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ROLE OF SOTAGLIFLOZIN IN MANAGING HEART FAILURE IN DIABETES

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Abstract

A chronic illness that impairs heart function is heart failure. This malfunction can put strain on other organs and be especially dangerous for those who have long-term conditions like diabetes and high blood pressure. Patients with diabetes are more likely to develop heart failure. Sotagliflozin is an oral medication used to treat diabetes. A dual sodium drug called sotagliflozin shows promise in the treatment of heart failure. An essential new family of medications for the treatment of diabetes is the sodium-dependent glucose transporter 2 (SGLT2) inhibitors. The goal of developing SGLT2 inhibitors has been to achieve high SGLT2 protein selectivity compared to SGLT1 protein. Treating diabetes with a single drug that combines the inhibition of SGLT1 and SGLT2 would offer complementing insulin-independent strategies. Thus, sotagliflozin (LX4211) was created as a dual SGLT1 and SGLT2 inhibitor. Large postprandial glucose decrease, increase of glucagon-like peptide 1, and mild urine glucose excretion are the distinguishing clinical aspects of dual inhibitor of SGLT1 and SGLT2. These characteristics might have an impact on how sotagliflozin is used clinically to treat diabetes.

Keywords: Sotagliflozin (LX4211), SGLT1 and SGLT2 inhibitors, pharmacokinetics, pharmacodynamics.

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Introduction

Heart failure is a chronic, complicated clinical diseases that develops as direct damage to heart function. This failure can put pressure on other organs in a chronic state and is particularly harmful to patients with chronic diseases like diabetes and hypertension. Diabetic patients run a higher risk of getting cardiovascular diseases. The development of sodium- glucose cotransporter (SGLT2) blockers is an important breakthrough in medicine. They were initially developed to assist people with type 2 diabetes. Heart failure is a complicated illness with a wide range of probable core causes and symptoms. It begins condition like type 2 diabetes, hypertension, and lipid-related issues, among others, progress to the most dangerous phases of heart failure and stroke. On May 26, 2023, USFDA approved Sotagliflozin is a blocker of the sodium-glucose cotransporter 2 (SGLT2), is an oral diabetes medication. (1) Sotagliflozin

also inhibits some SGLT1 in gastrointestinal tract. While SGLT1 blocker lowers the blood sugar level after meals by slowing absorption of glucose in intestine, SGLT2 inhibition enhances the elimination of glucose in the urine. People with type2 diabetes and heart failure currently progressing and either a decreased or retained ejection fraction, heart attack when gives soon after a treatment of degenerative heart failure. Diabetes, especially type 2 diabetes, is a chronic and complex disease, which requires a multi-targeted approach tailored to the single patient. SGLT inhibitors, a new class of oral hypoglycemic agents, have proved to be extremely effective and reliable in reducing hyperglycemia. It inhibits sodium-glucose co- transporters, thus decreasing the renal glucose threshold (to ~100mg/dL) and promoting urinary glucose excretion, without increasing the risk of hypoglycemia. The compound phloridzin, first isolated in 1835 by French chemist from the root bark of the apple tree and subsequently found to be improve blood glucose levels in animals. Phloridzin was abandoned as a potential treatment of type 2 diabetes. The main glucose transporter in non-insulin dependent tissues. The fundamental role in glucose and sodium transport across the brush border of gut and kidney cells, SGLT-1 is responsible for glucose absorption in small intestine, and reabsorption of nearly

10% of the filtered glucose, SGLT2 is inhibited, SGLT1 is forced to work at maximal transport capacity. SGLT on renal glucose reabsorption in both acute and chronic use of SGLT2 inhibitors. The currently available SGLT-2 inhibitors share similar pharmacokinetic characteristics and have similar effects on glycemic control; Sotagliflozin, acts on both sodium-glucose co-transporters 1 and 2. Sodium-dependent glucose transporter 2 (SGLT2) plays an important role in the regulation of blood glucose. It reabsorbs approximately 90% of the filtered glucose load. In patients with type2 diabetes, SGLT2 is overexpressed and glucose re-absorption continues, Diabetes is usually associated by dyslipidemia, which is characterized by abnormally high or low levels of HDL cholesterol, triglycerides, and other lipids. exacerbating hyperglycaemia. Urinary glucose excretion represents a viable treatment strategy for the for the management of type2 diabetes and potentially type1 diabetes as well. SGLT2 inhibitors are approved in the United states and other countries for the treatment of type 2 diabetes. SGLT1 is the primary transporter responsible for absorption of glucose in the gastrointestinal tract. SGLT1 is the primary transporter responsible for absorption of glucose in gastrointestinal tract. (2)

2. Diabetes causes Heart failure:

HF and diabetes are two related diseases that have a major effect on global public health. Diabetes, also known as diabetes mellitus, is a metabolic disease marked by elevated blood glucose. HF is a condition in which the heart has no ability to properly pump blood to meet the needs of the body. Diabetes along with HF are related in a complex, multifaceted manner. In people with diabetes, several pathways lead to the occurrence of HF. (3)

2.1 Insulin resistance:

The most prevalent kind of type 2 diabetes, occurs when cells become less responsive to the effects for insulin, impairing glucose uptake. Reduced cardiac function can result from the heart muscle cells' lower receptivity to the hormone's positive effects due to insulin resistance.

