Advanced Journal of Graduate Research
ISSN:2456-7108
Volume 14, Issue 1, pp. 3-8, January 2024
DOI: https://doi.org/10.21467/ajgr.14.1.3-8

GRADUATE REVIEWS

Utilization of SGLT-2 Inhibitors in Congestive Heart Failure Management

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Article History

Received: 24 January 2023
Revised: 11 September 2023
Accepted: 30 September 2023
Published: 14 October 2023

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Academic Year: 2021-22
Course Level: Master
Course Name: M.S. (Cardiology Elective)
Course year: 2nd Year

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ABSTRACT

Congestive heart failure (CHF) is a progressive condition where the heart cannot pump blood well enough to keep up with volume demand, which results in decreased oxygen perfusion throughout the periphery and vital body organs. This condition affects over six million Americans and is projected to increase by over 46% by the year 2030. By incorporating evidence from research conducted over the past ten years, several studies demonstrate the benefits of sodium-glucose co-transporter (SGLT-2) inhibitors in managing CHF patients. The glucose-lowering medication works to relieve fluid overload by excreting excess glucose and sodium while also increasing vasodilation and reducing cardiac preload. SGLT-2 inhibitors also have an anti-inflammatory effect that decreases epicardial adipose deposition, which relieves oxidative stress on the heart. In addition to the mainstay of medical management for CHF patients, SGLT-2 inhibitors have reduced exacerbations that are often life-threatening and improved overall quality of life by reducing morbidity and mortality.

Keywords: CHF, SGLT-2 Inhibitors, Diabetes Mellitus, Fluid overload

1 Introduction

Congestive heart failure (CHF) is among the most prevalent cardiovascular diseases impacting the United States. With over 6.2 million adults being affected, heart failure costs the American health care system approximately 30.7 billion dollars a year [1]. As more Americans develop risk factors for CHF, the rate of morbidity and mortality on account of heart failure is rising. Some risk factors include diabetes, hypertension, obesity, valvular heart disease, and ischemic myocardial events. With the rise in CHF, medical management has become a popular and developing field of research to prolong the life of these patients. With earlier identification of symptoms, providers can be more proactive in managing their patient's condition and help reduce exacerbations. CHF occurs when the heart cannot sufficiently pump oxygenated blood throughout the body, leading to fluid backup into the vena cava or the pulmonary vasculature.

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Depending on where the cardiac defect is located, patients can present with symptoms such as shortness of breath, difficulty breathing with activity, pleural effusions, peripheral edema, jugular venous distention, and many others. The most useful initial imaging study to assess the size and function of the cardiac chambers is an echocardiogram. With ultrasound imaging, an ejection fraction can be calculated, which demonstrates the percentage of blood leaving the left ventricle each time the heart contracts. It also reveals any valvular defects or cardiac chamber dilations, which will adversely affect the overall heart function. CHF has two sub-categories: systolic and diastolic heart failure. Systolic heart failure, also known as heart failure reduced ejection fraction (HFrEF), is when the ejection fraction is reduced to less than 45%. Diastolic heart failure, also known as heart failure preserved ejection fraction (HFpEF), is when the heart has impaired ventricular filling during diastole with the ejection fraction remaining above 45%. CHF can be classified in stages based on either functional capacity or objective assessment. Accurate staging of heart failure is important because it allows practitioners to optimize treatment to combat symptoms and prevent further cardiac damage. A growing field of research has supported the use of sodium-glucose co-transporter (SGLT-2) inhibitors in reducing morbidity and mortality in CHF patients compared to the mainstay of treatment modalities.

