

Clinical efficacy of sodium dependent glucose transporters 2 inhibitor in the treatment of heart failure

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Abstract. When it comes to diseases, heart failure is always an important issue for people around the whole world. Patients may suffer a lot when they have heart failure. Every year, there are a lot of people who dead because of having Heart Failure in and out of America. Nowadays, there are mainly two types of heart failures, HFrEF (heart failure reduced ejection fraction) and HFpEF (heart failure preserved ejection fraction). Research show that SGLT2 including Dapagliflozin, sotagliflozin, empagliflozin, and other types of inhibitors are effective when used to treat with heart failure patients regardless of whether they have had diseases like diabetes before. With the support of researches mentioned in the following passage, this idea will be reliable and we believe that with such kind of good news that the SGLT2 inhibitor are actually contributing to the process of dealing with HF, people who have been suffer from HF will one day be able to cured.

Keywords. SGLT2 inhibitors, HFrEF, HFpEF.

1. Introduction

1.1. What is SGLT2 inhibitor?

Sodium dependent glucose transporters 2 (SGLT2) inhibitor is a medicine that could eliminate the reabsorption of glucose by kidney and expel excessive glucose from the urine. This can reduce blood glucose and prevents people from diabetes. It is a type of prescription medical treatment approved by the FDA to allow patients take them with diet and help solve the problem of low blood sugar with type 2 diabetes. Initially, SGLT2 inhibitors were developed as oral antidiabetic drugs. Later clinical trial data showed that the renal function of diabetes patients with diabetes nephropathy was significantly improved. In individuals with nephropathy and type 2 diabetes, SGLT2 inhibitors are helpful in decreasing the advancement of renal disease, lowering heart failure, and lowering the risk of renal failure and mortality. Patients who do not have diabetes can benefit from SGLT2 inhibitors in terms of renal protection. Studies have shown that some of these drugs can also reduce the risk of heart disease in people who have had heart disease before. They can also reduce the need for hospitalization for heart failure.

1.2. The mechanism of SGLT2 inhibitors

SGLT2 inhibitor acts on "sodium-glucose cotransporter 2" that help peoples' kidneys reabsorb glucose (sugar) from their body or blood. After people take SGLT2 inhibitors, less of their blood sugar ends up in their kidneys and end up leaving peoples' body in their urine [1].

Improvement of ventricular loading conditions and preload reduction principally brought on by diuretic and natriuretic effects are two of the main ways SGLT2 inhibitors carry out their positive functions [2,3]. According to data, adding SGLT-2 inhibitors to a patient's basic medication can increase their chances of surviving and being healthy if they have heart failure with a low ejection fraction [4,5]. All six of the life-extending treatments for people with heart failure and low ejection fraction were first created to treat other cardiac metabolic disorders. The supporting data from the unique mechanism study was then used to determine the presumed mechanism of the benefit of HF treatment. The SGLT-2 inhibitor was initially created as a diabetes treatment for hyperglycemia. It can now be used to treat and prevent heart failure. In the United States, these therapies are now the ones with the quickest rate of growth [6].

The potential impact of SGLT-2 inhibitors on type 2 diabetes mellitus-related cardiac autonomic neuropathy is being studied. To understand their impact on Cardiac neuropathy, they conducted studies on various groups, parallel and cross-randomized, and assigned them to receive an SGLT-2 inhibitor vs a placebo. They specified two results: Change in square root of mean value of sum of squares of variations between adjacent RR intervals and change in standard deviation of all 5-minute average normal RR intervals. They draw the conclusion that SGLT-2 inhibitors don't appear to have a significant impact on type 2 diabetes mellitus patients [7].

1.3. Category of Heart Failure

There are mainly two types of heart failures, heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). These two types are quite different. They differ in the amount of blood delivered by the left ventricle or the ejection fraction every time when the heart beats. The difference in ejection fraction led to the difference in the possibility of risk and mortality. Heart failure with preserved ejection fraction causes about half of the 5 million heart failure cases in America. The disease is more common in elderly patients and women. The reason is that the active ventricular diastolic and passive ventricular compliance are abnormal. This will cause a lower stroke volume and cardiac output [8]. While on the other hand, Heart failure with reduced ejection fraction is a complex cardiovascular syndrome caused by left ventricular systolic dysfunction. This problem occurs when the left ventricular ejection fraction is 40% or less, accompanied by progressive left ventricular dilatation and poor cardiac remodeling. In addition, the core of diagnosis is that the level of natriuretic peptide is higher than the age and environment specific threshold, and left ventricular systolic dysfunction is measured by echocardiography [9]. These are how HFpEF and HFrEF are different.

