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Effectiveness of SGLT2 inhibitors in Patients with Reduced Ejection Fraction Heart Failure without Diabetes

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Abstract

Recent research shows that Sodium-glucose co-transporter 2 (SGLT2) inhibitors have benefits in the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with or without diabetes. SGLT2 inhibitors were initially researched as a class of antihyperglycemic drugs and were approved for the treatment of diabetes, but now they have been showing promising results in the outcome of heart failure in patients without diabetes. The associated benefits have increased interest in the use of these drugs. In particular, three of these drugs (dapagliflozin, canagliflozin, and empagliflozin) showed improvements in the cardiovascular endpoints, hospitalizations, and mortality in heart failure patients with and without diabetes as well as in those with cardiovascular risk factors when added to the current therapies of treatment of HFrEF, such as beta-blockers, Angiotensin-converting enzyme inhibitors (ACEi), Angiotensin receptor blockers (ARBs), Mineralocorticoid receptor antagonist (MRAs), and diuretics. More evidence-based recommendations can help practicing physicians incorporate SGLT2 inhibitors into the current recommended treatment of HFrEF. Hence, we hereby present a case of a patient who showed significant improvement after dapagliflozin was added to his current HF treatment regimen. We also review the evidence, efficacy, safety, and adverse effects of SGLT2 inhibitors.

Introduction

It is common for diabetes and heart failure to occur concomitantly and both conditions increase the risk of having the other when they occur independently. Statistics show a prevalence of 10%-47% of diabetes in heart failure (HF) patients and a prevalence of 9%-22% of heart failure in diabetes patients, and this is higher in older patients over 60 years old **[**1**]**. Having the two conditions together increases the mortality and morbidity rate and frequency of hospitalizations, especially in older patients. When compared to non-diabetic individuals, patients with HF and diabetes have poor prognoses. When a patient has both diabetes and HF, however, HF should be treated first because it has a worse prognosis. Pharmacotherapy of heart failure typically involves the use of a combination of 2 or 3 medications with the goal of relieving symptoms, reducing ventricular remodeling, reducing hospitalization and mortality, and improving survival. The most commonly used medications include beta blockers

(bisoprolol, carvedilol, and metoprolol), Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers (ARBs), vasodilators, diuretics, inotropes, mineralocorticoid receptor antagonists (MRAs), ivabradine and digoxin **[**2**]**. Beta-blockers, ACE inhibitors, and ARBs are effective in HF patients with or without diabetes. They reduce the mortality rate and frequency of hospitalizations. MRAs and ivabradine are equally effective in HF patients with or without diabetes, although with mineralocorticoid receptor antagonists, electrolytes and renal function should be closely monitored to check for hyperkalemia as there is a high chance of diabetic nephropathy comorbidity **[**3**]**. In addition, MRAs are mainly used in heart failure patients with ejection fraction (EF) < 35%. The challenge with treating the two conditions largely comes from some antidiabetic medications, which increase the risk and mortality of hospitalizations in heart failure patients. Metformin can sometimes be used in patients with HF compared to insulin and sulfonylureas. It does not have an increased risk of exacerbation in these patients. However, it is not recommended in patients with an eGFR <30 mL/ min/1.73 m2 or hepatic impairment because of the risk of lactic acidosis **[**4**]**. The dipeptidyl peptidase-4 (DPP-4) inhibitor (saxagliptin) is contraindicated in HF patients as it is associated with increased HF hospitalizations, whereas sitagliptin and linagliptin have a neutral effect **[**5**]**. Thiazolidinediones (glitazones) cause fluid retention and an increased risk of worsening HF and hospitalization; hence they are not recommended in such patients. **[**6**]**. Glucagon-like peptide-1(GLP-1) receptor agonists have no effect on the risk of heart failure hospitalization. Despite the fact that they can reduce the risk of stroke, myocardial infarction (MI), and cardiovascular death in patients with diabetes, they do not reduce the incidence of heart failure. Sulfonylureas and insulin are not preferred treatments in patients with heart failure, and if insulin is to be used, the patients should be monitored for worsening heart failure **[**4**]**. However, in light of all the controversies associated with antidiabetic medications, Sodium-glucose co-transporter 2 (SGLT2 inhibitors) have shown benefits in diabetic and nondiabetic patients with heart failure.

Case Presentation

We are reporting a case of a patient with heart failure with reduced ejection fraction (HFrEF) treated with an SGLT2 inhibitor. A 72-year-old male patient was admitted to our hospital several times for heart failure exacerbations. His medical history includes ischemic cardiomyopathy, heart failure with reduced EF (35%), NYHA III, dyslipidemia, and arterial hypertension stage II. In 2021 he had a myocardial infarction (STEMI). At that time, his left anterior descending artery (LAD) was occluded, and 3 stents were implanted in his LAD. Cardiac ultrasound revealed moderate left ventricular hypertrophy, reduced EF-35%, and akinesia of the apex. Diastolic dysfunction – restrictive type, high

diastolic filling pressure. Moderate mitral regurgitation and severe dilatation of the left atrium (LA vol/BSA -55ml/m2). PASP – 95 mmHg. ECG revealed sinus rhythm, HR – 75', and signs of left ventricular hypertrophy. CBC was normal, creatinine 64mmol/L, GFR- 106.6 mL/min/1.73 m², electrolytes - normal. TSH- 0.82 IU/mL, HbA1c -5,8%. BNP- 1500 pg/mL. His medications included Enalapril 10 mg 2 times a day, Carvedilol 3.125mg 2 times a day, Spironolactone 25mg once a day, CoPlavix 75/100 mg once a day, Torasemide 10 mg with potassium every 3rd day.