2 Current Standard of CHF Treatment

Once a diagnosis of CHF is made, the next step is tailoring medical management to decrease symptomatic exacerbations and prolong the life of patients. Treatment plans depend on whether patients have systolic or diastolic heart failure. In systolic heart failure, the ventricles are weakened so they cannot squeeze proficiently to produce adequate blood flow throughout the circulatory system. With decreased perfusion, the heart's ejection fraction decreases to a level of less than 45%. The cornerstone of treatment is aimed to decrease ventricular remodeling, decrease afterload, reduce detrimental effects of catecholamine release, and decrease sodium fluid retention. Diastolic heart failure occurs when the ventricles cannot relax due to stiffened thick cardiac tissue. In diastolic heart failure, patients will have a preserved or elevated ejection fraction ranging between 45 and 75%, making blood unable to properly circulate through a noncompliant or hypertrophied ventricle. In diastolic heart failure patients, medical management is tailored to decrease preload, vasodilate for better fluid perfusion, and stabilize rate control. Although management between systolic and diastolic heart failure is generally similar, there are vague guidelines for the use of diuretics in treating heart failure with preserved ejection fraction. Diastolic heart failure patients are more preload dependent, meaning the heart needs sufficient fluid to adequately pump through the ventricles and at a lower preload, there is less to pump. Diuretics may provide symptomatic relief to patients experiencing lung congestion during an acute exacerbation. However, diuretics can cause electrolyte abnormalities, renal stress, and hypotension which in turn will lower preload as well. More importantly, there is no support showing the long-term benefits of diuretic use in patients with diastolic heart failure [2]. Therefore, there is not a unanimous decision on the role of diuretics for HFpEF patients and providers should be cautious with their use of this medication. For both systolic and diastolic heart failure patients, medications that target angiotensin receptors have been the mainstay of management. For example, angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor/neprilysin inhibitors (ARNI) are extremely beneficial for their vasodilatory properties and relief of fluid retention [3]. In recent years, SGLT-2 inhibitors have been introduced in managing heart failure because it reduces arterial stiffness, plasma volume, and systolic blood pressure through its vasodilatory properties. The vasodilatory impact significantly improves mortality outcomes in patients combating heart failure, alone or in conjunction with diabetes [4]. With the success seen in recently developed research, SGLT-2 inhibitors are becoming a top recommendation and a crucial aspect of heart failure management.

3 Mechanism of Action in SGLT-2 Inhibitors

Within the proximal convoluted tubule of the kidneys, sodium-glucose co-transporters are responsible for transporting sodium and glucose across the membrane out of the filtrate into the interstitial fluid where it

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can be reabsorbed into the blood. With normal kidney function, these transporters act to reabsorb glucose and sodium back into the blood to maintain adequate blood plasma volumes. Once a threshold of excess glucose is reached, the proximal tubule does not have the capacity to reabsorb additional glucose, leaving it to be excreted in the urine. SGLT-2 inhibitors act as the name suggests, by preventing the reabsorption of sodium and glucose back into the blood, resulting in more glucose excretion and decreased blood glucose levels. The increase of glucose excretion is beneficial for diabetic patients because it lowers their circulating blood glucose level and hemoglobin A1C level by a minimum of 0.5% within one year [5]. As a secondary effect of SGLT-2 inhibitors, the increased volume excretion leads to a decrease in blood plasma volumes, therefore reducing cardiac afterload and preload stress on the heart. It also increases myocardial oxygen supply by stimulating the renin angiotensin aldosterone system to dilate circulatory vessels and increase endothelial function. All these effects succeed in preserving cardiac function in a way that can prevent and alter the progression of heart failure. Common side effects of this drug class include glucosuria, increased incidence of urinary tract infections, weight loss, dehydration, and low blood pressure. It is important to note the U.S. Food and Drug Administration (FDA) submitted a revision to their original 2015 recommendation for SGLT-2 inhibitor use in diabetic patients. They affirmed ketoacidosis is a serious side effect that can be life-threatening if medical treatment is not provided to correct the metabolic imbalance. There have also been several counts of urosepsis and pyelonephritis secondary to untreated urinary tract infections [6]. It is crucial for providers to tailor their treatment plans to each of their patients to avoid serious side effects that may cause more harm than good. If a patient on a SGLT-2 inhibitor is to undergo surgery, it is recommended they stop their medication at least four days before the scheduled surgery to avoid a ketoacidosis event. It is recommended if a patient is prone to urinary tract infections or has a history of ketoacidosis, to explore other options or heavily monitor their progress if they are placed on a SGLT-2 inhibitor.

