Article

HEART FAILURE PHARMACOTHERAPEUTICS WITH A REDUCED EJECTION FRACTION USING SODIUM–GLUCOSE CO-TRANSPORTER 2 INHIBITORS

Sachin Kumar[1] ,Anjali Shakya[1], Dr. Akhilesh Patel[1], Priya Rani[2], Shobhit Raj[1*]

1 Department of Pharmacy Practice, NIMS Institute of pharmacy, NIMS University Rajasthan, Jaipur-303121,India

2 Department of Pharmacology, National Institute of Medical Sciences & Research, Jaipur-303121

Corresponding Author*: Shobhit Raj, Department of Pharmacy Practice, NIMS Institute of pharmacy, NIMS University Rajasthan, Jaipur-303121,India

Email.id — Email ID:drshobhitraj@gmail.com

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Abstract:

They help people with diabetes keep their blood sugar levels in checkby lowering the level of glucose that is reabsorbed from the proximal renal tubules. In addition, these medications may help those people who have or are at risk of developing cardiovascular disease avoid heart attacks, strokes, and cardiovascular deaths, as well as heart failure and kidney failure. In people who do not have type 2 diabetes, the drugs can also be use in heart failure therapy and delay renal failure progression. To do this, the doctor will look at people suffering from heart failure with a low ejection fraction and diabetics who are at risk of heart failure. We will look at data from clinical trials to see if Sodium–glucose cotransporter 2 inhibitors can be used in the treatment of these people who is diabetics and having risk of heart failure, which can be very bad for their health. In addition, we look at how Sodium–glucose co-transporter 2 inhibitors might help the cardiovascular system. A class of drug called Sodium–glucose co-transporter 2 inhibitor can help those people who is suffering from or at risk of cardiovascular illness stay out of the hospital more often. This drug is called empagliflozin, ertugliflozin, canagliflozin, and dapagliflozin. In this, we take into account the EMPA-REG OUTCOME TRIAL and the DECLARE-TIMI 58 trial as well as the CANVAS and the VERTIS-Cardiovascular trials (such as type 2 diabetes). In addition, two separate studies have found that Dapagliflozin and Empagliflozin may be beneficial to patients who are suffering from heart failure, even if they also have diabetes. Discovery of Sodium–glucose co-transporter 2 inhibitors has given people with diabetes, heart disease, and renal failure new ways to get help. As for how they could help prevent or treat heart failure, that's still a question that needs to be worked out.

Key words: SGLT2 inhibitors, heart failure, diabetes, and renal disease

Introduction:

Heart failure (HF) happens when there is a problem in the heart's structure or function. This results in high pressures inside the heart and/or at rest and during activity, there is a drop in cardiac output. Cardiac failure (HF) is a medical condition that causes signs and symptoms that are caused by a heart defect. When the ejection fraction is less then 40% the situation is called heart failure with a low ejection fraction. Cause of death in Type II diabetes mellitus patient is heart failure and it is most common[1, 2]. One in five people with diabetes who are over 65 and have heart failure also have it[2,3]. Type II diabetes mellitus is also common in people who have heart failure. It happens in about 40% of people who go to the hospital for heart failure and up to 30% of people who have chronic heart failure in the community [4].

Despite the fact that there are many ways to treat heart failure, the prognosis is still bad [5]. A person who has Type 2 diabetes with cardic complication together is more likely to have cardiovascular disease and die from any cause, even if they do not have any other risk factors [6, 7]. In the past, it was thought that strict glucose control or the use of certain glucose-lowering medications could have a negative effect on the heart[8,9]. A meta-analysis found that stricter glucose control did not cut down on heart failure hospitalizations or death in comparison to less strict control of glucose [10]. Over the previous decade, a number of new drugs for lowering blood sugar have been tested in studies that look at cardiovascular outcomes, with a wide range of drugs being tested. Almost all of the drugs that stop dipeptidyl peptidase-4 were discovered to be safe for patients with type 2 diabetes. Also, it was found that both Sodium–glucose co-transporter 2 inhibitors and GLP1 (Glucagon-like peptide-1) antagonists improved cardiovascular health. This is surprising.

Sodium–glucose co-transporter 2 Inhibitors are being used to prevent heart failure.

