Heart Science and Heart Surgery Journal

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Mini Review *Volume 4 Issue 1*

Sodium-Glucose Co-Transporter 2 Inhibitor in Acute Heart Failure: *The Booster* of Decongestive Therapy?

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Received Date: May 26, 2022; **Published Date:** June 17, 2022

Abstract

The sodium-glucose cotransporter 2 (SGLT2) inhibitors (dapaglifozin and empaglifozin) have recently established to reduce the risk of cardiovascular death or worsening heart failure (HF) in patients with chronic HF. As heart failure is the burden in hospitalization, this disease is associated with high mortality, mobidity, and decreased quality of life, especially older age with acute heart failure (AHF). Two cornerstones of therapies in AHF are decongestive therapy and optimizing early initiation of chronic heart failure treatment. In several studies, empaglifozin seems to be beneficial in improving clinical outcome of patients with AHF. However, SGLT2 inibitors are not licensed in this setting. The close interaction between type 2 diabetes mellitus (T2DM) and AHF is providing the intriguing mechanisms of SGLT2 inhibitors for improving diuresis and natriuresis without interfering renin-angiotensin-aldosteron system. There are various trials have been ongoing for answering this big question.

Keywords: SGLT2 Inhibitors; Empaglifozin; Dapaglifozin; Acute Heart Failure

Abbreviations: SGLT2: Sodium-Glucose Cotransporter 2; HF: Heart Failure; AHF: Acute Heart Failure; T2DM: Type 2 Diabetes Mellitus; HFrEF: Heart Failure Reduced Ejection Fraction; SGLT2: Sodium-Glucose Cotransporter 2.

Introduction

Heart failure is the global burden and remains the critical problem of public health. There were more than 50 million people worldwide affected with this disease. The prognosis of patients with heart failure is still poor even though the are significant advances of medical treatment in heart failure [1]. Heart failure is the most common cause of rehospitalization in older patients [2]. The more increase of the prevalence of type 2 diabetes mellitus (T2DM), the more susceptible individuals to developing heart failure. T2DM is known as one of independent factor of mortality and morbiditiy of patients with heart failure [3,4]. The interesting statement was reported by Gunha, et al. [5] patients with T2DM had increased the needs of furosemide dose at admission by 24% and at discharge by 26% in the setting of acute heart failure (AHF). This study revealed that two-thirds of subjects with heart failure reduced ejection fraction (HFrEF) had history of uncontrolled T2DM and hypertension. In line with the previous statement, the higher mortality and morbidity of patients with T2DM in AHF is closely associated with diuretic resistance and unmet diuretic response [6,7].

More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors, empaglifozin and dapaglifozin, have been established to diminish the risk of cardiovascular death or hospitalization for chronic HFrEF. Moreover, empaglifozin

has similar clinical outcome in patients with chronic heart failure with preserved ejection fraction (HFpEF). Another agent, sotaglifozin, SGLT 1/2 inhibitor, could improve the clinical outcomes in patients with worsening heart failure and T2DM [8]. If the SGLT2 inhibitors allow the clinical benefit in the setting of AHF was unclear. The two fundamental therapies of AHF are decongestive treatment with diuretics and guideline-directed medical therapies of chronic heart failure during hospitalization period.

SLGT2 inhibitors are new agent of glucose-lowering therapy. They block SGLT2 protein located in the proximal convoluted tubule of the nephron. This protein induces the resorption of most 90% filtered glucose and the rest is controlled by SGLT1 protein. SGLT2 is blocking results in natriuresis and glycosuria allowing controlling plasma glucose concentrations [9]. This agent has special properties compared with other glucose-lowering agents since it does not interrupt with hormonal pathways (insulin, incretin). Moreover, SGLT2 inhibitor could improve cardiac energetics and metabolic pathways (kidney, vasculature, sympathetic nerve) to decrease the severity of heart failure.[1]

Mostly, patients with AHF come with presentation of volume overload (clinical congestion) while the worse condition with abrupt onset is commonly found in individuals with a significant rise in left ventricular filling pressure, yet volume overload is mild degree (fluid redistribution, hemodynamic congestion). Cox, et al. [10], in their study, DICTATE-AHF trial, stated that SGLT2 inhibitors have potential benefits for improving decongestive with several cautions (Table 1). The synergistic mechanism with loop diuretics improves natriuresis without interfering renin-angiotensin-aldosterone system. The improvement clinical outcomes of AHF are associated with increasing urine sodium production. This combined mechanism may confer additional benefits while eluding the interactions between electrolyte disturbances and neurohormonal activation [10,11].

Benefits	Risks
Cardiac	
Enhanced natriuresis The need of loop diuretic dose is declined and switched earlier to oral regimen	Induce hypovolemic and hypotension risk (concomitant with iv loop diuretics)
Diabetic	
Less hypoglycemia risk than insulin	Diabetic ketoacidosis
Cardiometabolic	
Optimize chronically beneficial therapy during hospitalization	Urinary tract infection or fungal risk

Table 1: Benefits and risk of SGLT2 inhibitor initiation in AHF.