4 Benefit of SGLT-2 Inhibitors for CHF Patients

4.1 The Anatomical Explanation of SGLT-2 Inhibitor Benefit for CHF Patients

With the establishment of SGLT-2 inhibitor's mechanism of action for diabetes treatment, more research has been completed to investigate the effects of these medications on the cardiovascular system. As the sodium glucose co-transporters within the proximal tubules are blocked, more sodium and glucose-condensed fluid is excreted through the urine. With decreased blood plasma volume circulating the body, stroke volume and vascular stiffness lessen to reduce damage to the heart. This mechanism not only improves cardiac function, but also relieves the individual's symptoms. Through the diuresis effect of SGLT-2 inhibitors, fluid pressure is taken off the body, relieving symptoms including peripheral edema and cough due to fluid backup into the pulmonary system. It also reduces oxidative stress because it lowers the secretion of inflammatory chemokines, clears adipose tissue located in the epicardium, and decreases cardiac intracellular sodium and calcium levels to prevent remodeling of cardiac tissue [7]. The reduction of oxidative stress of the myocardium helps alter myocardial fibrosis and prevents cardiac tissue remodeling while improving overall cardiac metabolism.

4.2 History of Studies Supporting SGLT-2 Inhibitor Use for Cardiac Patients

To measure outcomes in CHF patients using SGLT-2 inhibitors, studies have recorded CHF related hospitalizations and cardiovascular deaths. In 2015, a study performed on empagliflozin investigated a sample of diabetics with established cardiovascular disease. In three years, there was a reduction in major cardiovascular events, including myocardial infarction and stroke, by 14% in patients on empagliflozin compared to the control sample. There was a reduction in cardiovascular related deaths by 38% and reduction in hospitalizations secondary to CHF exacerbations by 35% [8]. The study was significant because it was the first collection of data performed in diabetic patients that showed major benefits to macrovascular event reduction, especially in patients with reduced ejection fraction. It also demonstrated a reduction in

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death, secondary to end stage renal disease by 39%. Two years later, another study trialed a larger group of diabetic patients with canagliflozin, which revealed similar trends to the previous study. There was a reduction in hospital admissions due to heart failure by 33% when compared to the placebo [9]. A subsequent study in 2019 set out to determine if the same cardiovascular benefits of SGLT-2 inhibitors were seen in patients despite their hemoglobin A1C status and a diagnosis of diabetes. Results found there was the same reduction rates in cardiovascular related hospitalizations and deaths in CHF patients regardless of having diabetes or not [4]. This study was valuable because it demonstrated the ability to treat non-diabetic patients with a glucose-reduction agent for a cardiovascular benefit secondary to its vasodilatory effect and reduction of stroke volume. After a consensus was formed supporting the cardiovascular benefits to SGLT-2 inhibitors, a research paper was published comparing efficacy in heart failure morbidity and mortality between empagliflozin, canagliflozin, and dapagliflozin. Results found there were broadly similar cardiovascular and renal benefits between each SGLT-2 inhibitor, demonstrating the validity of the class without a single medication being immensely superior [10]. Since the results of these major studies have been published, more research has been emerging supporting the original data.

4.3 Current Standard of Care Guidelines for CHF Patients

In 2023, the American Diabetes Association published an updated standard of care incorporating the use of SGLT-2 inhibitors for the use of diabetic patients with heart disease and heart failure. There is an outlined approach recommending the use of SGLT-2 inhibitors for type 2 diabetic patients with cardiovascular disease, heart failure, and/or chronic kidney disease. They caution providers that patients with longstanding diabetes will benefit from SGLT-2 inhibitors, but this class may need to replace another diabetes medication in the treatment regimen to avoid adverse effects and increased costs to the patient [11]. From a purely cardiovascular standpoint, the most recent American Heart Association guideline for heart failure supports the use of SGLT-2 inhibitors for patients with both systolic and diastolic heart failure. It is ranked as a 2a class recommendation for heart failure for patients with a reduced and preserved ejection fraction. This is a profound testimony showing how beneficial this class is because it now has a greater ranking than the previous standard of care, including ACE-I, ANRI, angiotensin II receptor blockers or beta blockers [3]. Specifically, dapagliflozin and empagliflozin are the two SGLT-2 inhibitors recommended by the American Heart Association. This class of medication is recommended for patients with chronic CHF to reduce hospital admissions and cardiovascular mortality.

