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Review Article

The journey of Sotagliflozin: from its status as a withdrawn candidate for the treatment of diabetes mellitus, to its repurposing as a groundbreaking drug for the management of heart failure

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Abstract
Sotagloflozin is a member of the antidiabetic class of sodium-dependent glucose cotransporter protein inhibitors. It is unique in its class due to its dual inhibitory action, as it can target and inhibit both type 1 and type 2 isoforms of the sodium glucose co-transporter (SGLT). SGLT inhibitors are small-molecule antagonists whose design was inspired by the natural product phlorizin. In May 2023, the United States Food and Drug Administration (U.S. FDA) approved sotagliflozin for the treatment of heart failure. The journey towards the discovery and optimization of this compound, as well as its ultimate repurposing in the setting of heart failure, is intriguing and continues to arouse interest and concern with regard to the safety and applicability of this repositioned candidate. This review offers an in-depth critical report of the journey of this compound, which has been marked by moments of both success and failure, towards its ultimate reproposing and a reported groundbreaking role in the scope of heart failure management.

Keywords: Sotagliflozin, SGLT-Inhibitors Drug Repurposing, Heart Failure, Diabetes

INTRODUCTION

THE DISCOVERY PROCESS; INSPIRED BY NATURE

While the traditional pathway of small-molecule drug discovery from naturally derived compounds may be considered by some to be an exhausted and inefficient approach towards targeted drug design, it cannot be disputed that a large proportion of the most widely and successfully employed medications in clinical circulation originate from a natural source[1]. Heparin, digoxin, paclitaxel, atropine, and penicillin are examples of naturally derived therapeutics that have inspired the design and development of drug classes for the management of a plethora of diseases, from thromboembolism to cancer. Phlorizin is another example of a natural compound that has inspired the development of a novel class of antidiabetic medications with potent widespread mechanisms that appear to be clinically relevant in multiple disease settings[2].

Phlorizin, a naturally occurring dihydrochalcone derivative[3], was originally extracted from the bark of apple trees, and as early as 1890 its mechanism of action was postulated[4]. In early animal studies it was found to induce glucosuria via what was described at the time as a 'kidney specific mechanism'[5,6]. Since its discovery nearly 100 years ago, it has been employed as an experimental tool in understanding the physiological mechanisms of glucosuria and glucose absorption[6]. Such investigations ultimately lead to the discovery and identification of SGLT proteins and phlorizin was considered the first non-selective prototype inhibitor of SGLT proteins[7,8]. Though potent, its clinical use is limited due to its poor bioavailability and its toxicity profile[8]. Yet this compound became the precursor for the development of selective SGLT inhibitors, essentially becoming the parent compound inspiring a novel class of potent antidiabetics.

THE TARGET: SODIUM DEPENDENT GLUCOSE CO-TRANSPORTERS

Sodium-glucose co-transporters are a group of membrane-localized transport proteins that are widely expressed in various human tissues[9]. They leverage the Na^+ electrochemical gradient (maintained by the Na^+/K^+ ATPase pump) to actively transport glucose against its concentration gradient into cells[10]. There are a total of 6 different isoforms of SGLT proteins (SGLT1-6), with SGLT1 and SGLT2 being the most widely studied members of this protein family[11]. SGLT1 was first isolated and identified in 1987 in a series of molecular studies that cloned and expressed mammalian SGLT1 from rabbit intestine[12], while human SGLT2 was subsequently cloned and characterized in molecular and cell-based immunocytochemistry studies[13]. A study by Vrhovac et al., using novel polyclonal affinity antibodies targeting the C-terminal regions of human SGLT1 and SGLT2 proteins, revealed the protein localization and expression profile of both isoforms in various human tissues (Table 1)[11]. The first crystal structure for bacterial sodium-dependent glucose transporter (vSGLT) was solved by X-ray crystallography, and revealed a

