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SHORT COMMUNICATION

Use of sodium glucose co-transporter 2 inhibitors in acute heart failure: a practical guidance

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Abstract

Aims Heart failure (HF) is the most frequent cause of hospital admission among patients 65 years or older. Patients hospitalized for acutely decompensated chronic HF and 'de novo' acute heart failure (AHF) continue to experience unacceptably high post-discharge readmission and mortality rates.

Methods and results Until recently, trials had failed to improve outcome in patients with AHF irrespective of ejection fraction with exception of sodium-glucose co-transporter 2 inhibitors (SGLT2i) that improved clinical outcomes in patients hospitalized for AHF in the Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE) and in the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials.

Conclusions This document reviews the potential utility of SGLT2i in patients hospitalized for AHF.

Keywords Sodium-glucose co-transporter 2 inhibitors; Acute heart failure; Outcomes

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Introduction

Heart failure (HF) is the most frequent cause of hospital admission among patients 65 years or older, and worldwide, there are over 1 million hospitalized patients each year with HF as a primary diagnosis.[1] Furthermore, the readmission rate, particularly within the first 3 months after discharge ('vulnerable phase'), is increasing, bearing an important economic and health care impact.[2,3] After each HF hospitalization, patients' clinical status deteriorates, often leading to recurrent hospitalizations and ultimately death.[4]

Although the outcomes for ambulatory HF patients have improved with the discovery of multiple evidence-based drug and device therapies, patients hospitalized for acutely decompensated and acute heart failure (AHF) continue to experience unacceptably high post-discharge readmission and mortality rates.[5] Furthermore, intra-hospital initiation of HF therapies may increase the long-term therapy adherence.[6]

With the exception of sacubitril/valsartan in the PIONEER-HF (Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode) trial,[7] showing superiority over enalapril to reduce N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and cardiovascular events in patients with heart failure and a reduced ejection fraction (HFrEF), until recently, several randomized controlled trials testing pharmacological interventions in patients hospitalized for AHF did not improve post-discharge outcomes, highlighting a critical unmet need.[8–10]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors significantly reduced the risk of cardiovascular (CV) death or hospitalization for HF in patients with chronic HF (irrespective of ejection fraction and diabetes status)[11,12] and in type 2 diabetes (T2D) patients with a recent worsening HF event (HFE).[13] Recently, empagliflozin improved clinical outcomes in patients hospitalized for AHF in the Study to Test the Effect

of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE; ClinicalTrials.gov Identifier: NCT04157751) trial.

In-hospital use of sodium-glucose co-transporter 2 inhibitors

The rapid onset of SGLT2 inhibitors benefits may be related to glucosuria-mediated osmotic diuresis and natriuresis, as well as anti-oxidative stress and anti-inflammatory effects, along with improved energetic efficiency, effects that make SGLT2 inhibitors ideal drugs for treating patients with AHF on top of standard of care.[14]

In the SOLOIST-WHF trial (N = 1222), sotagliflozin (or placebo) was initiated after an AHF episode in patients with T2D (49% of patients initiated therapy in-hospital and 51% within a median of 2 days after discharge). After a median follow-up of 9 months, the rate (per 100 patient-years) of total CV deaths, HF hospitalizations, or urgent HF visits was lower in the sotagliflozin group than in the placebo group [51.0 vs. 76.3; hazard ratio (HR), 0.67; 95% confidence interval (CI), 0.52 to 0.85; $P < 0.001$].[13] These findings strongly support an early initiation of sotagliflozin in patients with T2D who are hospitalized for HF. Still, after SOLOIST-WHF, data in patients without T2D were lacking and further replication of the observed results with other SGLT2 inhibitors in patients hospitalized for AHF was needed.

The EMPULSE trial recently filled this gap in knowledge by including AHF patients (N = 530) with and without diabetes, randomized in-hospital (median 3 days after admission) to either empagliflozin or placebo, and continuing treatment during the 90 days post-discharge (i.e. 'vulnerable phase'). EMPULSE used a hierarchical clinical composite endpoint of all-cause death, number of HFEs, including HF hospitalizations, urgent visits for HF, and unplanned outpatient visits, time to first HFE, and health-related quality of life (HR-QoL: ≥5-point difference in change from baseline in Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days) using the win ratio, a method that considers the order and clinical importance of the events, with death as the most important event. Empagliflozin (compared with placebo) improved the clinical composite endpoint: empagliflozin was superior in 53.9% of comparisons vs. 39.7% in placebo (6.4% were ties), yielding a win ratio of 1.36 in favour of empagliflozin (95% CI, 1.09 to 1.68; P = 0.0054). The improvement of the individual components of the composite was directionally concordant and the treatment effect was consistent regardless of diabetes status. Along with SOLOIST-WHF, these findings support a beneficial role in initiating SGLT2 inhibitors within the first few days of hospital stay among patients admitted for AHF (either 'de novo' or chronic decompensated) on top of standard of care.

