Efficacy of Continuing SGLT2 Inhibitors on Outcomes in Patients with Acute Decompensated Heart Failure

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Summary
Sodium-glucose cotransporter 2 inhibitor (SGLT2i) reduces mortality and morbidity in patients with chronic heart failure (HF). However, the clinical implication of SGLT2i therapy in patients with acute decompensated HF remains uncertain. We prospectively studied 86 type 2 diabetic mellitus (T2DM) patients (71.8 ± 12.1 years, 55 men) who were hospitalized for acute decompensated HF and received SGLT2i during the index hospitalization. Among the patients, 56 continued SGLT2i at discharge and 30 did not. The continued group experienced fewer HF re-hospitalizations than the discontinued group (24% versus 39%, $P = 0.008$) with a hazard ratio of 0.29 (95% confidence interval 0.10-0.85) adjusted for other significant potential confounders. In conclusion, long-term SGLT2i therapy might prevent unplanned HF re-hospitalization in patients with T2DM and acute decompensated HF.

Key words: Hemodynamics, Diabetes mellitus, B-type natriuretic peptide

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o date, large-scale clinical trials involving patients with T2DM have shown that sodium-glucose cotransporter 2 inhibitors (SGLT2i), which ameliorate hyperglycemia by decreasing renal glucose reabsorption, reduced the risk of HF hospitalization.11-13 The DAPA-HF trial and EMPEROR-Reduced trial further demonstrated that SGLT2i prevented the occurrence of worsening HF in patients with chronic HF with reduced ejection fraction, irrespective of the existence of T2DM.14,15 However, they did not include patients with acute decompensated heart failure (ADHF). Thus, it remains unknown whether the initiation of SGLT2i is effective in the setting of ADHF.

Our team previously reported that short-term SGLT2i therapy corrected volume overload and ameliorated symptomatic pulmonary congestion in patients with ADHF and T2DM.16 In this study, we investigated the impact of long-term SGLT2i therapy in patients with ADHF and T2DM.

Methods
This study was a single-center, non-randomized, open-labeled, prospective registry study designed to assess the efficacy of long-term SGLT2i therapy which was initiated during the index hospitalization in patients with T2 DM and ADHF. The Institutional Ethics Board of Toyama University Hospital approved the study protocol (#Rin 29-94), which complied with the Declaration of Helsinki. Written informed consent was obtained from all of the patients before enrollment.

Patient selection: All patients had an HbA1c level of 6.1% or higher and received guideline-directed medical therapy for HF at the time of SGLT2i initiation, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and diuretics, if applicable. Exclusion criteria were as follows: type 1 diabetes mellitus, previous use of SGLT2i, end-stage renal failure (estimated glomerular filtration rate (eGFR) < 20 mL/minute/1.73 m²), use of any mechanical circulatory supports, pregnancy or breastfeeding in the study period, history of hypersensitivity to the study drugs, severe ketosis, diabetic coma or precoma, or otherwise considered unsuitable. These patients did not receive SGLT2i and were not included in this study.

Study design: Patients who received SGLT2i during HF hospitalization between Feb 2016 and March 2019 were...
followed for 12 months. Before enrollment, patients were required to be hemodynamically stable, which was defined by 1) systolic blood pressure of at least 90 mmHg, 2) no dehydration, and 3) no use of intravenous vasodilators or inotropes during the preceding 24 hours. If a patient did not meet these criteria, they were not included in the study and did not receive SGLT2i.

SGLT2i was discontinued in several patients during the index hospitalization at the discretion of the attending physician. To investigate the long-term efficacy of SGLT2 in patients with ADHF, we compared the outcomes between the patients who continued SGLT2i after discharge and those who did not.

