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Use Of Sodium - Glucose Co - Transporter - 2 Inhibitors In Hospitalized Patients With Acute Heart Failure

Research Article

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Abstract

Background: Efficacy and safety of initiation of sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients hospitalized with acute heart failure are unclear.
Objective: To review available data regarding efficacy and safety of SGLT2 inhibitors in patients admitted to the hospital with acute heart failure.
Methods: Pubmed search up to June 1st, 2021. Search terms included SGLT2 inhibitors, diabetes, diabetic ketoacidosis, safety, mortality, empagliflozin, dapagliflozin, canagliflozin, sotagliflozin, ertugliflozin. Randomized trials, retrospective studies, case reports, pertinent reviews, and guidelines of professional societies are reviewed.
Results: Data reporting on the use of SGLT2 inhibitors for treatment of hospitalized patients with acute heart failure is limited to one pilot randomized trial (n=79) and a small (n=31) retrospective study. No clear benefits in hard cardiovascular (CV) outcomes or safety signals were shown in the 2 studies. A large (n=1,222) randomized trial evaluated the initiation of sotagliflozin before hospital discharge and within 3 days after discharge of patients with type 2 diabetes and acute heart failure. After a median follow-up of 9 months and compared with placebo, sotagliflozin was associated with significant reduction in the composite primary outcome of CV deaths and hospitalizations and urgent visits for heart failure; hazard ratio 0.67 (95% CI 0.52-0.85, P<0.001). Adverse effects of sotagliflozin included severe hypoglycemia (1.5% versus 0.3% with placebo), and small increase in hypotension (6% versus 4.6% with placebo). No diabetic ketoacidosis (DKA) were reported.
Conclusion: Very limited data suggest that in-hospital administration of SGLT2 inhibitors in the setting of acute heart failure might be safe. Initiation of sotagliflozin before and shortly after discharge of patients with type 2 diabetes admitted for acute heart failure may decrease CV events. Well-designed trials are urgently needed to evaluate efficacy and safety of initiation of SGLT2 inhibitors in hospitalized patients with acute heart failure with and without diabetes.

Keywords: SGLT2 Inhibitors; Acute Heart Failure; Euglycemic Diabetic Ketoacidosis; Safety; Empagliflozin; Sotagliflozin; Dapagliflozin; Hospitalization.

Introduction

In last few years strong evidence emerging from well-designed randomized trials showed significant decrease in CV and renal events and mortality with use of various SGLT2 inhibitors [1-5]. The most consistent CV benefit of SGLT2 inhibitors was a 25-30% reduction in hospitalization for worsening heart failure [1, 3-5]. This reduction was equally observed among patients with and without type 2 diabetes [3, 4]. However, these CV benefits were demonstrated in stable outpatients with chronic heart failure. It is not known whether initiation of SGLT2 inhibitors in hospitalized patients with acute heart failure will result in similar favorable outcomes. Moreover, the safety of use of SGLT2 inhibitors in the hospital setting in general is not well studied. The

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purpose of this review is to present available data with respect to efficacy and safety of SGLT2 inhibitors in patients admitted to the hospital with acute heart failure.

Available Studies Of Use Of SGLT2 Inhibitors In Acute Heart Failure

Randomized Trials

Only one pilot trial from Netherlands conducted by Damman et al [6], called EMPA-RESPONSE-AHF, was published to address this issue. This study was randomized, double-blind, but small (n=79, mean age 76 years, 33% women, 33% had type 2 diabetes) [6]. Thus, 40 patients with acute heart failure were randomized within 24h after hospital admission to empagliflozin 10mg/d and 39 patients to placebo for 30 days [6]. The primary outcomes were: change in dyspnea score (evaluated by visual analogue scale), diuretic response (defined as weight change per 40mg of furosemide), change in N-terminal pro brain natriuretic peptide (NT-pro-BNP), and length of stay [6]. No significant changes were observed in any of these outcomes. However, there was significant reduction with empagliflozin (10% versus 33% with placebo, P=0.014) in combined endpoint of in-hospital worsening heart failure (defined as worsening symptoms and/or signs of heart failure that require intensification of therapy or ventilatory, renal or circulatory support), rehospitalization for heart failure, or death at 60 days [6]. No episodes of ketoacidosis occurred in the empagliflozin group, and no difference between the 2 groups was noted in worsening renal function or acute kidney injury (AKI) [6].