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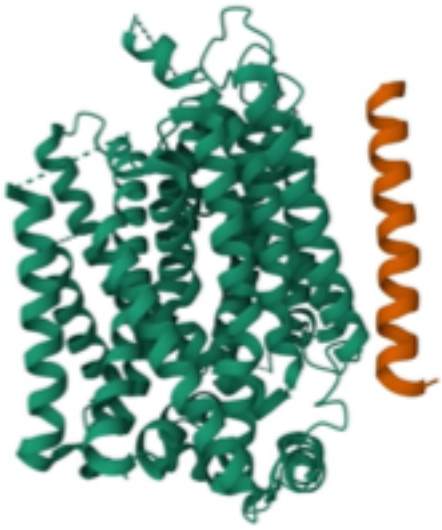
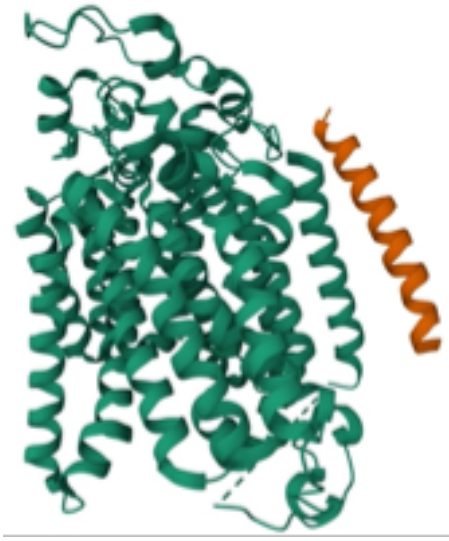
14 transmembrane helical structure with a central pore and core structural features similar to the leucine-transporter family[14]. Subsequent studies using cryo-electron microscopy (cryo-EM) were able to determine the structure of human SGLT1 and SGLT2 proteins in both the apo (unbound state) and substrate-bound conformation[15]. The human SGLT proteins are expressed and crystallized as complexes with the accessory protein MAP17, which is important for the stability and activity of SGLT proteins[16,17]. Of interest MAP17 upregulation has been implicated in inflammatory and malignant settings[18], this protein interaction may in itself, represent a potential therapeutic target of interest. Table 1 summarizes the main structural and physiological features of SGLT1 and SGLT2 proteins.

DRUG DEVELOPMENT: PRECLINICAL STUDIES LEADING TO THE DEVELOPMENT OF SOTAGLIFLOZIN AS AN ANTIDIABETIC AGENT

The natural compound phlorizin was extracted and identified in the late 19th century, and as early as 1886, its pharmacodynamic effect was recognized in a series of early animal studies. Its mechanism was postulated to be localized within the kidney[4]. In 1975 a group showed that the intravenous infusion of phlorizin in dogs induced glucosuria and reduced plasma glucose levels in an insulin-independent manner[19]. In this study, up to a 60% increase in glucose excretion was observed upon phlorizin infusion, with no effect on baseline glomerular filtration rate or renal blood flow[19]. Further organ bath studies on isolated rabbit kidneys have characterized the predominately competitive nature of SGLT inhibition[3]. The earliest clinical studies to determine the effect of intravenous phlorizin in human subjects were published in 1933, in which it was shown to induce glucosuria[20] and increase insulin sensitivity[21]. While potent, Phlorizin cannot be used clinically because of its poor pharmacokinetic and toxicity profile. Phlorizin has poor solubility and oral bioavailability[8]. In addition, another limiting factor was considered to be its non-selective action on SGLT proteins, inhibiting both SGLT2 localized in the kidney and well as SGLT1 which is predominately expressed in the intestine and regulates intestinal glucose absorption. Inhibition of SGLT1 and the consequent malabsorption of glucose in the intestine cause severe diarrhea and dehydration[8]. Additionally, phlorizin is rapidly metabolized by intestinal β-glucosidases to the active metabolite phloretin, a potent inhibitor of glucose transporter type-1 (GLUT 1) which inhibits critical glucose uptake in tissues, including the brain[8,22]. These limitations launched a discovery

Table 1: The main structural and physiological features of human SGLT 1 and SGLT2 proteins.

Human SGLT1	**Human SGLT2**
Structural Data and Tissue Expression	
 **Crystal structure of the human SGLT1-MAP17 heterodimer solved: (PDB: 7YNI)**	 **Crystal structure of the human SGLT2-MAP17 heterodimer solved: (PDB: 7YNK)**
Structure of human protein availiable solved by cyro-EM 2.95 Å	Structure of human protein availiable solved by cyro-EM 3.20 Å
Expressed in intestine and endometrial cells and heart low expression in the kidney	Expressed in kidney
Functional Role	
Transport of glucose, galactose from enterocytes to blood. Triggers the secretion of the incretins GCG and GIP that control food intake and energy homeostasis and gut secreted hormones GLP1 and PYY Transports glucose into endometrial epithelial cells, nutritional support for the embryo, endometrium preparation prior to conception.	D-glucose reabsorption from glomerular filtrate across the brush border of the early proximal tubules of the kidney. Reabsorbs approximately 90% of the filtered glucose load

campaign that led to the design and development of clinically successful SGLT inhibitors. Pharmaceutical companies have led extensive projects to develop and optimize phlorizin-based analogs with improved pharmacokinetic and pharmacodynamic properties[23]. Consequently, two branches of analogs were developed: O-glucoside analogs, such as T-1095, a precursor compound that was the first orally available SGLT2 inhibitor of its kind, showed a modest dose-dependent effect, and sister compounds sergliflozin and remogliflozin[24]. These compounds while orally active, did not possess optimum pharmacokinetic or selectivity properties compared with the next generation of compounds developed: C-glucoside analogs of phlorizin, including canagliflozin, dapagliflozin and empagliflozin[24]. Canagliflozin, a C-glucoside analog, was the first selective SGLT2 inhibitor approved for the treatment of type-2 diabetes mellitus (DM2) by the U.S. FDA in 2013. The next generation of analogs to be developed included sotagliflozin, whose chemical structure, in comparison to an earlier generation analog, empagliflozin, is depicted in figure 1.

