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RESEARCH ARTICLE

SGLT 2 INHIBITORS: NEWER PARADIGMS IN THE TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION

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Abstract

Heart Failure is a growing concern now a days. Many drugs are available for the treatment of heart failure but still there is increasing prevalence of heart failure. SGLT 2 inhibitors were initially developed for diabetes mellitus but they are found to be effective for Heart Failure with reduced ejection also. Many large scale randomized controlled trials also confirmed this and now they are recommended in the treatment of heart failure with reduced ejection fraction.

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Introduction:-

Now a days heart failure is considered as an emerging health problem (1). The reason behind the increasing incidence of heart failure is the increasing prevalence of diabetes mellitus specifically type 2. Since diabetes increases the risk of cardiovascular disorders like coronary artery disease resulting in ischemic heart disease or myocardial infarction that can present as heart failure. Diabetes also causes Heart failure perse in those without significant atherosclerosis.

Heart Failure is one of the leading cause of morbidity and mortality. It is also one of the leading cause for unplanned hospitalization. It significantly reduces the quality of life and also increase the healthcare expenditure (2).

Definition of Heart Failure

It is defined as the clinical syndrome that occurs due to structural or functional abnormalities of the heart resulting in impaired left ventricular filling or ejection (3). If the increase in LV filling pressure is causing heart failure then it is known as Heart Failure with preserved ejection fraction (HFpEF). If the cardiac output is decreased then it is known as heart failure with reduced ejection fraction (HFrEF).

Majority of the clinical manifestations of heart failure are due to compensatory mechanisms that sets due to the failure of the heart. These compensatory mechanisms are beneficial to some extent but in the long term they have deleterious effects like negative remodelling of the heart leading to permanent changes in the heart resulting in further progression of heart failure. Basically activation of sympathetic system (SNS), Renin Angiotensin Aldosterone system (RAAS) and the release of the local vasoactive peptides (VIP) like endothelin, nitric oxide, atrial natriuretic peptide are the main culprits behind all the symptoms and signs of heart failure. So, therapy is directed towards the suppression of these mechanisms. Now a days drugs like beta blockers that suppress the sympathetic nervous system, Diuretics, ACE inhibitors, ARBs that counter the effect of RAAS, are the cornerstones of therapy for heart failure. Even after optimal treatment heart failure is progressive and there may be episodes of decompensation. SGLT 2 inhibitors are the new addition in the armamentarium for treatment of heart failure with promising results.

History of SGLT 2 Inhibitors

Phlorizin, a chemical compound with glycosuric properties was discovered in the 19th century by Joseph von Mering, a German scientist (4). It was isolated from the bark of apple tree and is present in some other fruits also. It produces glycosuria by inhibiting a Sodium Glucose Co Transporter 2 in the kidneys. It also inhibits the absorption of glucose from the intestines. Later on, after more than 150 years SGLT 2 inhibitors are being used for the treatment of diabetes mellitus.

SGLT 2 Inhibitors are the new class of drugs available for the treatment of heart failure. Originally they were developed and approved for the treatment of type 2 diabetes (5). Later on they were found to be effective in reducing death and hospitalization due to heart failure in diabetics. Heart failure is a common comorbidity in diabetes as diabetes itself increases the risk of atherosclerosis leading to ischemic heart disease and heart failure per se also occurs in the absence of atherosclerosis.

Mechanism of action of SGLT 2 inhibitors in heart failure

SGLT 2 inhibitors primarily inhibit the reabsorption of glucose in PCT leading to glycosuria and also reduces hyperglycemia. As glucose is a solute it is excreted along with water that is it promotes diuresis also. Diuresis reduces total body water resulting in decreasing LV filling pressures and after load also (6). Along with glucose there is loss of sodium too which helps in reducing blood pressure. Some studies also show that SGLT 2 inhibitors have anti-inflammatory properties that have the potential to decrease molecular processes related to inflammation, such as extracellular matrix turnover and fibrosis as it decreases the fuel available for the macrophages (7,8,9). It is well known that macrophages are the major mediators of inflammation.

Many large clinical trials involving patients with type 2 diabetes have shown that inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of hospitalization for heart failure also. So to substantiate this effect many large scale trials are being done. Major trials evaluating the role of SGLT 2 inhibitors in heart failure are discussed below.

DAPA HF(Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)(10)

This was a prospective study done to evaluate the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients of heart failure with reduced ejection fraction, with or without diabetes. Results demonstrated that SGLT 2 inhibitor reduces the incidence of worsening heart failure or death from cardiovascular causes and also provides symptomatic relief irrespective of the presence or absence of diabetes.

EMPA-REG OUTCOME(Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes)(11)

This randomized controlled trial, was done to assess the effects of empagliflozin, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events. All the participants had known cardiovascular disease. It was found to reduce the risk of death from cardiovascular diseases. But there was no reduction in non fatal MI stroke.

DECLARE–TIMI 58(Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes)(12)

In this Randomized controlled trial, patients with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease like males of more than 55 years or females of more than 60 years, hypertension, dyslipidemia or history of tobacco use were taken into consideration. They were given Dapagliflozin and the patients were assessed for the outcomes like cardiovascular death, myocardial infarction, stroke, and death or hospitalization due to heart failure. The outcome validated the results of EMPA REG trial that SGLT2 inhibitors reduces the risk of composite death or hospitalization due to heart failure but no reduction in cardiovascular death excluding due to heart failure, myocardial infarction or stroke.

SCORED (Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease)(13)

The trial evaluated the effect of sotagliflozin on the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure in patients with diabetes mellitus and chronic kidney disease, independent of degree of albuminuria. The outcome of this trial strengthens the results of previous studies with SGLT 2 inhibitors that, sotagliflozin lowers the risk of composite deaths from cardiovascular causes, hospitalizations for heart failure, emergency visits for heart failure symptoms.

VERTIS CV (Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes)(14)

The VERTIS trial tested for the efficacy of Ertugliflozin in patients of type 2 diabetes with atherosclerotic cardiovascular disease. It was found to be noninferior to placebo with respect to major adverse cardiovascular events like death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

CANVAS Program (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes)(15)

It's a combination of two trials i.e. CANVAS trial and CANVAS R trial. The effects of canagliflozin on cardiovascular, kidney, and safety outcomes were assessed in this integrated trial. Cardiovascular outcomes that were studied are nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure. Renal outcomes were assessed with the help of regression of albuminuria, the need for renal-replacement therapy (dialysis or transplantation), or death from renal causes. The results showed that canagliflozin lowered the risk of hospitalization for heart failure, progression of albuminuria, and loss of kidney function.

Recommendation:-**for SGLT2 inhibitors in Heart failure (16)**

According to European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2021, SGLT2 inhibitors are now recommended for patients with heart failure and reduced ejection fraction. They are now elevated to a class I, level of evidence A recommendation. They are not recommended for HFpEF till now.

Conclusion:-

SGLT 2 Inhibitors are the latest addition in the therapy for heart failure with reduced ejection fraction in patients with or without diabetes. Many large scale trials substantiate the role of SGLT2 inhibitors not only as antidiabetic but as drug for heart failure that reduces the incidence of new onset heart failure or hospitalizations due to heart failure. Now there is Class 1 recommendation for giving SGLT 2 inhibitors in heart failure with reduced ejection fraction.

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