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Dapagliflozin: mechanism and safety in heart failure patients: A review

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ABSTRACT

Dapagliflozin, a specific inhibitor of sodium-glucose co transporter 2 (SGLT2), prevents the kidney's proximal tubule from reabsorbing glucose and increases glucosuria. Dapagliflozin lowers renal glucose reabsorption by blocking the transporter protein SGLT2 in the kidneys, which causes urine glucose excretion and a drop in blood glucose levels. Dapagliflozin's effectiveness is independent of insulin secretion and action, in contrast to oral antidiabetic medications from numerous other groups. Inhibiting sodium-glucose cotransporter 2 (SGLT2) has recently become a key treatment approach for lowering cardiovascular risk in Type 2 DM. The probability of heart failure (HF) hospitalization has been found to be decreased by sodium-glucose co-transporter 2 (SGLT2) inhibitors in extensive clinical trials in individuals with type 2 diabetes who are at high cardiovascular risk. This favorable outcome was seen quickly after randomization, pointing to a mechanism or mechanisms of action distinct from those often taken into account with traditional glucose-lowering treatments.

KEYWORDS- Dapagliflozin, Heart Failure, SGLT2 Inhibitors, Diabetes Mellitus.

INTRODUCTION

Congestive heart failure, often known as heart failure, is a condition where the heart muscle is unable to pump blood as efficiently as it should. Shortness of breath is frequently brought on by this because blood frequently backs up and fluid can accumulate in the lungs. The heart eventually becomes too weak or stiff to fill and pump blood adequately as a result of some heart disorders, such as coronary artery disease (coronary artery

disease) or excessive blood pressure (Heart.org). Heart failure with reduced left ventricular (LV) ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) have been identified as the two primary forms of heart failure since measures of left ventricular function were available (HFpEF). The clinical profile and symptomology of the two disorders are comparable. However, women are more likely to have HFpEF, and hypertension is more frequently present in the background. Most clinical investigations on therapies for HFrEF have employed an EF of 35–40% as an upper cut off. HFrEF is frequently described as an LV ejection fraction 40%. The cause is that as LVEF falls, morbidity and death rise. An LVEF > 40–50% has been used to define HFpEF[15]. Large-scale clinical studies involving people with type 2 diabetes have demonstrated that sodium-glucose cotransporter 2 (SGLT2) inhibitors lower the likelihood of being admitted to the hospital for heart failure. 1-4.The advantage of treatment with an SGLT2 inhibitor mainly represented the prevention of incident heart failure in these studies because the majority of patients did not have heart failure at baseline[4]. Inhibiting sodium-glucose cotransporter 2 (SGLT2) has recently gained prominence as a key treatment approach for lowering cardiovascular risk in T2DM. Individuals with HFrEF had a lower risk of cardiovascular mortality or HHF thanks to SGLT2 inhibition with dapagliflozin than patients without HFrEF. Large decreases in cardiovascular death and ACM in individuals with HFrEF were the primary cause of this difference.[14]

Dapagliflozin mechanism in heart failure

Digoxin, β blockers, RAAS inhibitors, angiotensin receptor-neprilysin inhibitors, diuretics, and other medications to decrease neurohormones, lessen volume overload, and enhance cardiac contractility are currently the standards of care for patients with HFrEF. Conventional diuretics do not reduce mortality in HF patients; they merely relieve symptoms[12] Specific processes for outcomes related to CV benefit have not yet been fully identified, but a number of plausible mechanisms have been hypothesized. Among these include improvements in myocardial metabolism, decreased preload and afterload (leading to improved ventricular loading), and changes in cardiac fibrosis. The sodium proton channel (NHE) in the cardiac myocytes has been demonstrated to be inhibited by SGLT2 inhibitors, which ultimately results in a decrease in intracellular calcium and the mitochondria-induced cellular damage at the core of myocardial remodeling. The SGLT2 inhibitors have been shown to have anti-inflammatory action in animal models, in addition to glucosuria by directly inhibiting glucose reabsorption in the proximal convoluted tubules. A drop in intraglomerular pressure, in turn, results in a reduction in glomerular filtration and tubular hypertrophy when SGLT2 channels are blocked. Afferent vasoconstriction, which is mediated by direct action, amplifies this effect further.[13]. Inhibition of SGLT2 improves subendocardial blood flow in HF patients by promoting natriuresis and osmotic diuresis, which reduces preload, and contracts plasma volume as well as blood pressure, arterial stiffness, and

afterload. Renal function preservation is also linked to SGLT2 inhibition. [12] In DEFINE-HF study it was reported that dapagliflozin did not substantially affect mean LFV; however, after 12 weeks of treatment, a considerably higher percentage of dapagliflozin-treated patients showed improvement in LFV and a significantly lower percentage showed no change or worsening in LFV. According to a theory, SGLT2 inhibitors are more effective at reducing interstitial fluid than traditional loop diuretics, which leads to congestion relief with little effect on blood volume. Osmotic diuresis is the process by which more fluid is cleared from the interstitial fluid space than from the circulating blood volume[9].

