneous fat area, percentage body fat, and fat mass. SGLT-2 inhibitors not only induce weight loss by facilitating

the excretion of glucose through urine but also ameliorate dysfunctional adipocytes in visceral fat tissue. This results in a decrease in leptin, visfatin, and plasminogen activator inhibitor-1 levels while increasing adiponectin levels, thereby effectively enhancing lipolysis and reducing visceral fat [61]. Several studies indicate that combining SGLT2 inhibitors with medications that decrease food intake can enhance their effectiveness as supplementary weight loss therapy, making these combined treatments appealing [62]. Proceeding from the endocrine system, there is ongoing debate about whether SGLT-2 will reduce insulin resistance. In the prospective study it has been shown that SGLT-2 inhibitors can enhance short-term insulin sensitivity in skeletal muscle. SGLT-2 inhibitors may effectively mitigate plasma glucose fluctuations, which are linked to glucotoxicity rates in skeletal muscles, particularly in individuals with a short duration of type 2 diabetes mellitus and elevated HOMA-IR and transaminase levels [63].

SGLT-2 inhibitors side effects

Despite SGLT-2 positive effects, one cannot forget about possible side effects. It is possible that these drugs have the adverse effect of reducing muscle mass and they increase the risk of sarcopenia. It is essential to consider not only the positive impact on body composition but also the potential negative effect of muscle mass reduction when using SGLT-2 inhibitors in type 2 diabetes mellitus [61]. In addition, some studies have documented various adverse effects linked to the administration of SGLT-2 inhibitors, including urinary tract infections and increased urine production. Several meta-analysis studies have indicated that individuals with type 2 diabetes mellitus who were prescribed SGLT-2 inhibitors had a notably increased risk of urinary tract infections compared to those who received a placebo or other oral anti-diabetic medications. Conversely, some studies have concluded that there was no significant disparity in UTI risk between patients treated with SGLT-22 inhibitors, regardless of sex or age. Consequently, the issue of UTI risk associated with SGLT2 inhibitors remains contentious [64, 65]. Caused by SGLT-2 drugs, substantial glycosuria, increases risk of genital mycotic infections (GMI). These infections are typically mild, as indicated by extensive systematic reviews and meta-analyses of these drugs. Moreover, these reviews have highlighted significant cardiovascular benefits through alternative mechanisms, rendering them appealing options for managing type 2 diabetes mellitus [66].

In summary, SGLT-2 inhibitors are modern medications that have a multifaceted impact on the body, providing benefits in controlling type 2 diabetes while supporting cardiovascular and renal functions, albeit necessitating monitoring for potential adverse effects.

V. Conclusion

Numerous potential mechanisms may elucidate the capacity of SGLT2 inhibitors to reduce cardiovascular (CV) risk, particularly hospitalization for heart failure (HF), in patients with or without type 2 diabetes mellitus (T2DM). The favorable effects seem to stem from the significant decrease in intracellular sodium levels, which are recognized for their cardioprotective role in averting oxidative stress and consequent cardiomyocyte demise. From a molecular standpoint, exposure to gliflozin treatment in patients' mimics conditions of nutrient and oxygen deprivation, prompting stimulation of autophagy. This mechanism aids in preserving cellular equilibrium through various degradative pathways. Consequently, since their incorporation into clinical practice, the perception of SGLT2 inhibitors' modes of action has evolved: from simple glycosuric agents with subsequent glucose reduction, enhancement of erythropoiesis, and stimulation of ketogenesis, to molecules targeting intracellular sodium levels. These actions culminate in a notable reduction in CV events. Based on clinical data, the utilization of SGLT2 inhibitors holds significant importance in managing HF patients. Therefore, SGLT2 inhibitors should be considered as first-line therapy, irrespective of concurrent medications. Indeed, in numerous trials, they have demonstrated efficacy regardless of baseline medication and the sequential approach to HF treatment, which often leads to delays, thereby influencing prognosis [52].

DISCLOSURE

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All authors have read and agreed with the published version of the manuscript.

Funding Statement: The Study Did Not Receive Special Funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable

Data Availability Statement: Not Applicable.

Conflict Of Interest: The authors declare no conflict of interest.

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