Retrospective Studies

In one small (n=31) retrospective Japanese study, Kambara et al [7] compared outcomes between 2 groups of patients with type 2 diabetes admitted for acute heart failure based on intake of SGLT2 inhibitors. Thus, the first group of patients (n=12) received an SGLT2 inhibitor within a (mean ±SD) 17±15h and a median 13h after admission, whereas the second group, called conventional treatment group (n=19), did not receive SGLT2 inhibitors [7]. Both groups were fairly balanced at baseline in terms of age (mean 73-75 years), comorbidities, and heart failure severity [7]. Of note, 9 of the 12 patients (75%) in the SGLT2 inhibitors group had severe heart failure with New York Heart Association (NYHA) class IV. Corresponding percentage was 53% in the conventional treatment group [7]. No significant differences between the 2 groups were observed in terms of clinical course and hospital stay [7]. Yet, rate of diuretic use at the time of discharge was significantly lower in the SGLT2 inhibitor group (n=8, 67%) compared with conventional treatment group (n=19, 100%), P =0.016 [7]. Moreover, the daily dose of loop diuretics was significantly lower in the SGLT2 inhibitor group (13±5 mg) versus the conventional group, (34 ±4 mg), P=0.008 [7]. Similarly, rate of using aldosterone blockers at discharge was lower in the SGLT2 inhibitor group compared with the conventional group, 17% and 57% respectively, P=0.032 [7]. In terms of safety, AKI was less frequent with SGLT2 inhibitors diagnosed in 16% of patients compared with 58% in the conventional treatment group, P=0.031 [7]. No episodes of hypoglycemia or ketoacidosis occurred in either group. These preliminary results are somewhat reassuring, particularly in terms of safety of starting SGLT2 inhibitors in hospitalized elderly patients with severe acute heart failure.

SGLT2 Inhibitors In Patients With Recent Episode Of Acute Heart Failure

Recently, the results of the "Effect of sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) were published [8]. The SOLOIST-WHF was a multi-center randomized double-blind placebo-controlled trial to evaluate efficacy and safety of sotagliflozin, a dual SGLT1/SGLT2 inhibitor, in patients with type 2 diabetes recently hospitalized for acute heart failure [8]. Sotagliflozin was initiated before discharge in 48.8% of patients and a median of 2 days after discharge in the remaining 51.2% of patients [8]. Thus, sotagliflozin was started shortly after and not during the actual episode of acute heart failure. The primary end point was the total number of deaths from CV causes and hospitalizations and urgent care visits for heart failure. The trial ended early after randomization of 608 patients to the sotagliflozin group and 614 to the placebo group because of loss of funding from the sponsor [8]. After a median follow-up of 9 months, rate of primary end-point events was significantly lower in the sotagliflozin group compared with the placebo group, 51.0 and 76.3 events per 100 patient-years, respectively, HR 0.67, 95% CI 0.52-0.85; P< 0.001) [8]. The reduction in events in the primary outcome was mainly driven by a significant reduction in hospitalizations and urgent visits for heart failure (HR, 0.64, 95% CI 0.49-0.83, P<0.001), where as reduction in CV death was not significant (HR 0.84, 95% CI 0.58-1.22, P=.0.36) [8]. Interestingly, the sotagliflozin effects were consistent in the prespecified subgroups of patients stratified by timing of intake of the first sotagliflozin dose i.e before versus after discharge [8]. Frequency of AKI was similar between sotagliflozin (4.1%) and placebo group (4.4%). However, in the sotagliflozin arm, there was increase in percentage of patients with severe hypoglycemia (1.5% versus 0.3% with placebo) and hypotension (6.0% versus 4.6% with placebo) [8].