SGLT inhibitors were developed in succession to optimize not only their oral bioavailability but also selectivity, around the same time, a number of animal studies in genetically modified mice revealed the impact of homozygous and heterozygous depression of SGLT1 and 2 expression and activity[25]. SGLT1 knockout mice exhibited persistent diarrhea, whereas mice carrying a heterozygous mutation exhibited good glycemic control without gastrointestinal side effects[25]. This finding highlights for the first time the benefits and safety of partial SGLT1 inhibition. Lexicon Pharmaceuticals thus launched a discovery program to develop drug candidates with varying levels of SGLT1 and 2 inhibition[26]. Sotagliflozin was developed with dual inhibitory action, expressing more potent effects on SGLT2, with an IC50[1] of 0.0018 µM for SGLT2 vs IC50 0.036 µM for SGLT1[22,27]. Sotagliflizin shows 20-fold selectivity for SGLT2; however, it is 10-times more active against SGLT1 than empagliflozin and other selective SGLT2 inhibitors[26,27]. Figure 2 shows the molecular interactions and key structure-activity relationship (SAR) features of sotagliflozin and empagliflozin docked within the SGLT1 and SLGT2 binding pocket in optimized confirmation. Docking was performed using the Schrödinger's Glide Module[28,29].

The pharmacokinetic profile of sotagliflozin was determined in a single- and multiple-dose study using radiolabeled

1. IC50: concentration in which half the maximal inhibitory effect is achieved.

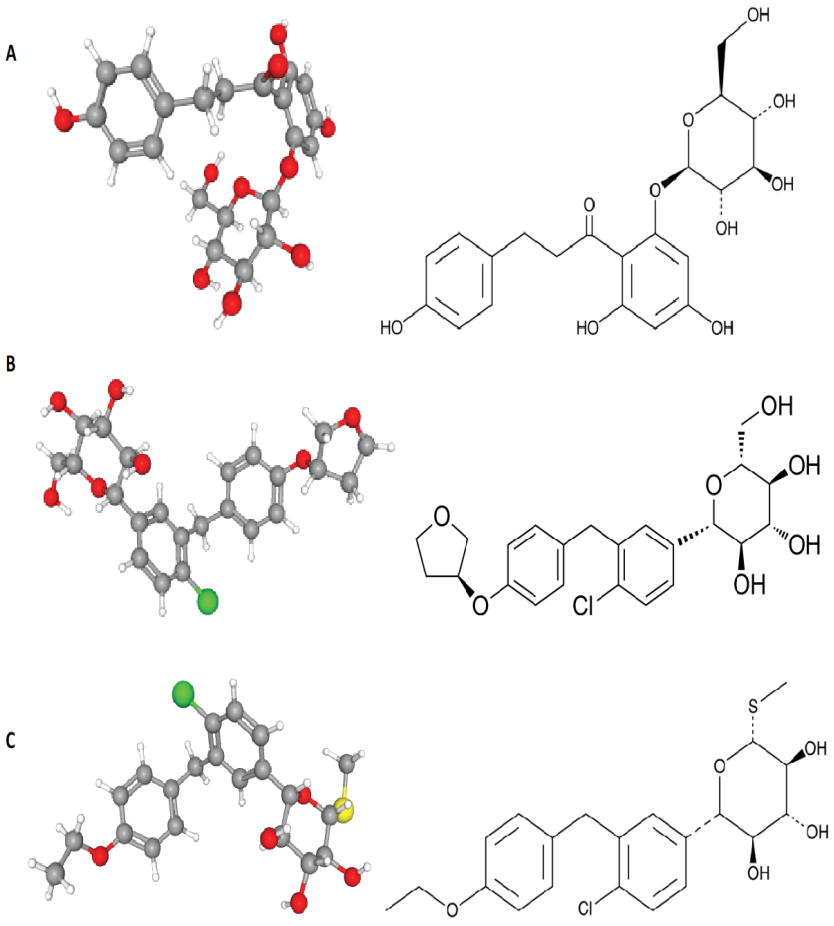


Figure 1. The chemical structure of (A) Phlorizin, and (C) Empagliflozin and (C) Sotagliflozin in 3D (left) and 2D (right) conformations. Structures retrieved from PubChem.