Variables evaluated: Baseline characteristics including demographics and laboratory data at index discharge were retrieved. Blood tests including plasma B-type natriuretic peptide (BNP) level and eGFR were performed at 3, 6, and 12-month follow-up. Adjustment of medical therapy, except for SGLT2i, was permitted as real-world clinical practice. Adjustment of SGLT2i was not permitted during the observational period in principle. When adjusted, the follow-up was terminated at that time. If a patient died due to a non-cardiovascular disease, their follow-up was also terminated at that time. The primary outcome was an unplanned HF hospitalization. The secondary outcomes were cardiovascular death and changes in plasma BNP level and eGFR from baseline levels.

Statistical analyses: Continuous variables are expressed as the mean and standard deviation. Categorical variables are expressed as absolute numbers and percentages. A paired t-test was applied to compare paired continuous parameters, and Fisher’s exact test was used to compare paired categorical variables. Differences in changes in BNP and eGFR over time between the two groups stratified by the SGLT2i continuation were investigated using multivariate analysis of variance.

Time-to-event data were evaluated using Kaplan-Meier estimates and Cox proportional hazards models to investigate the impact of baseline variables, including the continuation of SGLT2i, on clinical outcomes. Variables that were significant (P < 0.05) in the univariate analyses were included in the multivariate analyses. The statistical analyses were performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA). The level of significance was defined as P < 0.05.

Results

Baseline characteristics: Of the 100 patients included in this study, 63 continued SGLT2i after the index discharge and the other 37 discontinued SGLT2i due to the following reasons: 22 due to adverse events (symptomatic hypotension and suspected urinary tract infection), 6 due to an adjustment for diabetic treatment, and 9 due to a decision by the attending physician (Figure 1). Seven patients who were lost to follow-up in each group were excluded from the study. Thus, a total of 86 patients (72 ± 12 years, 55 men) were finally included, consisting of 56 in the continuation group and 30 in the discontinuation group (Table I). Of the 56 patients in the continuation group, SGLT2i was discontinued in 7 patients, and follow-up was terminated at that time (Figure 1).

In the continuation group, canagliflozin was used in 31 patients, dapagliflozin in 14 patients, and empagliflozin in 11 patients. Reduced left ventricular ejection fraction (< 40%) was observed in 45 patients (52%), mid-range ejection fraction (40-49%) in 16 patients (19%), and preserved ejection fraction (≥ 50%) in 25 patients (29%).
The changes in plasma BNP level from baseline are presented in Figure 3. BNP level remained unchanged in the continuation group whereas it increased gradually in the discontinuation group with a significant between-group difference throughout the observation period (time-averaged percent change, \(-13.3\%\) versus +53.7%; \(P = 0.048\)).

The changes in eGFR are presented in Figure 4. From baseline to 3 months, similar changes were observed in both groups. However, from 3 months to 12 months, the eGFR remained unchanged in the continuation group, whereas it declined steadily in the discontinuation group. There was no significant between-group difference in the time-averaged reduction in eGFR throughout the observation period. On the other hand, the change in eGFR was significantly different between the groups at different time points (\(P\) for interaction = 0.003).

**Discussion**

The present study investigated the impact of continued SGLT2i therapy upon the post-discharge clinical outcomes in patients with ADHF and T2DM. The major find-
Figure 2. Freedom from unplanned HF hospitalization.

Table II. Impacts of Baseline Characteristics Including SGLT2i Use on the Primary Endpoint