Empagliflozin, an Sodium–glucose co-transporter 2 inhibitor, showed for the first time that it may be able to prevent diabetic patients from developing heart failure who are at the risk of having heart failure in the EMPA-REG OUTCOME TRIAL [11]. Patients who had type 2 diabetes were allocated at random to take empagliflozin 10mg, 25mg, or placebo with their standard of care diabetes treatment. Empagliflozin was given to people with type 2 diabetes who are at the risk of having heart failure. As part of a randomised study, this medicine slashed the risk of three main cardiovascular events: myocardial infarction, stroke, and cardiovascular death. It also cut the possibility of dying from any reason and hospitalisation for heart failure. Empagliflozin's effectiveness was found to be the same for all types of patients.

There was a study called DECLARE-TIMI 58[12] that looked at patients having type 2 diabetes with history of cardiovascular illness were given either dapagliflozin or a placebo. There were a large number of cardiovascular mortality or hospitalisation for heart failure that were the most important results. It has no effect on heart failure when people took dapagliflozin instead of a placebo. However, there was no discernible change in Major adverse cardiovascular events seen.

Table1. Empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin were found to reduce heart failure hospitalisation and CVdeath

Relative risk reduction (RRR)	HHF	CV death
EMPA-REG OUTCOME (empagliflozin) (RRR)	35% ↓	38% ↓
VERTIS CV (ertugliflozin) (RRR)	30% ↓	8% ↓
CANVAS program (canagliflozin) (RRR)	33% ↓	13% ↓
DECLARE TIMI (dapagliflozin) (RRR)	27% ↓	2% ↓

Randomly, Type 2 diabetics with chronic kidney disease patients were given canagliflozin or a placebo in a study called CREDENCE [15]. Some patients taking canagliflozin did not have end-stage renal disease, a rise in serum creatinine, or died fromcauses of kidney failure or cardiovascular disease as patients who take

In the like manner CANVAS study [13], it was found that people who took canagliflozin were less likely to have heart problems than people who took a placebo. Ertugliflozin was found to be no better than a placebo in the VERTIS-Cardiovascular study[14] when it came to having a heart attack or stroke. However, it was found that all of the Sodium–glucose co-transporter 2 Inhibitors were linked to a the number of people has decreased significantly. of heart failure hospitalizations (Table 1).

placebo(a relative risk reduction of 30 percent). Also, The group on canagliflozin had a decreased risk of cardiovascular mortality, heart attack, and stroke than the placebo group.

A large number of patients who took SGLT2 inhibitors did not have heart failure at first when they started the research. This meant that the drug had a bigger impact on preventing it than on treating the disease itself. In this study, it was thought that the mechanisms of action of glucose-lowering medicines were different from the ones that are usually blamed for the cardiovascular benefits of these medicines [16, 17, 18, 19, 20, 21]. Also, they have been shown to slow down the development of kidney disease [11, 21, and 22]. It doesn't look like better glycemic control is the reason for the better cardiovascular and renal outcomes. This means that even if you don't have diabetes, the benefits may be worth it[11].

In large scale patients taking Sodium–glucose co-transporter 2 inhibitors, randomised studies were

about 30-35% less patients have heart failure-related hospitalizations than people who took a placebo [23–24].This most noticeable benefit was in people who had a left ventricular ejection fraction of less than 30% before the treatment.

The European Society of Cardiology's recommendations for 2019 are as follows[25]: the HFA article on the potency of novel glucose-lowering drugs[26], and the clinical practise update on heart failure[27], type 2 diabetes patients with the risk of having cardic complication should utilise Sodium–glucose co-transporter 2 inhibitors. People who is taking type 2 diabetes with previous history of cardiovascular disease or having high risk of cardiovascular complication should not be hospitalised for heart failure in October 2020 the European Society of Cardiology's recommended.

Pharmacotherapy of Sodium–glucose co-transporter 2 inhibitors in heart failure

The DAPA-HF group was the first to see how important these problems were [8]. This study looked at 4744 people who had heart failure that ranged from "New York Heart Association class II to IV" and had a 40% or lower ejection fraction. Dapagliflozin 10 mg a day, or a placebo, was given to them in addition to their other medicines. People who took dapagliflozin were less likely to get heart failure or die from cardiovascular causes than people who took a placebo. This was true even if they had type 2 diabetes, which is linked to heart failure, as it is with diabetes. Dapagliflozin users had a lower risk of mortality from any cause and a lower risk of having heart failure hospitalisation and cardiovascular mortality than people who took a placebo drug. They had the same thing happen to both diabetics and non-diabetics: Dapagliflozin caused more symptoms in the group that took it for eight months than in the other group that did not. This means that they had more symptoms than the people who took the placebos, which is what the study was about.