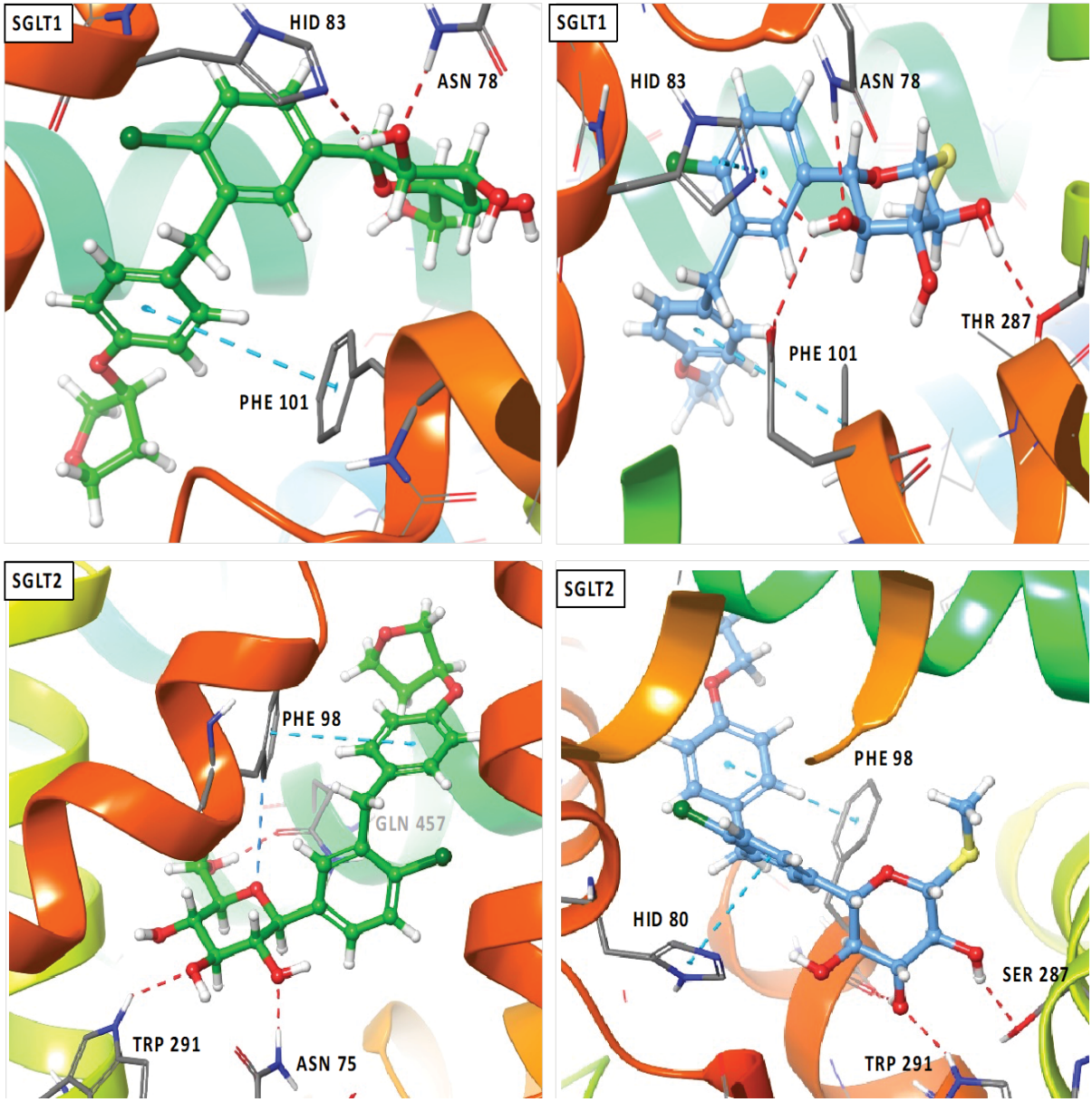


Figure 2. Empagliflozin in green and Sotagliflozin in blue docked in the SGLT1 (top panels) and SGLT2 (bottom panels) binding pocket with key molecular interactions depicted as dotted lines: hydrogen bonds in red and pi-pi stacking interactions shown in blue. Key binding residues in the protein binding pocket are annotated. Multiple hydrogen bonds are observed indicating a high affinity interaction in the binding pocket.