Dapagliflozin in patients with reduced ejection fraction

Heart failure patients with LVEF > 40% (HFpEF and HFmrEF) are a sizable patient population with significant unmet medical needs and no clear guideline-directed management. The first medications that are not neurohormonal modulators, SGLT2 inhibitors are being investigated for heart failure with LVEF > 40%. Due to this, this class of agents may be more effective and safe than those that have already been subjected to testing. Patients with higher LVEF may experience more hypotension and experience less benefit from peripheral vasodilatation compared to those with HFrEF, when vasodilator-type medications are obviously beneficial. SGLT2 inhibitors have been demonstrated to decrease obesity, attenuate epicardial fat accumulation or its release of harmful adipokines, improve endothelial function, and lower inflammation—mechanistic factors that are particularly connected to heart failure in the presence of higher LVEF. They also have been shown to improve diastolic function in patients with diabetes and LVEF 50%. In fact, we did not notice any heterogeneity in the therapeutic response to dapagliflozin based on LVEF in patients with HFrEF, and more recent results from SCORED and SOLOIST-WHF indicate that sotagliflozin medication was beneficial for recently admitted patients with HFpEF [11]. One study reported that risk of the primary composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes was lower in the dapagliflozin group than in the placebo group in a randomized, placebo-controlled trial involving patients with heart failure and a reduced left ventricular ejection fraction. The total number of heart failure hospitalizations and deaths from cardiovascular causes were both lower in the dapagliflozin group as well as each of the three components of the composite outcome. The Kansas City Cardiomyopathy Questionnaire revealed that dapagliflozin usage also reduced heart failure symptoms [4] High BMI raises the chance of non-fatal outcomes and, to a lesser extent, the risk of mortality. Patients with class II/III obesity had the greatest event rates for the primary composite outcome, and the same was true for HF episodes that worsened. Additionally, in DAPA-HF, patients with class II/III obesity had

poorer symptoms, with an average KCCQ-TSS score that was significantly lower than that of patients in the normal/underweight category (17 points lower on average). Obese HFrEF patients have poorer symptoms, a higher probability of hospitalisation for worsening HF, and are more likely to develop diabetes and other health issues such atrial fibrillation and obstructive sleep apnea [10]

Safety of Dapagliflozin in heart failure patients

In one of the study it was reported that dapagliflozin added to other therapies recommended by guidelines decreased the risk of mortality and heart failure hospitalization and improved symptoms in patients with heart failure and reduced ejection fraction in the placebo-controlled DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure). The efficacy and safety of dapagliflozin were consistent across the age range of the study [7]. Patients with an ischemic aetiology had a higher risk of cardiovascular death and all-cause death than patients with a non-ischaemic aetiology, but their risk of hospitalisation for HF was reduced. Dapagliflozin also reduced the risk of worsening HF episodes, cardiovascular death, and all-cause death and improved symptoms to a similar level in individuals with and without an ischemic aetiology when combined to traditional guideline-recommended treatments[5]. One of the study reported that apagliflozin's overall safety profile was equivalent to the placebo group's, with both patient groups experiencing adverse events at roughly the same rates. Although renal adverse events (AEs) were more frequent in the dapagliflozin group, a greater percentage of patients using dapagliflozin moved into a better UACR category. However, it is still unclear what these alterations mean clinically. Given that patients with HF are frequently volume overloaded at baseline, the same frequency of AEs of volume reduction seen in both treatment groups suggests that these patients may be less likely to encounter hypovolemia adverse effects.[2] Another study reported that across the wide range of baseline SBP examined in DAPA-HF, dapagliflozin lowered the risk of mortality and worsening heart failure and improved symptoms. Even in patients with SBP 110 mmHg, there was no appreciable difference between dapagliflozin and placebo in terms of adverse events or treatment discontinuation.[1]

Conclusion

Dapagliflozin is overall beneficial in reducing the cardiovascular death and hospitalization in patients with heart failure. The beneficial effects of this SGLT2 inhibitor in patients were more convenient than those of traditional medication interventional treatments. It was also found that dapagliflozin in safe and effective in patients with or without cardiovascular disease. Dapagliflozin is relatively safer in patients with renal failure as compared to other drugs, however more studies and research needs to be done to establish these facts.

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