The EMPEROR-REDUCED TRIAL is the only one study that included Patients with symptomatic heart failure, a low ejection fraction, and high natriuretic peptides, with or without T2DM, in addition to the DAPA-HF trial. The research included patients with more significant dysfunction of the left ventricle. In the analysis, patients with more significant dysfunction of the left ventricle received priority care. The major aims of this study were cardiovascular death or heart failure hospitalisation. The overall number of heart failure hospitalizations needed to be tracked as a secondary aim. The risk of cardiovascular mortality or The number of people admitted to the hospital for heart failure has decreased by 25%. The overall number of heart failure hospitalizations was also reduced by 30%. Empagliflozin reduced the number of times participants went to the emergency department for IV heart failure therapy and improved their performance on a cardiomyopathy test in Kansas City. In Table 2, contrast the clinical outcomes of

the DAPA-HF and EMPEROR-REDUCED investigations.

Table 2 *Comparison of the clinical outcomes of DAPA-HF and EMPEROR-REDUCED trials*

Clinical outcomes	Cardiovascular death or HHF	Cardiovascular death	HHF
EMPEROR-Reduced(N = 3730) Empagliflozin versus Placebo HR (CI)	0.75 (0.65–0.86)	0.92 (0.75–1.12)	0.69 (0.59–0.81)
DAPA-HF (N = 4744) Dapagliflozin versus Placebo HR (CI)	0.75 (0.65–0.85)	0.82 (0.69–0.98)	0.70 (0.59–0.83)

Sodium–glucose co-transporter 2 inhibitors: biological processes and consequences in heart failure

There is still a lot we don't know about how Sodium–glucose co-transporter 2 inhibitors work in people with heart failure, even though it has been shown that these drugs have a wide range of metabolic, hemodynamic, and organ-specific effects [Figure 1]. Also, people who take Sodium–glucose co-transporter 2 inhibitors have a side effect called natriuresis and uricosuria, as well as glycosuria [22, 28–32]. Another set of metabolic effects includes Muscle cells with enhanced insulin sensitivity and glucose absorption[32, 33], less neoglucogenesis and greater ketogenesis [12, 33]. They also help the body distribute fat around the body [33, 34] because of the renal calorie loss that comes with glycosuria and because they make people want to lose weight [21, 29, 30].

The intake of Sodium–glucose co-transporter 2 inhibitors also led to increase in the haemoglobin of blood . Ephedrine users go through a lot of different things, like osmotic diuresis, plasma and interstitial fluid volume decrease, to make their hearts work less hard[28, 35, 36]. If you take Sodium–glucose co-transporter 2 inhibitors instead of diuretics, they may cause more fluid to be removed from the interstitial space than from the plasma, which could help avoid the depletion of plasma volume and hypo perfusion that diuretics can cause[37]. However, the Hemodynamic and metabolic benefits are unlikely to be the primary reason for the prevention of heart failure and therapy.

Sodium-hydrogen exchanger-1 is more active when you have type 2 diabetes or heart failure because your body needs more of it to get the sodium and hydrogen it needs[38]. This makes Sodium–glucose co-transporter 2 inhibitors good because they stop sodium-hydrogen exchanger-1 from working [38]. People who take Sodium–glucose co-transporter 2 inhibitors, which work by blocking the sodium-hydrogen exchanger-1 receptors, may be able to protect their heart from having too much harmful intracellular calcium overload [39, 40].

Sodium–glucose co-transporter 2 inhibitors may also have an impact on cardiac muscle metabolism[38, 41], as well as a way to cut down on myocardial oxidative stress [42]. Insulin resistance is the same thing that causes type 2 diabetes and heart failure[43]. Heart obtained Energy from free fatty acids in insulin-resistant instead of glucose, as a result, heart metabolic efficiency is reduced (inadequate ATP synthesis) [44]. Sodium–glucose co-transporter 2 inhibitors help keep the function of heart normal by encouraging the body to switch from Free fatty acids to glucose metabolism. This causes the heart to make more ATP, which helps it stay healthy.