^{14}C-sotagliflozin[27]. In this study, doses up to 500 mg were administered orally. After administration of a single oral dose peak plasma concentrations were observed at 1.25-3 hours post administration[27]. The estimated oral bioavailability of sotagliflozin was 71% and the apparent volume of distribution was 9392 L[27]. Sotagliflozin was found to be largely protein-bound in the plasma (98%) and underwent hepatic metabolism to 3-O-glucuronide-sotagliflozin (designated as the M19 metabolite in the study). Approximately 94% of radiolabeled sotagliflozin was detected as the M19 metabolite, which was found to be essentially inactive; 275-times less active against both SGLT1 and SGLT2 compared to the parent drug[27]. The primary route of metabolism was via glucuronidation by the UDP-glucuronosyltransferase enzyme UGT1A9 and, to a lesser extent, UGT1A1 and UGT2B7 enzyme subtypes, while the remaining 6% of radiolabeled sotagloflozin was subjected to oxidation via CYP3A4[27]. Sotagliflozin was primarily eliminated via the renal route, with 57% of the administered drug excreted in urine and 37% excreted in feces[27]. Maximal plasma concentrations of 165 ng/mL sotagliflozin were observed in trial subjects after seven days, with a steady-state concentration reached in an estimated 5 days[27]. The reported half-life in this study was 29 h, indicating that a single daily dose regimen would be suitable for establishing therapeutic plasma

concentrations[27]. The calculated clearance of sotagliflozin was found to–261-374 L/h in healthy volunteers and 239 L/h in diabetic subjects[26]. It is important to highlight that there are no reported data for the estimated volume of distribution or calculated clearance of sotagliflozin in patients with heart failure. Patients with heart failure often present with an altered physiological state as a result of altered cardiac output and hemodynamic parameters, which undoubtedly affect parameters such as hepatic and renal elimination, as well as the apparent volume of distribution.

CLINICAL STUDIES- WHY WASN'T SOTAGLIFLOZIN APPROVED BY THE U.S. FDA FOR DIABETES?

Following the success of selective SGLT2 inhibitors, such as dapagliflozin and empagliflozin, to improve glycemic control in the setting of DM2, it was anticipated that non-selective agents, such as sotagliflozin, would have an even greater therapeutic effect[30]. Indeed, phase 1 clinical studies have reported a significant reduction in postprandial plasma glucose levels attributed to SGLT1 inhibition, while a proportionate increase in urinary glucose excretion was observed[27]. Phase 2 clinical studies similarly revealed that sotagliflozin significantly reduced glycosylated hemoglobin levels (HbA1C) by 0.92%-1.25% (from a baseline level of 8.1%) compared with placebo arms[26,31]. In most studies, sotagliflozin-induced urinary glucose excretion (UGE) was modest compared to that of established SGLT2 inhibitors, such as canagliflozin[26]. UGE, measured over a period of 24 hours after a 300 mg dose of sotagliflozin, was found to be nearly half that of 100 mg canagliflozin (50 mg vs. 80–100 mg/24 h)[26]. For sotagliflozin, maximal UGE was achieved at lower doses, whereas a reduction in post-prandial glucose levels was attained by increasing the doses beyond this threshold[27]. The therapeutic significance of intestinal SGLT1 inhibition by sotagliflozin was further highlighted in a number of clinical studies, where an elevation in glucagon-like peptide-1 (GLP-1) and peptide YY (PPY) was observed, along with a significant reduction in postprandial insulin release[31].

Clinical studies in patients with type-1 diabetes mellitus (DM1) echoed the findings in preclinical mouse models, in which sotagliflozin was found to improve glycemic control and reduce exogenous insulin dependence[26,30]. Phase 3 clinical trials in which sotagliflozin was administered to DM1 pateints with DM1 on insulin therapy reported an improvement in glycemic control and a significant reduction in glycated hemoglobin (HbA1C) levels, as well as a reduction in required insulin dosage, body weight, and systolic blood pressure after a 6-week period of treatment[32-34].

The incidence of drug-induced side effects has also been assessed in clinical studies, notably the occurrence of episodes of diabetic ketoacidosis (DKA), genital mycotic infections, diarrhea and hypoglycaemia[30]. In the inTandem trials, sotagliflozin was found to cause diarrhea in 4.1% of patients, versus 2.3% in the placebo arm[33], an effect attributed to intestinal glucose malabsorption due to SGLT1 inhibition[30]. The incidence of genital mycotic infections was comparable to that of other approved SGLT2 inhibitors, and was attributed to increased urinary glucose concentrations[33]. The most critical and ultimately limiting adverse event observed with sotagloflozin treatment was an increased incidence of DKA[30]. In the inTandem3 trial, patients receiving sotagliflozin had a significantly higher incidence of DKA episodes (3%) than those in the placebo group (0.6%)[33,34].

Despite its therapeutic efficacy, sotagliflozin was denied U.S. FDA approval, mainly due to concerns over the incidence of DKA in the treatment arms during clinical trials[35]. However, in 2019, the European Medicines Agency (EMA) granted approval for the use of sotagloflozin (under the trade name Zynquista) as an adjunct therapy alongside insulin treatment for DM1 patients with poor glycemic control. Market authorization in Europe was subsequently withdrawn in 2022, upon request of Lexicon for 'commercial purposes'[36].