2. A summary of sgl2 inhibitor as a treatment of HF

2.1. Effect of SGLT inhibitors in HFrEF when they are used for patients

Dapagliflozin [10] can be used to deal with HF that has a decreased fraction of ejection. When patients with heart failure with a low ratio of ejection take the medication dapagliflozin, research shows that the risk of their condition getting worse or even leading to death is significantly reduced when compared to patients who only received a placebo, even though some patients may or may not have diabetes.

During the experiment, together with the study's sponsor, AstraZeneca, the executive committee planned the trial and monitored its execution and analysis. Execution and reporting of the trial were done in line with the analysis plan contained of protocol and statistical methods, both of them are actually fully able to access in the complete word in the work on the publication of the Journal of Medicine in the area of New England. The regional ethics committees approved of the experiment. A separate data and safety monitoring committee was keeping an eye on the safety of the trial's patient participants. A different academy-purposed team from the University of Glasgow supported the

sponsor's findings. After the first writer, who can get full access to the data, wrote that manuscript, all writers reviewed and revised it. Patients had to be at least 18 years old, have an ejection fraction of forty percent or less, and exhibit NYHA class 1, class 3, or class 4 diseases so they can be eligible. The minimum N-terminal pro-B-type natriuretic peptide concentration required patients to take them at an amount of six hundred pg every milliliter. Regardless of their history of heart failure hospitalization, patients with baseline heart atrial arrhythmias or heart atrial flutter required to have a certain level of no less than 900 pg per milliliter.

People who are suffering HF were asked to experience normal pharmaceutical therapy, such as an inhibitor that can convert enzyme, a thing that can block the receiving of angiotensin, or beta-blocker working together with some sacubitril-valsartan, in the absence of contraindications or intolerable side effects. Additionally, the use of a mineralocorticoid receptor antagonist was encouraged. Drug dosages were tailored for each patient in accordance with the instructions in the guidelines. Patients with type 2 diabetes who continued to use glucose-lowering drugs may have their dosages adjusted as necessary. The dosage of sulfonylurea and insulin may be specifically reduced to lessen the risk of hypoglycemia. Type 1 diabetes, recent use of an SGLT2 inhibitor, the presence of hypotension symptoms or a systolic blood pressure below 95 mmHg, and an estimated glomerular filtration rate of less than thirty ml for every 1.73 cubic mm of body surface area per minute were all exclusion criteria.

The patients then undergo a 14-day observation period. Their trial inclusion and exclusion were examined throughout this time, and their fundamental data were collected. The patients were then given dapagliflozin or a look-alike placebo. After taking medications at random or a placebo, these individuals were monitored for a number of days.

Worsening HF or death from cardiovascular causes were the main outcomes. Unplanned hospitalization or emergency medical care that necessitates intravenous HF treatment is a worsening of heart failure. A composition for HF is another result. As a result of this study, the possibility of having a worse heart failure or even deaths were decreased by the use of dapagliflozin when compared to the placebo group. Each of the factor that may lead to heart failure is significantly lower in the dapagliflozin group. Therefore, dapagliflozin can effectively deal with heart failure.

2.2. Effect of SGLT inhibitors in HFpEF during their trials with HF patients

Empagliflozin is effective when used to deal with HFpEF. While HFpEF has drug treatments, therapy options for patients with HFpEF are rather limited. Research shows that empagliflozin can be used to lower the risk of cardiovascular death and other problems caused by heart failure, no matter whether or not the people who have HF also has diabetes. The study of the research group is to determine some effects from SGLT2 inhibition with empagliflozin as one of the main outcomes of heart failure. The research was procedure with proper experiments techniques, like it uses the double-blind technique, placebo-controlled technique, and event driven trial. Most people who attended in the study are male & female that aged at least 18 years old with NYHA class 2, 3, and 4 chronic HF and a left EF of more than forty percent. This agreement requires that the N-terminal precursor level of natriuretic peptide in patients is higher than 300 pg/ml, or the NT proBNP level in patients with atrial fibrillation is higher than 900 pg/ml. Patients with conditions that can alter their clinical course and are unrelated to heart failure, as well as those with conditions that could jeopardize their safety or restrict their ability to participate in the research, will be excluded [11].

Patients that are qualified were double-blindedly and randomly distributed to two half-and-half groups after a four to twenty-eight days of screening period. They got standard care along with either a placebo or 10 mg of empagliflozin every day. The estimated glomerular filtration rate, which is able to meet the requirement because of geographic region, status about diabetes, and milliliters every minute every 1.73 cubic meters of the surface area of the body or no bigger than 60 milliliters every minute every 1.73 cubic meters, is also measured during the screening period, along with the left ejection fraction of the ventricles. Half of the people who suffer from HF will no longer have the disease diabetes when they are at an enrollment, the researchers expect. After that, patients were observed periodically

based on their health condition. The outcome of the experiment shows a composition of different situations that led by the presence of HF, the occurrence for HF, also, the rate of decrease in the eGFR during the whole process.