People of type 2 diabetes with coronary artery disease who took empagliflozin for six months saw their The mass index of the left ventricle is decreasing and their diastolic function improve[16]. In addition, the DAPA-HF study found that people with type 2 diabetes had a statistically a substantial reduction in left ventricular mass[21]. This shows that people who is taking empagliflozin may have their heart reshaped in the opposite way.

It is well-known that increased neurohormonal activity causes a rise in oxidative stress and other types of cell stress, which leads to dysfunction of cardiomyocyte and death. Another theory says that Sodium–glucose co-transporter 2 inhibitors make cells starve by blocking energy overflow sensors. Sirtuin 1 (SIRT1), for example, is activated when there is not enough food in the body. This stops the activity of Pathways that cause inflammation, reduces cell stress, and encourages autophagy [9]. As you can see, there are many ways this could help reverse dysfunction of mitochondrial and slow down cell death and cardiomyocyte dysfunction[28, 42]. This could make the heart less fibrotic, as well as improve adipokine balance, endothelial function, vascular resistance and arterial stiffness, [45, 46, 47, 48].

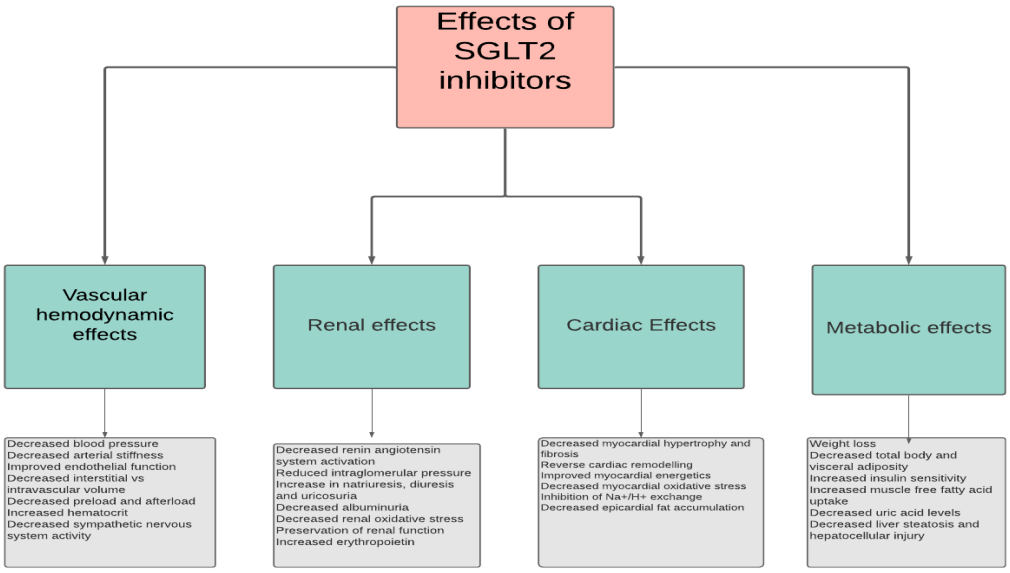

Fig. 1 *Figure summarising the biological effects of SGLT2 inhibitors*

Conclusions

An excellent illustration of how things function is the discovery of sodium–glucose co-transporter 2 inhibitors. The medications were designed to assist patients manage their blood sugar levels when they were originally developed. As a result, they appear to have a greater impact on cardic failure and are Renal failure is being slowed down. It may be especially beneficial for those who suffer from heart failure and have a low heart rate, which is a typical complication of the disease. Sodium–glucose co-transporter 2 inhibitors are also being researched in people with heart failure and a stable ejection fraction to determine whether they can assist. [49]. People with type 2 diabetes and heart failure, empagliflozin reduces hospitalisation for heart failure and cardiovascular death.

Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin all can take people with type 2 diabetes and who already have heart disease or who are at high risk of developing heart disease. It also says that dapagliflozin and empagliflozin should be used to treat Heart failure with reduced ejection fraction, no matter whether the patient has type 2 diabetes [50]. “In the future, more big clinical trials will be done to see how well different Sodium–glucose co-transporter 2 inhibitors work for people with heart failure”.

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