Despite having included a smaller number of patients (n = 80), the EMPA-RESPONSE-AHF trial showed that 10 mg of empagliflozin increased urinary output and reduced a combined endpoint of worsening HF, rehospitalization for HF, or death at 60 days compared with placebo, although no difference was observed in visual analogue scale dyspnoea score, diuretic response, length of stay, or change in NT-proBNP between empagliflozin and placebo.[15]

Safety considerations

The safety profile of SGLT2 inhibitors is now well established in chronic settings with several thousands of patients enrolled in multiple clinical trials. The SOLOIST-WHF and EMPULSE trials showed that SGLT2 inhibitors are also safe in the AHF setting without excess risk compared with placebo. For example, in SOLOIST-WHF, the frequency of adverse events in the sotagliflozin and placebo groups were, respectively, symptomatic hypotension 6.0% vs. 4.6%, volume depletion 9.4% vs. 8.8%, urinary tract infection 4.8% vs. 5.1%, acute kidney injury 4.1% vs. 4.4%, and severe hypoglycaemia 1.5% vs. 0.3%. In EMPULSE, the frequency of adverse events in the empagliflozin and placebo groups were,

Table 1 A practical guide to sodium-glucose co-transporter 2 inhibitors utilization in acute heart failure patients

I. **Eligibility**
AHF patients, irrespective of diabetes status, LVEF, or chronic decompensated vs. de novo AHF
II. **Exclusion**
eGFR < 20 mL/min/1.73 m^2
Symptomatic hypotension (caution in patients with SBP < 100 mmHg)
Use of IV vasodilators, inotropes, or increase in IV loop diuretics within the past 6 h
Type 1 diabetes
History of ketoacidosis
III. **Caution**
Hypovolaemic patients
History of severe UTIs or urosepsis
IV. **Monitoring**
Blood pressure (at least daily while in-hospital)
Baseline and periodic monitoring of renal function (daily while in-hospital)[a]
Monitor volume status with clinical examination (at least daily while in-hospital)
Acute illness or major surgery[b]
V. **Information for patients**
Genital hygiene (daily)
Ensure adequate hydration and balanced diet

AHF, acute heart failure; eGFR, estimated glomerular filtration rate; IV, intravenous; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; UTIs, urinary tract infections.

[a]Modest decrease in eGFR (3–4 mL/min) is expected upon therapy initiation due to intrinsic renal haemodynamics, although sodium-glucose co-transporter 2 inhibitors have shown to be reno-protective agents.

[b]It is recommended to withhold therapy if limited oral intake or 3 days prior to major surgery.

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respectively, symptomatic hypotension 1.2% vs. 1.5%, volume depletion 12.7% vs. 10.2%, urinary tract infection 4.2% vs. 6.4%, acute renal failure 7.7% vs. 12.1%, and severe hypoglycaemia 1.9% vs. 1.5%. In EMPA-RESPONSE-AHF, no adverse effects on blood pressure or renal function were found. Diabetic ketoacidosis was rare and reported in <1% of the patients.

Who are the suitable candidates for in-hospital sodium-glucose co-transporter 2 inhibitor initiation?

Patients hospitalized for AHF without symptomatic hypotension, inotropic support, with need for increasing IV diuretic dose, or using IV vasodilators within the previous 6 h may be eligible for therapy. On the other hand, unstable patients requiring inotropic support, as well as patients with estimated glomerular filtration rate (eGFR) below 20 mL/min and those with a high risk of ketoacidosis, were excluded from the trials with SGLT2 inhibitors and are currently not eligible for therapy, at least until further studies targeting more unstable AHF populations are conducted.

In the aforementioned trials, SGLT2 inhibitors or placebo were given on top of standard AHF therapy, which included loop diuretics, renin–angiotensin–aldosterone system inhibitors, and beta-blockers for most patients. Hence, the efficacy and safety of SGLT2 inhibitors may be generalizable to AHF patients treated with these background therapies.

A practical guide based on current evidence and expert opinion is provided in *Table 1*, as guidance for hospital services utilizing empagliflozin in the AHF setting.

Conclusions

Sodium-glucose co-transporter 2 inhibitors improve clinical outcomes and are safe in patients with AHF and, unless contraindicated, should be rapidly initiated (within the first 5 days) in patients admitted to the hospital for decompensated HF.

Conflict of interest

J.P.F. is consultant for Boehringer-Ingelheim. J.P. received consultancy and speaker fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Novartis, Servier, and Vifor Pharma. B.M. declares advisory and speaker fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Servier, Novartis, and Vifor Pharma. C.A. has received honoraria for consulting services for Boehringer-Ingelheim and AstraZeneca. F.F. received consultancy and speaker fees from Novartis, Servier, AstraZeneca, Boehringer-Ingelheim, Bayer, and Vifor Pharma.

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