SOTAGLIFLOZIN REPURPOSED AND REBRANDED FOR HEART FAILURE

Real-world evidence has provided the basis for the premise that this new class of anti-diabetic medications may provide benefits in cardiovascular and renal diseases[35]. In 2015, the results of the first study assessing the effect of the SGLT2 inhibitor empagliflozin on cardiovascular disease (EMPA-REG OUTCOME) was published[37]. In this randomized, double-blind, placebo-controlled study of 7000 patients diagnosed with DM2, as well as an established cardiovascular disease, a 38% reduction in the relative risk of death due to a cardiovascular event was reported when compared with placebo[37]. The findings of this study spearheaded a number of further studies assessing the benefits of SGLT inhibition in cardiovascular disease[38,39]. In light of the fact that SGLT1 is highly expressed in myocardial tissues, namely cardiomyocytes and myocardial capillaries[40], and the fact that its expression appears to be upregulated in the setting of cardiovascular diseases in human and animal tissues[41,42], it was postulated that sotagliflozin may impart an added benefit in the setting of cardiovascular diseases owing to its dual inhibitory action. A study published in 2018 demonstrated that patients carrying a haplotype of three SGLT1-specific loss-of-function mutations presented with a reduced incidence of diabetes and cardiometabolic sequela[43].

Sotagliflozin was rebranded with the new trade name Inpefa and was clinically assessed for cardiovascular disease. In a multicenter, double-blind, placebo-controlled trial, the efficacy of sotagliflozin in preventing cardiovascular events in patients with DM2 and chronic kidney disease was studied[44]. Originally, the primary endpoint in the study was the number of deaths attributable to a cardiovascular event, yet this was changed owing to mitigating circumstances to a composite endpoint comprising cardiovascular death and hospitalizations/ emergency visits due to hearth failure (HF)[44]. The circumstances cited in the study happened to be the premature cessation of the trial at 16 months due to the loss of funding from the sponsor, which was reportedly a result of the COVID-19 pandemic. The findings of this study showed that patients taking sotagliflozin had a 25% lower risk of death due to cardiovascular events and hospitalizations due to heart failure (composite outcome): 5.6 events/100 patient-years for the sotagliflozin study arm versus 7.5 events/100 patient-years for the placebo arm[44]. In the span

of the 16-month trial, the rate of cardiovascular-related deaths in the sotagliflozin arm was 2.2/100 patient-years compared with 2.4/100 patient-years in the placebo arm[44]. In this study, the incidence of DKA was 0.6% and 0.3% in the placebo group[44].

A post hoc analysis of a following study was published in August 2023: the SOLOIST-WHF trial (effect of sotagliflozin on cardiovascular events in patients with type 2 diabetes after worsening heart failure)[45]. The SOLOIST-WHF trial aimed to assess the efficacy of sotagliflozin versus placebo in decreasing mortality and heart failure-related events among patients with DM2 who were recently admitted for worsening heart failure (both patients with preserved and reduced ejection fractions were indiscriminately enrolled in the trial). A similar composite endpoint was evaluated: the number of cardiovascular related deaths in addition to number of heart failure related hospitalizations or urgent visits within 30 days and 90 days after hospital discharge from the original event[45]. This phase 3 international, randomized, placebo-controlled trial assessed 290 patients who were started on 200 mg sotagliflozin prior to or upon hospital discharge, compared to 306 patients who received placebo[45]. In a period of 9 months, sotagloflozin was found to reduce cardiovascular mortality and heart failure-related events by 40% compared to placebo[45]. While the trial reported that sotagliflozin was well tolerated, there was a higher incidence of severe hypoglycemia (0.7% vs. 0.3%), diarrhea (3.4% vs. 1.3%), genital infections (0.3% vs. 0%), and volume depletion (7.2% vs. 5.6%) than in the control group. The SOLOIST-WHF trial was terminated prematurely owing to a lack of sufficient funding in the advent of COVID-19[45].

GAPS IN OUR UNDERSTANDING, AND PLAUSIBLE MECHANISMS OF ACTION IN THE SETTING OF HEATH FAILURE

In May 2023, the U.S. FDA granted approval for the use of sotagliflozin in patients with heart failure, type 2 diabetes mellitus, chronic kidney disease, or other cardiovascular risk factors[46]. While the findings of both clinical studies assessing sotagliflozin in the setting of heart failure are strikingly positive, with a 25-40% reduction in overall cardiovascular risk and mortality, they have a number of limitations. Both trials were terminated early due to the withdrawal of funding, as a consequence of the economically frugal climate during the COVID-19 pandemic. As a result of the reduced trial period, there was not a sufficient number of cardiovascular-related deaths reported, so composite endpoints were instead employed, which considered any hospitalization or urgent cardiovascular-related events together with the deaths. Previous studies assessing other SGLT2 inhibitors were conducted over an average period of 5 years, which was considered a minimum period to effectively assess the impact of the agents in reducing cardiovascular mortality[2]. There is a possible risk that the use of a composite endpoint may have overstated the actual impact of sotagliflozin therapy in the patient population, which was only observed for less than a quarter of the duration in previous SGLT2 inhibitor trials.

