



Early Initiation of SGLT2 Inhibitor is Important Irrespective of Ejection Fraction

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Introduction

Sodium Glucose Cotransporter inhibitor (SGLT_i) has revolutionized the medical management of heart failure in the last decade. This molecule was initially described as a glucose-lowering agent but now it has been recommended in patients with chronic heart failure irrespective of ejection fraction and diabetic status. SGLT₂ inhibitor reduces preload by natriuresis and diuresis, reduces afterload, decreases pulmonary artery pressure, improves myocardial energetics, and decreases myocardial fibrosis. It also reduces NT-pro BNP levels in heart failure patients, decreases serum uric acid, and promotes weight loss. It has also been proposed that this molecule has a favorable effect on vascular remodeling. SGLT-2i improves cardiac output and attenuates maladaptive cardiac remodeling, chronic inflammation, oxidative stress, and endothelial dysfunction (ED) by restoring the activity of nitric oxide (NO) within the vascular endothelium. As was foreseeable this molecule became one of the foundation pillars in the management of heart failure with reduced as well as preserved ejection fraction. SGLT₂i also has a reno-protective effect, particularly in patients with heart failure and diabetes.

Evidence with SGLT2 inhibitor in Heart failure with preserved ejection fraction (HFpEF)

DELIVER TRIAL has evaluated the effect of dapagliflozin on total (first and recurrent) heart failure events in patients with heart failure having preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF). A total of 6263 patients with LVEF of more than 40 %, NYHA Class II-IV, and high NT-pro BNP (>300pg/ml in sinus rhythm and > 600pg/ml in patients with atrial fibrillation) were included over the total study period of two years. Dapagliflozin 10 mg was compared to placebo. In patients with HFmrEF and HFpEF, dapagliflozin reduced the risk of total heart failure events and heart failure-related hospital admissions.⁽¹⁾

EMPEROR PRESERVED trial has shown that Empagliflozin has reduced the combined risk of cardiovascular death and hospitalization in patients with HFpEF regardless of their diabetic status. It was a double-blinded randomized control trial with 5988 patients of LVEF more than 40% and NYHA class II-IV. Empagliflozin 10 mg was compared to placebo. In the 26-month follow up there is a lower risk of hospitalization for heart failure in the Empagliflozin group. Hypotension and uncomplicated genital tract infections were more common in the Empagliflozin group.⁽²⁾

Evidence with SGLT2 inhibitor in Heart failure with reduced ejection fraction (HFrEF)

EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) study and the **DAPA-HF** (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial demonstrated that SGLT2 inhibitors improve cardiovascular outcomes in patients with HF with reduced ejection fraction, regardless of diabetic status.^{(3), (4)}

Effect of SGLT2 inhibitor in acute heart failure

The **EMPULSE** trial showed that Empagliflozin was beneficial in reducing adverse events among patients with acute decompensated heart failure (ADHF). In this trial, 530 patients with ADHF were randomized to Empagliflozin (n= 265) 10 mg once daily versus placebo (n= 265). Patients with a systolic blood pressure of more than 100 mm Hg, no intravenous diuretics or inotropes, and elevated NT- pro BNP level > 1600 pg/ml were included in this study. Median LVEF was 31%. At 90 days follow-up Empagliflozin was associated with significant clinical benefit. There was more weight loss (decongestion), improved quality of life, and fewer deaths in the Empagliflozin arm.⁽⁵⁾

Effect of SGLT2 inhibitor on Post-ACS patients

The **EMMY** trial showed that acute administration of Empagliflozin 10 mg is superior to placebo in reducing NT-pro BNP levels at 26 weeks in patients with myocardial infarction. This is a small study with a sample size of 476. AMI patients with elevated creatine kinase (>800U/L) and troponin (more than 10 times of upper normal limit) were enrolled. Only 13 % were diabetic population.⁽⁶⁾

Effect of SGLT2 Inhibitors on Kidney

SGLT2 inhibitors decrease glycosylated haemoglobin levels and have shown favourable effects on the kidney in large clinical trials involving patients with type 2 diabetes.⁽⁷⁾ The **CREDESCENCE**

(Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial showed that long-term administration of Canagliflozin conferred renal and cardiovascular protection in patients with type 2 diabetes with chronic kidney disease.⁽⁸⁾ In the **EMPA-REG OUTCOME** trial Empagliflozin was associated with favourable renal outcomes in diabetic patients with stage 2 and 3 CKD.⁽⁹⁾ Recently Dapagliflozin was also evaluated in patients with chronic kidney disease (CKD) in the **DAPA-CKD** trial.⁽¹⁰⁾ 4304 participants with an estimated glomerular filtration rate (eGFR) of 25 to 75 ml per minute per 1.73 m² of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. In this trial irrespective of the diabetic status of the patient composite of primary outcome was lower in the Dapagliflozin arm compared to the placebo. Osmotic diuresis and natriuresis are the proposed mechanisms. One possible mechanism for the protective effects of SGLT-2 inhibitor therapy might be the activation of tubulo-glomerular feedback by increased outflow of sodium, chloride, and glucose to distal parts of the nephron, including the macula densa. Subsequently, there is afferent arteriolar constriction and reduction of intraglomerular pressure.

Effect of SGLT2 inhibitor on myocardial remodeling

Dapagliflozin reduces extracellular free water (ECF) volume in diabetic patients with HFpEF. In contrast to classical diuretics, which affect blood plasma volume, SGLT-2i efficiently lowers edema by reducing pathological HF-related sodium retention and interstitial fluid volume. Studies have shown that a reduction in ECF volume is

evident by cardiac MRI (T1 mapping)⁽¹¹⁾. Effect of the SGLT2 inhibitor Empagliflozin on tissue sodium content, assessed non-invasively by Na-MRI, in euvolemic patients with CHF under stable conditions has been seen in a randomized clinical trial. Empagliflozin can reduce skin sodium content as well as bone marrow sodium content in patients with stable CHF compared to baseline as well as to placebo after 1 and 3 months of treatment.⁽¹²⁾

Adverse Effects

SGLT2 inhibitors are generally well tolerated. Hypotension is the most common adverse effect although generally, it is not severe. The risk of genital infection, urinary tract infection, Fournier's gangrene, and pyelonephritis is present. SGLT2 inhibitors can sometimes lead to euglycemic diabetic ketoacidosis (DKA). Canagliflozin was associated with an increased risk of limb amputation.

Guideline

As per the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, SGLT2 inhibitors have Class I A recommendations for chronic heart failure with LVEF less than 40% (HFrEF). In symptomatic chronic heart failure, this molecule provides intermediate economic values. The guideline recommends (Class of Recommendation 2a) that SGLT2 inhibitors "can be beneficial in decreasing HF hospitalizations and cardiovascular mortality" in patients with HFpEF (LVEF \geq 50%).⁽¹³⁾

Early initiation of SGLT2 inhibitors is preferable in every patient with HFrEF along with RAAS blocker, Beta-blocker, and mineralocorticoid antagonist. Every patient with chronic heart failure with LVEF of less than 40% should have all these four pillars of therapy before hospital discharge unless contraindicated. The dose can be titrated every 1-2 weeks during follow-up. SGLT2 inhibitors are practically hemodynamically neutral so the chance of symptomatic hypotension is low.

As per 2021 ESC guidelines, Dapagliflozin or Empagliflozin are recommended (Class 1 A), along with an ACE-I/ARNI, a beta-blocker, and an MRA, for patients with HFrEF irrespective of diabetes status to reduce heart failure hospitalization and CV death.⁽¹⁴⁾ As per the 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, SGLT2 inhibitors are recommended (Class 1 A) for patients with HFmrEF and HFpEF irrespective of diabetes status to reduce heart failure hospitalization and CV death.⁽¹⁵⁾

Conclusion

SGLT2 inhibitors have altered the landscape of treatment options in patients with heart failure with preserved as well as reduced ejection fraction irrespective of diabetic status. This molecule was initially introduced as an anti-diabetic agent but now it has established its role as essential medical therapy for heart failure. Numerous cardiovascular outcome trials (CVOT) have shown that they can reduce heart failure hospitalization, improve quality of life, and reduce cardiovascular morbidity and mortality. Sufficient data exist to support the incorporation of this ground-breaking therapy to enhance patient outcomes. Strategies to promote patient accessibility to this molecule should be considered a priority.

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