| Variable                              | Univariate analysis | All patients (n = 86) | Multivariate analysis |
|---------------------------------------|---------------------|-----------------------|-----------------------|
|                                       | 95% CI              | Hazard ratio          | P value               | 95% CI              | Hazard ratio          | P value               |
| Continuation of SGLT2i               | 0.12-0.77           | 0.30                  | 0.011                 | 0.10-0.86           | 0.29                  | 0.021                 |
| Age                                   | 1.00-1.10           | 1.05                  | 0.033                 | -                   | -                     | 0.700                 |
| Male                                  | -                   | -                     | 0.744                 | -                   | -                     | 0.291                 |
| Body mass index                       | 0.75-0.99           | 0.87                  | 0.031                 | -                   | -                     | 0.291                 |
| Systolic blood pressure               | -                   | -                     | 0.749                 | -                   | -                     | 0.291                 |
| Heart rate                            | -                   | -                     | 0.671                 | -                   | -                     | 0.700                 |
| HbA1c                                 | -                   | -                     | 0.120                 | -                   | -                     | 0.291                 |
| Fasting blood sugar                   | -                   | -                     | 0.120                 | -                   | -                     | 0.291                 |
| Left ventricular ejection fraction    | -                   | -                     | 0.575                 | -                   | -                     | 0.700                 |
| Ischemic etiology                     | -                   | -                     | 0.758                 | -                   | -                     | 0.700                 |
| Cardiac resynchronization therapy     | -                   | -                     | 0.896                 | -                   | -                     | 0.700                 |
| Implantable cardiac defibrillator     | -                   | -                     | 0.388                 | -                   | -                     | 0.700                 |
| Atrial fibrillation                   | -                   | -                     | 0.099                 | -                   | -                     | 0.396                 |
| Hemoglobin                            | 0.61-0.98           | 0.79                  | 0.035                 | -                   | -                     | 0.396                 |
| Hematocrit                            | -                   | -                     | 0.071                 | -                   | -                     | 0.396                 |
| Serum albumin                         | -                   | -                     | 0.579                 | -                   | -                     | 0.396                 |
| Serum sodium (per 3.95-mEq/L increase)| 0.42-0.90           | 0.61                  | 0.015                 | -                   | -                     | 0.106                 |
| Serum potassium                       | -                   | -                     | 0.916                 | -                   | -                     | 0.106                 |
| eGFR (per 22.7- mL/minute/1.73 m² increase) | 0.19-0.73           | 0.40                  | 0.002                 | 0.22-0.88           | 0.47                  | 0.015                 |
| BNP (per 230.8-pg/mL increase)        | -                   | -                     | 0.114                 | -                   | -                     | 0.106                 |
| Beta-blockers                         | -                   | -                     | 0.213                 | -                   | -                     | 0.106                 |
| ACEI/ARB                              | -                   | -                     | 0.137                 | -                   | -                     | 0.106                 |
| Loop diuretics                        | -                   | -                     | 0.073                 | -                   | -                     | 0.106                 |
| Furosemide (per 10 mg/day increase)   | 1.01-1.32           | 1.17                  | 0.043                 | -                   | -                     | 0.178                 |
| MRA                                   | -                   | -                     | 0.567                 | -                   | -                     | 0.178                 |
| Thiazides                             | -                   | -                     | 0.861                 | -                   | -                     | 0.178                 |
| Sulfonamides                          | -                   | -                     | 0.081                 | -                   | -                     | 0.178                 |
| DPP-4i                                 | -                   | -                     | 0.674                 | -                   | -                     | 0.178                 |
| Biguanides                             | -                   | -                     | 0.399                 | -                   | -                     | 0.178                 |
| Insulin                               | -                   | -                     | 0.629                 | -                   | -                     | 0.178                 |

HbA1c indicates glycated hemoglobin; eGFR, estimated glomerular filtration rate; BNP, b-type natriuretic peptide; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; and DPP-4i, dipeptidyl peptidase-4 inhibitors.
ings were as follows. (1) The primary outcome of unplanned HF hospitalization rate was lower in the continuation group than in the discontinuation group. (2) BNP level remained lower in the continuation group than the discontinuation group. (3) eGFR remained unchanged in the continuation group, whereas it decreased following the third month in the discontinuation group.