Mechanism Of Action Of SGLT2 Inhibitors In Acute Heart Failure

In a sub-study of the EMPA-RESPONSE-AHF, Boorsma et al [9] examined the effects of empagliflozin on renal glucose and sodium handling in patients with acute heart failure. Empagliflozin significantly increased urinary glucose concentration compared with placebo with a peak in fractional increase in glucose excretion at 24h. Thereafter, urinary glucose gradually declined but remained significantly higher than placebo up to the last measurement at day 30 [9]. However, empagliflozin did not increase fractional excretion of sodium (FeNa) at any time as compared with placebo [9]. The authors concluded that empagliflozin stimulated osmotic diuresis through increased glycosuria rather than by enhancing natriuresis [9]. In contrast, in euvolemic outpatients with chronic heart failure, Griffin et al [10] have shown that empagliflozin caused significant natriuresis within 3 hours as compared with placebo, and this natriuretic effect was sustained during the 14 days of therapy.

Potential Advantages Of Using SGLT2 Inhibitors In Acute Heart Failure

Rapidity Of Action Of SGLT2 Inhibitors

In the EMPA-RESPONSE-AHF trial, urine output was significantly increased from day 1 after empagliflozin administration compared with placebo; 3442 ± 1922ml and 2400 ± 993ml, respectively; P=0.013 [6]. The increased in urine output persisted to the last urine collection at day 4 [6].

Lack Of Evidence Of Neurohormonal Activation

Diuretic administration leads to activation of renin-angiotensin aldosterone system that hinders further sodium urinary excretion and may contribute to diuretic resistance [11]. In EMPA-RESPONSE-AHF trial, plasma aldosterone levels did not change after empagliflozin and renin concentrations transiently increased for 72 h post empagliflozin then levels became similar to those post placebo [6]. Likewise, in patients with chronic heart failure, no significant increase in plasma aldosterone and renin activity was demonstrated after empagliflozin 10 mg/d [10]. On the other hand, in young healthy volunteers (mean age 33 years), Zanchi et al [12] have shown that plasma aldosterone levels and renin activity increased 1 month after intake of the same previous dose of empagliflozin. Thus, it is possible that the hormonal response to empagliflozin varies according to the patient's health status.

Safety Concerns Of Using Sglt2 Inhibitors In Hospitalized Patients

Ketoacidosis

Diabetic ketoacidosis (DKA) is an uncommon, but serious adverse effect of all SGLT2 inhibitors. It is commonly described as "euglycemic" DKA because plasma glucose levels are commonly below 250 mg/dl [13-15]. In a large retrospective study from the state of Victoria in Australia, Hamblin et al [16] estimated that incidence of DKA was 1.02 per 1000 (95% CI 0.74-1.41) in users of SGLT2 inhibitors versus 0.69 per 1000 (95% CI 0.58-0.82) in non-users; odds ratio (OR) 1.48 (95% CI 1.02-2.15; P=0.037). Mechanisms of euglycemic DKA associated with use of SGLT2 inhibitors include insulin deficiency as result of glycosuria, increase glucagon, and shift of metabolism to favor ketosis [13-15]. No sufficient data exist regarding the incidence of ketoacidosis among subjects using SGLT2 inhibitors who do not have diabetes. In 2 large randomized trials of outpatient use of dapagliflozin and empagliflozin, ketoacidosis was not reported among subjects without diabetes [3-4]. Meanwhile, in one trial, DKA occurred in 3 patients (0.1%) with type 2 diabetes in the dapagliflozin group versus none in the placebo group [3]. Major risk factors that predispose to DKA with use of SGLT2 inhibitors include: fasting (leading to decrease insulin release), stress of infection (leading to release of anti-insulin hormones), and surgery (frequently associated with fasting, stress, and holding insulin) [13-15]. Since hospitalization may involve many of these risk factors, ketoacidosis represents a major concern in hospitalized patients with acute heart failure. Indeed, incidence of DKA markedly rises among hospitalized patients who were treated with SGLT2 inhibitors. Thus, the study of Hamblin et al [16] showed that during hospitalization, DKA developed in 38% of patients with type 2 diabetes using SGLT2 inhibitors compared with 2% among patients with type 2 diabetes using other diabetes medications, OR 37.4 (95% CI 8.0-175.9; P<0.001).