Interestingly, in both studies, there was no data provided on any of the other hemodynamic parameters typically reported in the assessment of heart failure progression. A recent post-hoc analysis of data from the SCORED study focused on 3.9% of the patients randomized into the study who had left ventricular hypertrophy, which was assessed only at the beginning of the 16 month trial upon screening and patient stratification[47]. No follow up measurements have been reported. Post-hoc analysis in this subset of patients reported similar findings to those of the parent study: sotagliflozin reduced cardiovascular risk irrespective of blood pressure status[47]. Typical parameters employed to assess cardiac function in heart failure include measurement of cardiac output, ejection fraction, and electrocardiography (ECG) assessment[48,49]. Assessment of structural morphology, such as ventricular hypertrophy, was not reported in either study. Ventricular remodelling and hypertrophic cardiomyopathy are characteristic features of worsening heart failure[48,49]. Some agents with known cardioprotective effects in the setting of heart failure, such as spironolactone, have been shown via cardiac magnetic resonance imaging to reverse cardiac remodelling and prevent structural changes in the setting of cardiomyopathies, specifically severe heart failure[50]. For a drug with an apparent 20-40% reduction in the risk of cardiovascular-related mortality and incidents, it would be expected that some supporting data would expand upon the hemodynamic or structural benefit imparted by the drug using well-established cardiovascular imaging techniques. It is possible that, owing to the mitigating circumstances of the trial, such data could not be feasibly collected at the time. Nevertheless, such data is essential for understanding the underlying pharmacodynamic mechanisms and role of SGLT inhibition in the backdrop of cardiovascular pathologies.

The mechanism of action of sotagliflozin and other SGLT inhibitors in the scope of heart failure remains unclear. Recently published preclinical studies in animal models have shed light on some of the suggested mechanisms. Young et al. reported that sotagliflozin improved cardiac output in mouse models of cardiac pressure overload achieved via transverse aortic constriction (TAC) [51]. Mice were divided into treatment and control groups and fed either a normal diet or high-fat diet followed by oral sotagliflizin treatment. Mice in the normal diet group treated with sotagliflozin were protected from cardiac hypertrophy and expressed fewer histological markers of cardiac fibrosis induced by TAC. However, this effect was less evident in mice in the high-fat diet group[51]. In another study, both empagliflozin and sotagliflozin were evaluated in a zebrafish model of diabetes and heart failure with reduced ejection fraction, and their survival and myocardial contractility were assessed[52]. The DM-HF zebrafish model showed attenuated cardiac contractility and function, poor locomotion, and reduced survival rates [52]. Cardiac function improved upon treatment with either empagliflozin or sotaglilflozin, an effect that was postulated to be a result of sodium-hydrogen exchanger-1 inhibition in this study[52]. It was observed However, in terms of survival and locomotion, the group treated with sotagliflozin had less favorable outcomes, with lower survival rates than the empagliflozin group[52]. In further studies involving rodent models, sotagloflozin was found to be cardioprotective in rat models of myocardial infarction (MI)[53].

MI was induced in rats via left anterior descending coronary artery ligation, and intraperitoneal sotaglfolozin was found to reduce the size of infarcted tissue, in addition to reducing both ventricular hypertrophy and apoptosis compared with the control group[53]. In infarcted tissue SGLT1 expression has been shown to be upregulated; activating downstream pro-inflammatory pathways and increasing oxidative stress[54]. Zhong et al., demonstrated that the cardioprotective effect of sotagliflozin was mediated via the inhibition of the NLRP3 inflammasome and NF-κB/TNF-α signalling cascade, key inflammatory pathways implicated in the pathogenesis of both endothelial dysfunction and structural cardiomyopathies[53].

