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SGLT2 inhibitors as heart failure drugs

Introduction

Heart failure is a clinical syndrome that causes either a structural or functional abnormality that reduces the ability of the ventricle to relax appropriately to fill with blood or to pump effectively to push the blood out.[1] Heart failure is further subdivided into heart failure with reduced ejection fraction (HFrEF) in which the ejection fraction is ≤ 40% and heart failure with preserved ejection fraction (HFpEF) in which the ejection fraction is ≥ 50%.

Epidemiology

Heart failure is a growing problem worldwide. The American Heart Association estimates that 6.2 million people with heart failure were living in the US between 2013–2016.[2] Worldwide, there are about 23 million people living with this diagnosis.[3] The disease can be symptomatic or asymptomatic. Patients presenting with symptomatic heart failure can be challenging to diagnose. Asymptomatic heart failure is even harder to detect. Among patients with symptomatic heart failure, a considerable majority require hospitalizations. In the United States, 1 million hospitalizations were recorded with a principal diagnosis of heart

failure in 2004.[4] For patients > 65 years of age admitted to the hospital, 1 in 5 cases is due to heart failure.[5]

Current Treatment Modalities

Due to a high number of patients with this disease, many treatment modalities have been developed over the years to manage heart failure. These include lifestyle interventions including a low salt diet, fluid restriction, regular exercise, smoking cessation, weight loss, and many others.

When it comes to pharmacologic therapy, several drugs have been approved and are actively being used to treat heart failure. The drug therapy, moreover, can be divided into the drugs that provide a mortality benefit, and those that only provide symptomatic relief. Also, even though there are some drugs that can be used in both HFrEF and HFpEF, there are others that are recommended for one or another, but not both. For example, diuretics are used in both conditions to treat volume overload. For the management of hypertension, mineralocorticoid receptor antagonists (MRA) are the initial favored agent in HFpEF if the patient does not have diabetes. For patients with diabetes and HFpEF, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are preferred. In patients with HFrEF, the primary treatment of hypertension includes ACEI/ARB and a β-blocker. MRAs are secondary agents for hypertensive control.

A major component of the management of heart failure is the management of diabetes. Uncontrolled diabetes is a known risk

factor for atherosclerotic disease and can culminate in ischemic cardiomyopathy and heart failure in many patients. Several drugs have proven benefits in the treatment of both conditions. ACEI/ARB reduce albuminuria and slow down progression of diabetic kidney disease, while at the same time providing mortality benefit to patients with HFrEF.

Lately, a new class of drugs has gained prominence. These are sodium-glucose co-transporter 2 (SGLT2) inhibitors. They provide benefits both in the management of heart failure and diabetes by their unique mechanism of action. In this piece, we will focus on their beneficial effects on heart failure.

SGLT2 inhibitor mechanism of action

SGLT2 inhibitors bind to SGLT2 receptors in the proximal tubule and prevent reabsorption of glucose. This leads to glucosuria and a decline in plasma glucose concentration.[6] In a study with empagliflozin, there was a 50% inhibition of filtered glucose reabsorption.[7]

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By inhibiting glucose reabsorption, SGLT2 inhibitors lead to osmotic diuresis and natriuresis. This helps to reduce preload.[8] In addition, this also leads to weight loss, which is an important contributor to improved outcomes in patients with heart failure.

These drugs also improve endothelial function and cause vasodilation. This results in a reduction of afterload.[9,10,11,12] In a post hoc analysis of data from a phase III trial,[9] patients with type 2 diabetes mellitus and hypertension were divided in two cohorts. One cohort was treated with empagliflozin for 12 weeks and the other was treated with the same drug for 24 weeks. In cohort 1, the mean reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 12 weeks was -3.9 mmHg (P < .001) and -1.5 mmHg (P < .001). In cohort 2, SBP reduction was -3.6 mmHg (P < .001) and DBP reduction was -1.3 mmHg (P < .001). The use of empagliflozin was associated with significant (P < .001) reductions in pulse pressure (PP) and mean arterial pressure (MAP) as well.

Similarly, in a pilot study,[12] the diuretic effect of dapagliflozin was compared to hydrochlorothiazide. After 2 days of initiation, the former caused a diuresis of 2000 mL/24hr to the latter's 2100 mL/24hr, almost the same. Dapagliflozin also caused a 4.02% flow mediated dilation of the brachial artery compared to 2.63% with hydrochlorothiazide (P = .02). This trial also showed that dapagliflozin acts as a "glucoretic" compound, essentially causing both glucosuria and free water clearance without interfering with the other urinary electrolytes.

Finally, in the EMPA-REG OUTCOME trial, the use of empagliflozin was associated with a significantly (P = .002) reduced risk of hospitalizations from heart failure.[13]

All these trials show that by decreasing preload and afterload, and by increasing osmotic diuresis and free water clearance, SGLT2

inhibitors have a very favorable effect on reducing hospitalizations for heart failure.

SGLT2 inhibitors can also reduce cardiac fibrosis.[14,15] In a post hoc exploratory analysis,[15] the biomarkers that cause adverse cardiovascular outcomes were found to be attenuated with the use of canagliflozin.

In addition, these drugs can improve myocardial metabolism. This, in turn, improves cardiac efficiency. [16,17] In a Phase III study,[18] the use of canagliflozin was associated with development of plasma ketones including circulating β-hydroxybutyrate. This β-hydroxybutyrate is taken up very avidly by the heart. The fractional extraction of β-hydroxybutyrate by the heart is ~40% compared to that of glucose ~2%.[19] In the overnight fasted state, β-hydroxybutyrate contributes 15% of resting cardiac energy expenditure. Cardiac efficiency is therefore, improved.

Conclusions

Heart failure is a devastating disease which carries considerable morbidity and mortality. Many drugs have improved patient outcomes for this disease but there is still room for more. With the advent of SGLT2 inhibitors, we have a class of drugs that can help control diabetes and also reduce symptoms and hospitalizations from heart failure.

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