2.2 Hyperglycemia:

Diabetes-related persistently elevated blood sugar levels can harm the heart's blood arteries and nerves as well as other parts of the body. The capacity of the heart to receive enough blood flow and oxygen can be compromised by this damage, also known as microvascular or macrovascular problems, which can result in cardiac dysfunction.

2.3 Oxidative load: Diabetes is linked to increased reactive oxygen species generation and weakened antioxidant defences, which results in oxidative stress. HF may develop as a result of this oxidative stress, which can harm the blood vessels and heart muscle cell.

2.4 Inflammation: Chronic inflammation is a common component of diabetic problems. The development of atherosclerosis (the constriction and stiffening of arteries) or myocardial fibrosis (the damage of the heart muscle), each of which can impair cardiac function, can be facilitated by inflammation in the arteries as well as the heart muscle. (3)

2.5 Hypertension: Diabetes and hypertension regularly interact with one another. Diabetes and hypertension put the

heart under additional strain, increasing the risk of hypertensive heart disease and HF.

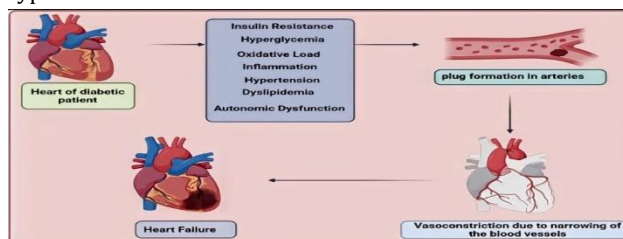


Fig 1. The Mechanism Pathway behind Heart-Failure

2.6 Currently available treatment for heart failure.

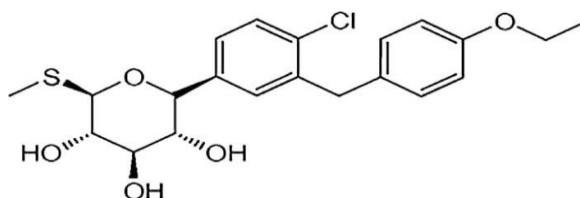
Heart failure can be treated with a variety of medications. These medications improve heart health, lower the risk of hospitalization and mortality, and do so in a variety of ways. The current available treatment for heart failure is described in the following. (4)

Table 1. Currently available and MOA, doses for Heart Failure.

Drug	Class of drug	Mechanism of action	Dosage
Valsartan losartan	Angiotensin II receptor blockers	Relax blood vessels, lowering blood pressure, increasing blood flow, and reducing the strain on heart. The drugs have many of the same benefits as ACE inhibitors	40 -50mg
Eplerenone	Aldosterone antagonist	The might increase the lifespans of those with severe heart failure low ejection fraction (HFrEF).	20-50mg

3. Structure of Sotagliflozin:

Sotagliflozin, also known as LX4211, is a small, orally available molecule, which inhibits both SGLT-1 and SGLT-2. In humans the selectivity for SGLT-2, however, is 20-fold greater compared to SGLT-1, with an IC₅₀ (concentration causing half of maximal inhibition) of 0.0018 μM and of 0.036 μM for SGLT-2 and SGLT-1, respectively. Its chemical structure, (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-methylsulfonyloxane-3,4,5-triol, is Sotagliflozin's effectiveness in inhibiting SGLT-2 is similar to



that of the selective SGLT-2 inhibitors dapagliflozin and canagliflozin, but it is > 10-fold more potent than the latter molecules in inhibiting SGLT-1. Its effects on SGLT-1 in other tissues are, however, less known.