Studies are yet to determine the exact mechanism by which sotagloflozin and other SGLT inhibitors confer protection against cardiovascular disease. A number of reviews have postulated that the effect may actually be a result of a combination of factors[30] including the following, as illustrated in figure 3:

- Diuretic effect resulting in a reduction in blood pressure (preload)
- Reduction in oxidative stress and inflammation.
- Reversing endothelial dysfunction and vascular stiffness may lead to a reduction in afterload.
- Improved myocardial energy utilization
- Regulation of the renin-angiotensin-aldosterone axis: implicated in cardiac remodelling and hypertrophy

CONCLUSION

Clinical studies have undoubtedly highlighted the benefit of sotagliflozin in reducing cardiovascular risk in the setting of heart failure, chronic kidney disease, and diabetes. However, considering its safety profile, the limitations of published clinical studies, and a lack of understanding of its perceived

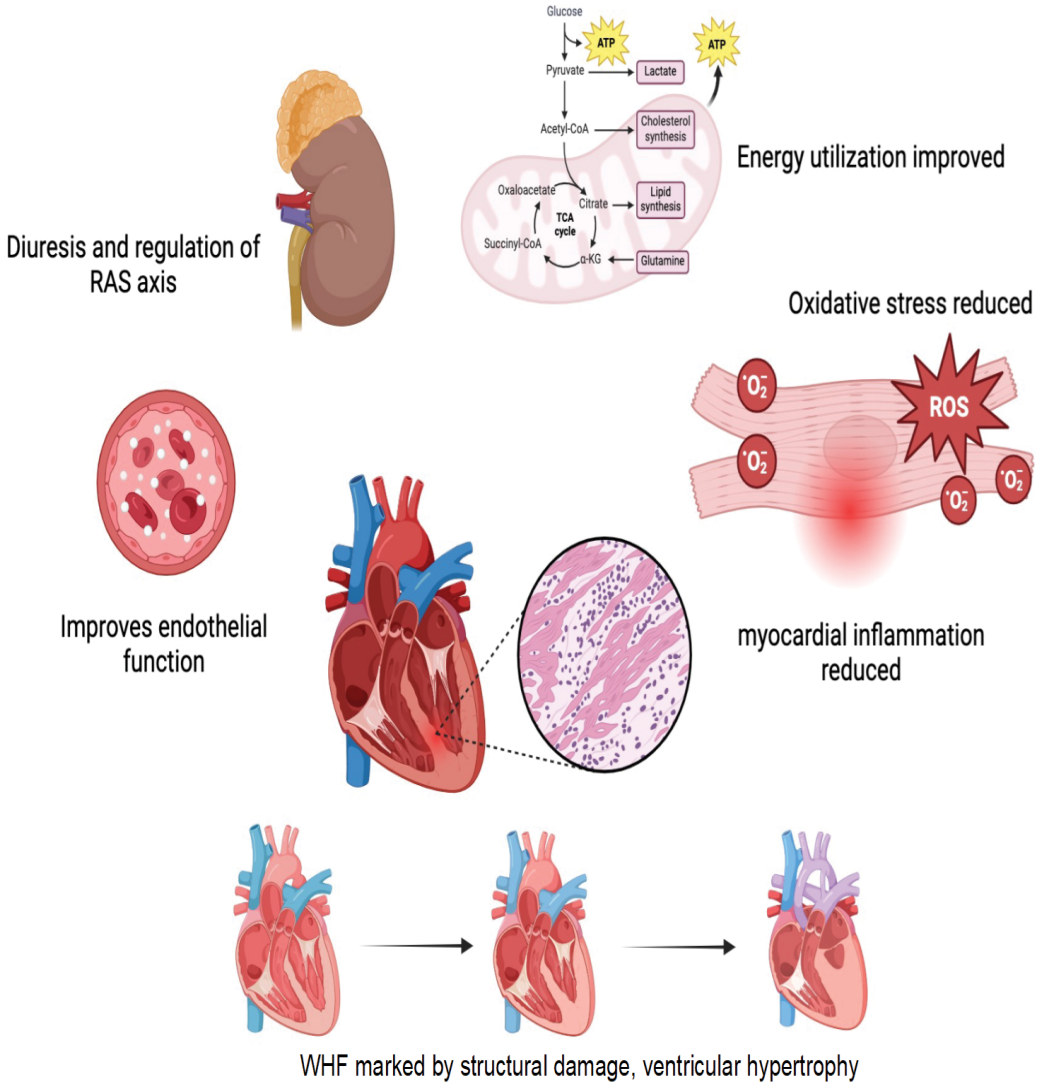


Figure 3. Summary of the various mechanisms and pharmacodynamic effects that are suspected to be imparted by sotagliflozin in preventing worsening heart failure (WHF) and alleviating cardiovascular risk. (RAS: renin angiotensin aldosterone system, ROS: reactive oxygen species). (Biorender.com was used to create the figure).

mechanism in cardiovascular diseases, further studies and a cautious post-marketing surveillance initiative are necessary to verify and understand the mechanism of its arguable groundbreaking role in the therapeutic management of heart failure.

CONFLICTS OF INTEREST

The author reports no conflicts of interest in this work.

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