5 Comparing Systolic and Diastolic Heart Failure Management

An additional point of conversation is whether SGLT-2 inhibitors are equally as beneficial in diastolic heart failure patients as they are in systolic heart failure patients. In diastolic heart failure, adequate preload should be maintained so fluid can pump through a thickened ventricle to avoid decreased cardiac output. A decrease in fluid volume is beneficial in patients with systolic heart failure to relieve fluid overload symptoms. In diastolic heart failure patients, fluid volumes need to be preserved so blood can adequately pump through thickened ventricles. The addition of a medication that relieves fluid overload in diastolic heart failure patients raises the concern for hypotension. A 2022 study proposed that SGLT-2 inhibitors help diminish epicardial fat accumulation, reduce inflammation, and increase secretion of adipokines, which contribute to the inflammatory disease process of heart failure [7]. These factors are especially prevalent when heart failure involves a high left ventricular ejection fraction, demonstrating their protective mechanism for patients with diastolic heart failure. A randomized trial of hospitalized patients with HFpEF found that administration of sotagliflozin before hospital discharge led to a significantly lower number of cardiovascular related deaths and additional hospital readmissions compared to the placebo [12]. An additional study published by the New England Journal of Medicine compared the use of dapagliflozin in patients with HFpEF and HFrEF. Results showed a similar benefit to heart failure patients using a SGLT-2 inhibitor despite an ejection fraction being above or below 60%. Both sample sizes had a decrease in symptomatic exacerbations and cardiovascular related deaths compared to the placebo group [13]. The

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value of the study shows that SGLT-2 inhibitors are equally effective in patients with heart failure regardless of their ejection fraction status. Although the pathophysiology of systolic and diastolic heart failure is different, SGLT-2 inhibitors appear to be cardioprotective and decrease mortality in both settings. Based on these findings, it will be simpler for health care providers to manage their patient's exacerbations and long-term treatment plans. As a result, patients with heart failure will receive equally beneficial care, despite their sub-class heart failure status.

6 Conclusion

Over the past ten years, there have been major advances in demonstrating the superior outcomes of SGLT-2 inhibitors in patients with congestive heart failure. The standard of care is moving towards SGLT-2 inhibitors in any patient with heart disease, despite hemoglobin A1C level. It is even more popular in patients with reduced ejection fraction and/or chronic kidney disease. Compared to the mainstay of treatment, which includes ACE-I, ANRI, beta blockers, and diuretics, the addition of SGLT-2 inhibitors reduces rates of hospital admissions and cardiac related deaths. Future studies should be performed exclusively in non-diabetic patients with CHF to expand on SGLT-2 inhibitor usage for its cardioprotective mechanism. Additional research can be geared toward investigating the cardiovascular benefit of other diabetes medications for managing heart failure. For example, glucagon-like peptide-1 agonists have been an exploding topic of research in recent years for many reasons. Outcomes in patients using SGLT-2 inhibitors not only lead to longer life expectancy, but also reduce frequency in symptomatic exacerbations and macrovascular events such as myocardial infarction and stroke. Beside the clear benefit to this specific patient demographic, there is an immense relief of hospital resources secondary to the reduction of frequent interventions of cardiac episodes. It is an exciting field that will continue to expand and greatly benefit the CHF community.

7 Declarations

7.1 Study Limitations

Most of the available literature studies the effects of SGLT-2 inhibitors on patients with both CHF and diabetes mellitus. Additional literature should be published focused on a patient population with CHF alone without a diagnosis of diabetes mellitus.

7.2 Competing Interests

The authors declared that no conflict of interests exist in this work.

7.3 Publisher's Note

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How to Cite this Article:

A. Daniels and D. Bank, "Utilization of SGLT-2 Inhibitors in Congestive Heart Failure Management", *Adv. J. Grad. Res.*, vol. 14, no. 1, pp. 3–8, Oct. 2023. https://doi.org/10.21467/ajgr.14.1.3-8

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