Acute Kidney Injury

Treatment with SGLT2 inhibitors is associated with transient initial worsening in renal function as reflected by decline in estimated glomerular filtration rate (eGFR) in the first few weeks to months after initiation of therapy [17, 18]. This is followed by long-term slowing in decline in renal function [17, 18]. Similarly, in patients with acute heart failure, Boorsma et al [9] showed that empagliflozin caused a significant early decrease in eGFR in the first 72 h (-10 ±12 ml/min/1.73 m^2 versus -2±12 ml/min/1.73 m^2 with placebo, P=0.009).

Hypotension

SGLT2 inhibitors may lower systolic and diastolic blood pressure without increasing heart rate [1]. In the EMPA-RESPONSE-CHF trial, no increase in frequency of hypotension occurred in the empagliflozin group (5% versus 8% with placebo). However, according to the study protocol, empagliflozin was discontinued if systolic blood pressure is < 90 mmHg, or <100 mmHg if associated with signs/symptoms of hypotension [6].

Current Guidelines Regarding In-Hospital Use Of SGLT-2 Inhibitors

In view of the increasing number of DKA episodes recorded in hospitalized patients receiving SGFLT2 inhibitors, the latest guidelines released by the American Diabetes Association (ADA) stated that SGLT2 inhibitors are not recommended for routine in-hospital use and should be avoided in all cases of severe illness [19].

Clinical Implications

Clearly, efficacy and safety of SGLT2 inhibitors among hospitalized patients with acute heart failure is not sufficiently studied. Limited data from a single pilot randomized trial and one smaller retrospective study suggest that they might be safe in this setting. The randomized, double-blind SOLOIST-WHF Trial suggests that administration of sotagliflozin before and within 3 days after hospital discharge may be generally safe and effective in reduction of subsequent heart failure hospitalization. Accordingly, it may be reasonable to start SGLT2 inhibitors cautiously after stabilization of patient's condition 1-3 days before discharge. This short duration allows monitoring of vital signs, and basic pertinent laboratory data (blood glucose, electrolytes, and kidney function) after starting the SGLT2 inhibitors. Two randomized trials are underway to evaluate efficacy and safety of SHGLT2 inhibitors in patients with acute heart failure [20, 21]. The EMPULSE trial will randomize approximately 500 hospitalized patients with acute heart failure to either empagliflozin 10 mg/d or placebo (1:1 ratio) regardless of ejection fraction or diabetes status. Patients will receive the study drug after clinical stabilization between 24 h and 5 days after admission for 90 days [20]. The DICTATE-AHF trial is a smaller (n=240), open-label study that evaluates efficacy and safety of dapagliflozin 10 mg/d in patients with type 2 diabetes admitted with acute heart failure [21]. Dapagliflozin treatment will be initiated within 24 hours after admission and treatment lasts for 5 days or until hospital discharge [21].

Conclusion

Strong evidence derived from well-designed trials has shown beneficial effects of SGLT2 inhibitors with respect to reduction in incidence of worsening heart failure in outpatients with and without type 2 diabetes. No major safety concerns emerged in these trials [3, 4]. Meanwhile, safety and efficacy of SGLT2 inhibitors were not adequately evaluated in hospitalized patients. This issue is crucial because hospitalized patients are particularly vulnerable to develop ketoacidosis as adverse effect of SGLT2 inhibitors. Results of ongoing trials will help determine safety and efficacy of SGLT2 inhibitors in hospitalized patients with acute heart failure. Until then, SGLT2 inhibitors might be started with caution shortly before discharge after stabilization of patient's condition.

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