Furthermore, there are various studies that are aimed at offering the benefits of SGLT inhibitors in cardiac remodelling and biomarkers related to improvement of chronic heart failure (primary study: DAPA-HF/dapaglifozin and EMPEROR/empaglifozin [NCT03057977; NCT03057951]). However, there is a lack of data for use in the setting of AHF. The DICTATE-HF study is currently involving patients with decompensated HF admitted to hospital requiring intravenous loop diuretics to see the change of the body weight with the addition of dapaglifozin to standard diuretic agent. This trial includes all ejection fractions with T2DM (NCT04298229). DICTATE-AHF focuses on early initiation within 24 hours of AHF hospitalization [10]. As the continuum of acute HF, the are several trials investigating across the AHF episodes (Figure 1). DICTATE-AHF reinforces the recent trial from EMPA-RESPONSE. This trial was a blinded pilot study, randomized proposing empaglifozin use in 80 hospitalized patients with AHF. It revealed that there was no difference in the primary endpoints of diuretic response, dyspnea, length of stay, or natriuretic response level during hospitalization between placebo or empaglifozin. Yet, this pilot study was seemed to be lack of closed diuretic protocol [12].

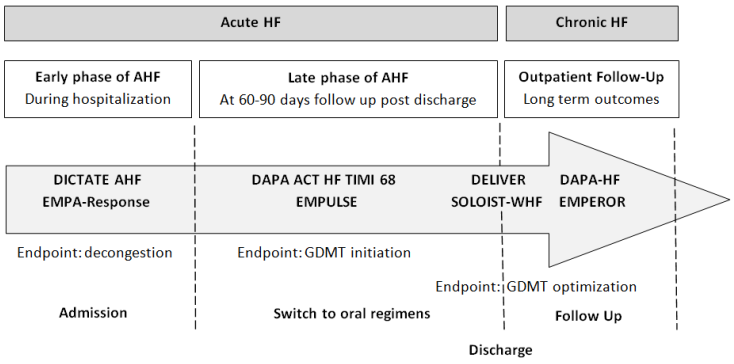

Figure 1: The continuum study of SGLT2 inhibitors in heart failure.

The next phase of AHF has been investigated by EMPULSE (NCT04157751) and DAPA ACT HF TIMI 68 (NCT04363697) trials. Both of trials focused on delayed initiation of SGLT2 inhibitors after stabilization to evaluate 60 to 90-day post discharge clinical outcomes [8,10]. EMPULSE trial was double-blinded, randomized investigating 530 patients with acute decompensated chronic heart failure regardless of ejection fraction receiving empaglifozin 10 mg od or placebo. This study revealed that initiation of empaglifozin had statistically significant of clinical benefits in the 90 days follow-up. The health condition related to Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) showed significantly higher at 90 days follow-up in the empaglifozin group (95%CI: 33.3-39.1) than in the placebo group (95%CI 28.8-34.7). The result of primary endpoints consistently revealed in all subgroups (AHF status, diabetes, sociodemographics, N-terminal pro-brain natriuretic peptide (NT-proBNP) level, renal function, ejection fraction, and atrial fibrillation). Empaglifozin could improve haemodynamically at 30 days follow-up related to a lower reduction in NT-proBNP level (95%CI: 0.82-0.98) [8]. DAPA ACT HF TIMI 68 is currently involving 2400 individuals to evaluate the primary outcomes of cardiovascular death and worsening heart failure at day 60 in the between dapaglifozin and placebo group. As the completion of study, the continuing studies have been delivered by SOLOIST-WHF (NCT03521934) and DELIVER (NCT03619213) including patients either after resolving AHF episode or in the outpatient setting [10].

All those ongoing studies will inevitably answer whether SGLT2 inhibitors can diminish diuretic dose or increase diuretic response in patients with AHF regardless of diabetic status. Hallow, et al. [13]. could demonstrate that dapaglifozin enhance a stronger effect on interstitial fluid than blood volume. It should be promising to improve interstitial congestion. Another study from Ohara, et al. [14], stated that dapaglifozin improve urine output initiating a greater decrease in extracellular than intracellular volume. Yet, in subgroup analysis of T2DM population, furosemide was found to be superior to dapaglifozin in lowering extracellular fluid [14]. Synergistic mechanism between dapaglifozin and bumetanide was also demonstrated by Wilcox, et al. [15], implying the initial sodium secretion increased after 1 week initiation of loop diuretic. Hypoglycemia is the current concern while using SGLT2 inhibitors in acute episode of HF. One-half of all patients with AHF have increased blood glucose at initial presentation. Indeed, admission hyperglycemia is the predominant reflection of chronic elevated blood glucose, not an acute hyperglycemia related to AHF episode. The current studies address the evidence gap between standard insulin therapy and in-hospital use of SGLT2 inhibitors during hospitalization. Outpatient glycemic status will be one of strategy in the term of initiation and titration dose of SGLT2 inhibitors during hospitalization [10].

Despite the several facts of SGLT2 inhibitors were beneficial in combined with diuretics, these agents were not licensed, and thus we do not have sufficient data regarding SGLT2 inhibitor and diuretic combination. It seems to be reasonable in the addition of SGLT2 inhibitors to a standard regimen of loop diuretics in the setting of AHF decompensation, providing to improve clinical and hemodynamic outcomes. However, further studies should help elaborate exactly how SGLT2 inhibitors undertake the diuretic response in cardiovascular outcome.

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