Even though he was very compliant with his medications, diet, and exercise program, he was still symptomatic. He had been experiencing symptoms of heart failure. Also, He had marked limitations in his activity due to shortness of breath, even during less-than-ordinary activity, e.g., walking short distances (20—100 m), which was consistent with NYHA III. The patient was not diabetic. We added dapagliflozin 10 mg once a day to his standard medication regimen. Interestingly, he experienced symptomatic improvement and increased exercise tolerance a few weeks later.

Repeated cardiac ultrasound one month later revealed improvement of the cardiac function: moderate hypertrophy of the left ventricle, reduced EF-40%. Diastolic dysfunction – impaired relaxation type, normal diastolic filling pressure. Moderate mitral regurgitation and moderate dilatation of the left atrium (LA vol/BSA -40ml/m2). PASP – 55 mmHg.

Repeated BNP - 670 pg/mL.

Discussion

SGLT2 inhibitors have been shown to decrease mortality rates in patients with diabetes and concomitant Heart Failure. Studies demonstrate reduced glycated hemoglobin, with a low or insignificant risk of hypoglycemia in these patients. They are also heavily preferred due to their consistent body weight profile. Other benefits reported with SGLT2 use are a consistent reduction in Uric acids level and hypertension **[**7**]**. SGLT2 inhibitors have also been shown to reduce the risk of development of the cardio-renal syndrome and cardiac compliance as nonfatal MI, or nonfatal stroke **[**8**]**.

On the other hand, the use of SGLT2-i can be potentially associated with some adverse effects. However, the balance between positive and negative effects is in favor of clinical effectiveness **[**7**]**. Emerging data from post-marketing studies indicate their adverse effects, such as diabetic ketoacidosis, genital and urinary tract infection, cancer, bone fracture, and foot and leg amputation **[**8**]**. Most reported adverse events are genital mycotic infections, while urinary tract infections and events

linked to volume depletion are rather rare. Concern about the risk of ketoacidosis and bone fractures has been recently raised, which deserves caution and further evaluation [9]. However, caution is recommended in fragile elderly patients and patients with chronic kidney disease. An increased risk of genital mycotic infections is observed, but urinary tract infections are rare. Concern about an unexpected risk of euglycemic ketoacidosis has been recently reported. Possible renal protection deserves further attention [10]. Canagliflozin use is likely an important contributing factor in increasing the risk of acute kidney injury [11]. The recent use of sodium-glucose cotransporter 2 (SGLT2) inhibitors has shed light on another possible mechanism of euglycemic DKA. Clinicians may also be misled by the presence of pseudo normoglycemia [12]. Thus, there is a need for a better understanding of the risk profile of SGLT2 inhibitors.

Efficacy and Cardiovascular Outcomes of SGLT2 Inhibitors in the Treatment of HF

The dapagliflozin heart failure study (DAPA-HF) was different from the previous studies we looked at. Here, the primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death [13]. 4744 (only 42% had T2D) with NYHA class II, III, or IV heart failure and an ejection fraction of 40 % or less were randomized to receive either dapagliflozin (at a dose of 10 mg once a day) or placebo in addition to background recommended therapy. The primary outcome occurred in 16.3% in the dapagliflozin group vs 21.2% in the placebo group. 1st worsening of HF events occurred in 10% in the dapagliflozin group vs 13.7% in PBO. CV death occurred in 9.6% with dapagliflozin and 11.5% with PBO. Death from any cause occurred in 11.6% vs. 13.9%, respectively. Findings in those with diabetes were similar to those without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups. In conclusion, among those with HFrEF, the risk of worsening HF or death from CV causes was lower with dapagliflozin, regardless of the presence or absence of diabetes.

Empagliflozin showed the same benefits in patients with HFrEF (NYHA II, III, or IV) with or without diabetes [14]. In the EMPEROR-Reduced trial, a primary outcome event occurred in 19.4% of patients in the empagliflozin group and in 24.7% in the placebo group. The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group. Empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

Conclusion

As SGLT2 inhibitors are already recommended by the European society of cardiology and the American heart association, we intend to use these medications in a larger number of patients with HFrEF who are still symptomatic despite receiving optimal medical treatment for heart failure, regardless of diabetic status. As the studies showed they decrease the rate of heart failure exacerbations and cardiovascular death in patients with HFrEF with or without diabetes. The results of the SGLT2i trials are revolutionizing the treatment of those with heart failure.

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