

Review Article

Role of SGLT2 Inhibitors in Heart Failure

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Abstract

Sodium-glucose co-transporter 2 (SGLT2) inhibitors belong to a new class of anti-diabetic medications that decrease blood glucose levels by increased urinary glucose excretion, along with increased sodium excretion (natriuresis) and diuresis. We reviewed current clinical and animal studies to evaluate the effects of SGLT2 inhibitors in patient with heart failure and unfolded the numerous important positive roles that

SGLT2 inhibitors play to decrease heart-failure related hospitalization, heart-failure related mortality, to prevent new-onset cardiac failure and to improve cardiac failure with normal ejection fraction. US Food and Drug Administration (FDA) has recently approved dapagliflozin (a SGLT2 inhibitor) to treat patients with heart failure.

Keywords: Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors; Dapagliflozin; Empagliflozin; Heart Failure; Diabetes Mellitus

1. Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of anti-diabetic medications that decrease blood glucose levels by increased urinary glucose excretion, with complementary diuresis and natriuresis [1]. These are one of the few anti-diabetic medications which act through insulin-independent mechanism. Heart failure (HF) is a clinical syndrome result from a structural or functional cardiac disorder that impairs the ability of pumping blood to the body [2]. There is a high prevalence of HF amongst United States population with 6.6 million peoples having HF and it is forecasted to reach 8.5 million by the end of next decade [3]. We reviewed current studies and found that SGLT2 inhibitors play a critical role in heart failure.

2. Discussion

2.1 Decrease heart failure related hospitalization

Recent studies have shown that SGLT2 inhibitors can significantly lower the rates of hospitalization of heart failure. EMPA-REG investigations conducted by Zinman B, et al [4]. revealed that the rates of hospitalization for heart failure were quite lower in the empagliflozin group in comparison to placebo group (2.7% versus 4.1%; 35% relative risk reduction). Canagliflozin was also reported to reduce the hospitalization of heart failure from 8.7%₀ to 5.5%₀(Hazard ratio 0.67) form CANVAS trial [5]. Similarly, dapagliflozin also reduced hospitalization of heart failure (hazard ratio 0.73, 95% CI, 0.61-0.88) from the DECLARE-TIMI study [6]. In a meta-analysis by Zelniker TA, et al, [7] it was concluded that a 23% reduction in the risk of hospitalization occurs with

SGLT2 inhibitors and with similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of heart failure. In the CVD-REAL study, use of SGLT2 inhibitors, versus other glucose-lowering drugs, was also associated with lower rates of HHF (hazard ratio, 0.61; 95% confidence interval, 0.51-0.73; P<0.001) [8]. In addition, Milton Packer analyzed that the benefits of SGLT2 inhibitors in heart failure and a reduced ejection fraction were not influenced by background therapy and has an independent beneficial effect in reducing heart failure related mortality [9].

2.2 Decrease heart failure related mortality

Bassi NS, et al. [10] used published sources to estimate the US population of patients with HF_rEF eligible for SGLT2-inhibitor's therapy and the numbers needed to treat, to prevent or postpone overt death. They found that optimal implementation of SGLT2 inhibitors therapy was empirically estimated to prevent up to 34,125 deaths per year (range 21840-49140 deaths per year). Thus with the optimum use of SGLT2 inhibitors, a large number of deaths could be prevented. The CVD-REALU study [8] also revealed that the use of SGLT2 inhibitors, versus other glucose-lowering drugs, was associated with lower rates of death (hazard ratio, 0.49; 95% confidence interval, 0.41-0.57; P<0.001) and heart-failure related hospitalization or death (hazard ratio, 0.54; 95% confidence interval, 0.48-0.60; P<0.001) with no significant heterogeneity by country. McMurray JJV, et al. [11] reported that the all-cause mortality rate was significantly reduced with dapagliflozin compared to the placebo (11.6 versus 13.9 percent; hazard ratio, 0.83; 95% CI 0.71-0.97) and death from cardiovascular causes was also significantly reduced with dapagliflozin (9.6 versus 11.5 percent; HR 0.82; 95% CI 0.69-0.98).

2.3 Heart failure prevention

Overall studies implicated that SGLT2 inhibitors could effectively attenuate left ventricular remodeling and prevent the new-onset heart failure. Pre-specified secondary analysis of Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOM) showed that empagliflozin reduced new-onset HF and hospitalization with HF [12]. Empagliflozin showed positive impact with reduction in cardiac hypertrophy and fibrosis in a rat metabolic syndrome model with pre-diabetes [13]. In the EMPA-HEART CardioLink-6 study, Verma S, et al. [14] found an improvement in left ventricular ejection fraction with a reduction in cardiac hypertrophy (measured as cardiac mass) with empagliflozin treatment. Yurista SR, et al. [15] reported an improvement in cardiac function after myocardial infarction (MI) with left ventricular dysfunction in non-diabetic rats after the use of of empagliflozin.

2.4 Diastolic function improvement

Concurrent studies have demonstrated the role of the SGLT2 inhibitors for the prevention and management of heart failure with preserved ejection fraction, for which no current treatments have demonstrated any impact to reduce mortality. From a study including 42 patients with type 2 diabetes mellitus, Otagaki M, et al. [16] found that addition of tofogliflozin in patients with type 2 diabetes mellitus had a positive impact on left ventricular systolic and diastolic function. Chrysant SG, et al. [17] also demonstrated that SGLT2 inhibitors (because they cause natriuresis and diuresis) could be a good choice to treat patients with HFpEF alone or in combination with diuretics and other drugs. Kolijin D, et al. [18] reported that acute empagliflozin in human and rat HFpEF myocardium reduces inflammatory/oxidative stress and improves the NO-

sGC-cGMP-cascade and PKGI α activity via reduced PKGI α oxidation. Consequently, leading to improved cardiomyocyte function via PKGI α and its concomitant anti-oxidative effect. Cappetta D, et al. [19] also found that dapagliflozin improves diastolic function and exerts a positive effect on the myocardium, possibly targeting coronary endothelium. Empagliflozin therapy is also reported to improve cardiac function (both systolic and diastolic) in experimental myocardial infarction in rat as compared to vehicle therapy ($p < 0.05$). Moreover, the animals treated only with vehicle had hypertrophy of myocytes along with cardiac fibrosis [20].

3. Conclusion

Given the aforementioned literature, the role of SGLT2 inhibitors in decreasing heart failure related hospitalization; decreasing heart failure related deaths; preventing of new onset heart failure and improving heart failure with preserved ejection fraction, has become quite obvious. Acknowledging the clinical trials' results depicting the benefits of SGLT2 inhibitors in heart failure US Food and Drug Administration (FDA) has recently approved Dapagliflozin for patients with heart failure [21]. The additional benefit of this drug is that it has been prescribed in patient with Diabetes Mellitus for years with high efficacy and minimal side effects like urinary tract infections.

Conflict of Interest

Authors declare no conflict of interest.

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