In the experiment, empagliflozin's inhibition of SGLT2 decreased the overall potential possibility of the death or hospitalization of blood vessels in humans' heart for HF by 21% for those who attended the experiment and also have HFpEF. Such kind of reduction was primarily attributable to empagliflozin's 29% decrease in the risk of HF hospital treatments. Almost all of the established subgroups which includes individuals who have diabetes or people who don't have diabetes. This kind of situation exhibit the effect of occurrence of outcome facts with consistency. Empagliflozin resulted in some longer periods as well before the first heart failure hospitalization and a decrease in the overall number of heart failure hospitalizations. Research data also shows that the effects of SGLT2 inhibition don't vary greatly with heart failure.

Although empagliflozin therapy decreased the frequency of heart failure hospitalizations in the present study, it did not appear to have an impact on the number of cardiovascular or other cause-related fatalities. This study shows that empagliflozin reduced the possibility of having some kind of heart blood vessel problem or HF hospitalization to people with HFpEF. Such kind of great and brilliant benefit was seen in both those with and without diabetes, and it persisted across different ejection fraction categories.

2.3. The clinical efficacy of SGLT inhibitor in HF regardless of EF

Heart failure can also be categorized into acute HF or chronic HF. Compared to chronic heart failure, acute HF is less common. A heart attack is one of the most major frequent reasons for acute HF. The arteries that feed blood to the heart muscle are blocked, which is the source of this. Viruses, severe infections, allergic reactions, pulmonary thrombosis, particular medications, and illnesses that can harm the heart muscle are some more causes [12]. The most typical sign of sudden heart failure is shortness of breath. Rapid swelling and fluid retention symptoms, which are characterized by a fast gain in weight that reaches several pounds in less than 24 hours, can also be signs of acute heart failure. Other symptoms include asthma, coughing, trouble falling asleep or lying flat, and irregular pulse. It can occasionally be linked to a history of cardiomyopathy. Accidental hospitalization is typically necessary for acute heart failure. The prognosis is typically poor, and there is a substantial chance of mortality and readmission following discharge. You should seek emergency medical attention if you suffer abrupt or painful symptoms. Conversely, the onset of chronic heart failure is more gradual. It is something that the heart will be weakened for several reasons and cannot supply an enough amount of blood in order to sustain the body. Such kind of bad feeling that breaths are short, weakness, weariness, and difficulty exercising are all signs of chronic heart failure.

Research shows that sotagliflozin can be used in people who are suffering from the disease of diabetes and HF that is worsening, and can help them to end up with a significantly lowered number of possibility to lose their life from blood vessel reasons and hospital treatments and HF when compared to the effect brought to the research by the use of the technique of placebos.

According to research done by Deepak L. and his co-researchers, they done the study like following [13]. Their trial was a involving several different trials. These trials make use of different techniques like the placebo technique and randomizing technique. Study participants must be between the ages of 18 and 85, be hospitalized owing to heart failure symptoms and signs, and have received intravenous diuretics. Additionally, the patient must have either kind of diabetes diagnosed before the time of having some reliable lab data and statistics supporting the diagnosis at the time of the index admission. To ensure the validity of this research, patients who didn't fit these criteria were excluded. Patients who took part in the experiment receive 200 mg of sotagliflozin either before or within 3 days after they left the hospital. According to the initial estimates for these trials, 947 primary outcome events from people who are suffering from a fraction based on ejection of ventricular less than half would give the entire trial more than eighty-five percent of ability to find a lower possibility of the happening of event in the sotagliflozin group, and almost all possibility and ability to seek out the very same decrease or risk in a

whole. As a result, enrollment is restricted to no more than 1100 individuals having a left heart blood vessel ejection ratio of fifty percent or even a bigger number.

The analysis's findings demonstrate that people with diabetes who experienced heart failure have a considerably reduced rate of health problems while using SGLT2 and SGLT1 sotagliflozin than when taking a placebo. This demonstrates the value of SGLT2 in patients with worsening heart failure before or shortly after discharge. Increased excrete of glucose called renal was recognized as a mechanism leading to natriuretic and diuretic effects. There have been reports of favorable effects on endothelial progenitor cells. However, it is currently unclear from the ongoing trial if the presence of inhibitors resulted in any therapeutic advantages.

3. Conclusion

In conclusion, based on these experiments above, we can see explanations about the mechanization of SGLT2, and we can see that heart failure can be technically two types, HFrEF and HFpEF. As a treatment SGLT inhibitors, Dapagliflozin, perform great in HFrEF and the Empagliflozin done well in HFpEF. Also, research show that the clinical efficacy of SGLT inhibitor in HF regardless of HF types are also great. These effects are proved by several researches or experiments and the results all shows that SGLT2 inhibitors are beneficial to heart failure patients. So, with the support of data, experiments, research, and statistics, we can see that SGLT inhibitor is a really good news for those who are suffering HF when they were proved to be useful for the cure of the disease.

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