**SGLT2i and worsening HF:** To the best of our knowledge, this is the first study that investigated the long-term efficacy of SGLT2i therapy in patients with ADHF and T2 DM. Because this was a non-randomized study, participants had different characteristics, including hematocrit, serum albumin, and age between the groups. Nevertheless, multivariate analysis showed that continuation of SGLT2i and eGFR were independent predictors of worsening HF events. The impact of SGLT2i on outcomes observed in the present study was comparable to other studies including chronic HF patients receiving SGLT2i.14,15 Given our findings, continuous administration of SGLT2i would be beneficial, instead of transient administration, even after the improvement of ADHF, probably to prevent recurrent HF.

**SGLT2i and BNP:** The beneficial effect of SGLT2i on plasma BNP level has been reported in several previous studies among chronic HF patients.13-19 We previously reported that short-term SGLT2i therapy could successfully reduce the BNP level in HF patients.10 The decrease in BNP level at an early stage of SGLT2i administration is presumed to reflect the acute diuretic effect. However, many previous studies, including ours, reported that the acute diuretic effect by SGLT2i is transient and unsustainable. Here, we demonstrated that the BNP level remained lower in the continuation group. Recent studies reported some of the direct myocardial effects of SGLT2i, such as improvement of the transduction of oxygen consumption into work efficiency under conditions of hyperketonemia,20 modulation of pathways responsible for cardiomyocyte homeostasis via autophagy,21 inhibition of cardiomyocyte Na+/H+ exchanger,22 and decreases in cardiomyocyte hypertrophy, perivascular fibrosis, and epicardial adipose tissue.23,24 These important mechanisms may explain the beneficial effect of SGLT2i on BNP level.

**SGLT2i and renal function:** We revealed different courses of eGFR between the groups in the present study. In eGFR, there was no difference between the groups during the initial 3 months. However, from 3 to 12 months, the eGFR was stable in the continuation group, while it declined steadily in the discontinuation group. The effect on renal function observed in the present study is similar to those observed previously with SGLT2i in the CRE-DENCE trial.25 The benefit of renal function may become greater after 12 months as the CRE-DENCE trial indicated. However, unlike that trial, the patients in the present study had HF, and more than 60% of the patients were taking loop diuretics. Loop diuretics inhibit a sodium-potassium-chloride cotransporter (NKCC2) at the apical membrane of macula densa cells, stimulating renin secretion,26 and inhibiting tubuloglomerular feedback.27 On the other hand, SGLT2i can have a renoprotective action via a tubuloglomerular feedback mechanism.28 Therefore, SGLT2i might cancel the adverse effect of loop diuretics on renal function. However, no previous study assessed the effects of combined use of loop diuretics and SGLT2i on renal outcomes in patients with HF. Further research should aim to clarify the effect on renal outcome of the combined use of loop diuretics and SGLT2i.

**Limitations:** The sample size was small and the observation period was only one year. Given the low event number, the number of potential confounders included in the multivariate analyses was restricted. A large-scale multicenter study with a longer follow-up period is required. A similar type of SGLT2i was not used in the present study. It remains unclear whether such beneficial effects are consistent across every SGLT2i. However, several large placebo-controlled cardiovascular outcomes trials using the 3 SGLT2is suggested that they might exert a beneficial effect as a class effect on HF condition.29 The non-randomized and open-labeled study design mean that sources of bias could not be eliminated. Inter-group comparison has selection bias with different background characteristics between two groups, although the results for the primary efficacy outcome remained significant in our
analysis with multiple imputations. Of note, the discontinuation of SGLT2i was at the discretion of the attending physician. Lastly, the DAPA-HF trial and EMPEROR-Reduced trial revealed that SGLT2i reduced the risk of worsening HF or cardiovascular death, independently of diabetes status, whereas we did not include patients without T2DM in this study. Further studies are warranted to determine the efficacy of SGLT2i for ADHF.

Conclusion

Among T2DM patients who were hospitalized for ADHF, those who continued SGLT2i had a lower risk of worsening HF than those who discontinued SGLT2i.

Disclosure

Conflicts of interest: The authors declare that there are no conflicts of interest to report.

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