4. Mechanism of action:

Sotagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, has been introduced to treat diabetes. It prevents the sodium-glucose cotransporter-2 (SGLT2) enzymes in the kidney's proximal convoluted tubule. Since it is involved in 90 % of the reabsorption of filtered glucose, the SGLT2 transporter is an excellent protein for targeting for the therapy of diabetes. Typically, a 180 mg/dL blood glucose level corresponds to the renal limit for reabsorption of glucose. (5)

Distribution and role of SGLT-1 and SGLT-2:

To identify locations of SGLT-2 in the human kidney and SGLT-1 in the human kidney, small intestine, liver, heart and lung. In the kidneys, hSGLT-2 and hSGLT-1 were found on the brush border membrane (BBM) of proximal tubule S1/S2 and S3 segments, respectively. However, in contrast to rodents, hSGLT-1 was not expressed in the ascending limb of Henle and in the macula densa. Moreover, the expression of both hSGLTs was identical for both sexes. In the small intestine, hSGLT-1 was expressed on the BBM of enterocytes and subapical vesicles. It was found in alveolar epithelial type 2 cells and in bronchiolar Clara cells

Dual SGLT-1 and SGLT-2 Inhibition:

Given that SGLT-1 inhibition enhances GLP-1 secretion and DPP-4 inhibition prolongs endogenous GLP-1 half-life, a synergic effect on glucose control in type 2 diabetes is to be expected. In patients with type 2 diabetes. GLP-1 levels of from baseline]. Intriguingly, an improvement in beta cell incretin sensitivity has been described in Type 2 diabetes patients treated with dapagliflozin, and a mild increase in GLP-1 levels has also been observed with empagliflozin. These gliflozin's, however, have no inhibitory action on SGLT-1 and should not therefore be able to directly increase GLP-1 secretion. Its pancreatic alpha cells secrete GLP-1, with possible prevailing paracrine effects, makes this mechanism particularly interesting. The utility of co-administering DPP-4 inhibitors and SGLT-2 inhibitors is now well established, although with apparently less than additive efficacy. (6)

A significant increase in active GLP-1, after a meal challenge containing glucose, was observed in the combination therapy groups compared to the others, suggesting a synergic effect of the two drugs. The effects of combination therapy with GLP-1 and Sotagliflozin might give positive and stronger results

- SGLT1 is the primary transporter for absorption of glucose and galactose in the GI tract.
- Pharmacologic inhibition by Sotagliflozin is independent of insulin and does not depend on kidney function.

Preclinical studies of Sotagliflozin:

Lexicon Pharmaceuticals developed a drug discovery programme that evaluated several drug candidates with differing degrees of SGLT1 and SGLT2 inhibition. SGLT2 and SGLT1, produced greater improvements in glycemic control and A1C than selective SGLT2 inhibitors, but did not trigger diarrhoea or other apparent gastrointestinal related adverse effects. The ability of Sotagliflozin in vitro to inhibit SGLT1 and SGLT2 was established. Sotagliflozin inhibited SGLT2 with an IC₅₀ of 0.0018µM, and it inhibited SGLT1 with an IC₅₀ of 0.036µM. These results indicated that

Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2 with approximately 20-fold selectivity for SGLT2 over SGLT1.11 This dual inhibition was confirmed in animal pharmacology studies that demonstrated that Sotagliflozin can produce increased UGE, delivery of glucose increased postprandial GLP-1. These results were associated with significant reductions in postprandial glucose. (7)

Initial phase 1 studies of Sotagliflozin:

The initial single-dose and multiple-dose studies of Sotagliflozin were performed in healthy subjects to identify its pharmacokinetic and pharmacodynamics properties. A range of doses up to 500mg in a liquid formulation was evaluated. The maximum circulating concentration on day 7 of Sotagliflozin after multiple-dose administration was 165ng/mL, and the total exposure was 1172 ngh/mL. The pharmacokinetic half-life was 29 h, supporting once-daily dosing. The maximum UGE was 36 g on day 7 after multiple dosing. This UGE reflects a SGLT2 effect in the kidney, but it is less than reported with high doses of selective SGLT2 inhibitors. For example, 24 h UGE of 60–70 g has been reported after administration of canagliflozin in healthy subjects.¹⁵ The apparently lower UGE with Sotagliflozin may relate to intestinal SGLT1 inhibition; lower peak postprandial glucose levels mean less glucose is filtered by the kidney than with a selective SGLT2 inhibitor. (8)

Phase 2 study of Sotagliflozin in renal impairment:

While renal impairment studies often focus solely on pharmacokinetics, the Sotagliflozin renal impairment study was designed to demonstrate significant improvements in glycemic control.²¹ It was considered as a proof of concept for dual inhibition of SGLT1 and SGLT2. The renal impairment study randomly assigned 31 patients with type 2 diabetes and moderate to severe renal impairment [defined as estimated glomerular filtration rate (eGFR) between 15 and 59mL/min/1.73m²] to either Sotagliflozin 400mgqd or placebo. Treatment was given for 7days. A pre-specified analysis divided the population into those with eGFR 45–59mL/min/1.73m² and those with eGFR. The cut-off of 45mL/min/1.73m² was chosen because the US Food and Drug Administration (FDA) guidelines for selective SGLT2 inhibitors advise against their use in patients with this degree of renal impairment due to lack of efficacy. The safety in the study supported further evaluation of the 400mgqd dosage in longer term studies of renal impairment. There were no serious adverse events, no discontinuations due to adverse events, and the overall incidences of adverse events were similar with Sotagliflozin and placebo. (9)

Phase 2 study of Sotagliflozin in diabetes:

A phase 2 study of Sotagliflozin in type 1 diabetes was recently completed.²² It was initiated with a pioneer group of three patients treated in an open-label fashion with Sotagliflozin 400mg. The experience in these three patients was used to determine how best to adjust and evaluate insulin dosing in a subsequent cohort of patients randomized to Sotagliflozin versus placebo. While the full results of the randomized cohort have yet to be published, a perspective of the pioneer group experience is provided here to describe the potential profile of dual inhibition of SGLT1 and SGLT2 in

type 2 diabetes. The patient experienced a substantial reduction in the time spent with glucose values >180mg/dL, from 29% at baseline to 10% with Sotagliflozin. (10)

Clinical trials of Sotagliflozin:

Patients were randomly selected to receive either a placebo or Sotagliflozin 200 mg once day and depending on side effects, the dose may be increased to 400 mg. before or within three days of hospital discharge if they met all qualifying and stability requirements. With the help of interactive-response technology, randomization was carried out strategically and was divided into groups based on the geographic region of enrolment, as well as the baseline left ventricular ejection fraction. For the first four months, visits to track progress were scheduled every two weeks, and then every four months after. (11)

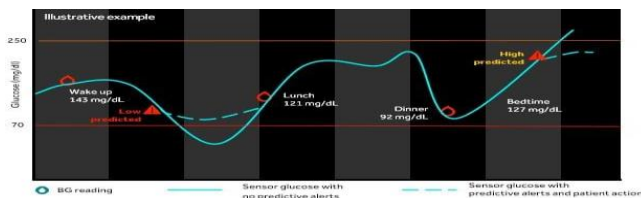
Sotagliflozin added to optimized insulin regimens:

Sotagliflozin added to stable insulin therapy:

The inTandem3 study was conducted at 133 centers worldwide and compared the effects of Sotagliflozin 400mg versus placebo when added onto stable insulin therapy for a total of 24weeks. Patients in the Sotagliflozin group demonstrated an overall drop in A1C from a baseline of 0.79%, compared with 0.33% in the placebo group. In the treatment group the total insulin dose, basal insulin dose, and bolus insulin dose were all significantly decreased by -5.25units, -2.60units, and -2.84units, respectively. Serious adverse events were higher in the Sotagliflozin group compared with placebo (6.9% versus 3.3%) leading to more adverse event withdrawals from the treatment group (6.3% versus 2.3%). Hypoglycemia is discussed in the following. Acidosis-related adverse events were higher in the Sotagliflozin group compared with the placebo group (8.6% versus 2.4%), as was the rate of DKA episodes (3% versus 0.6%). The rate of DKA was higher in the Sotagliflozin group regardless of whether CSII or MDI was used. (12)

5. Continuous glucose monitoring in diabetes patients:

Although A1C is the gold standard for assessing glucose control, there are limitations to using A1C as the sole marker of effective glucose control. A1C does not capture glucose variability or day-to-day disease control. Other indices including continuous glucose monitoring (CGM) and time in range may better capture the patient experience. In addition, time in range has been associated with the risk of micro



vascular complications. (13)

Fig.2 Continuous Monitoring of Sotagliflozin from Wake up to bed time

Sotagliflozin 200mg increased the time within the target glucose range by 1h17min compared with placebo ($p=0.026$) and Sotagliflozin 400mg increased the time within the target glucose range by 2h 49min compared with placebo

($p180\text{mg/dl}$ with Sotagliflozin 200mg compared with placebo and nearly 3h with Sotagliflozin 400mg. There was a numeric decrease in hypoglycemia (events/patient/day) and percentage of time spent/ day with glucose. The incidence, prevalence, and severity of hypoglycemia across. (14)

After using Sotagliflozin drug:

Continuous glucose monitoring of the first patient to receive Sotagliflozin for the treatment of diabetes. Recordings are shown after standardized meals.

6. Conclusion

It will also be used to treat heart failure in 2023. Heart failure, commonly referred to as cardiac arrest, is a global issue that can be helped by medication. A powerful medication for treating heart failure is sotagliflozin. Clinical testing have approved it as a powerful therapy and it can also be used to cure diabetic patients' heart failure. When taken alongside other antidiabetic drugs, sotagliflozin can effectively reduce blood sugar levels because it inhibits the kidneys' ability to absorb glucose and promotes the excretion of glucose in the urine. It's also shown other benefits like improved blood pressure control, weight loss, and kidney function. For patients with heart failure, sotagliflozin has great promise as a therapy alternative.

7. Author contributions

All authors are contributed equally.

8. Financial support

None

9. Declaration of Competing Interest

The authors have no conflicts of interest to declare.

10. Acknowledgements

None

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