Asploro Cardiovascular Case Reports and Research

Editorial

DOI: https://doi.org/10.36502/2024/ACCRR.6102

Latest Trends of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-i) for Heart Failure (HF) and Chronic Kidney Disease (CKD)

Hiroshi Bando[1,2iD*]

[1]*Medical Research/Tokushima University, Tokushima, Japan*

[2]*Japan Low Carbohydrate Diet Promotion Association, Kyoto, Japan*

Corresponding Author: **Hiroshi Bando** ORCID iD

Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan;
Email:pianomed@bronze.ocn.ne.jp

Received date: 20 May 2024; **Accepted date**: 20 June 2024; **Published date**: 26 June 2024

Citation: Bando H. Latest Trends of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-I) for Heart Failure (HF) and Chronic Kidney Disease (CKD). Asp Cardio Case Rep and Res. 2024 Jun 26;1(1):5-8.

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2-i) have been effective for heart failure (HF), chronic kidney disease (CKD), and type 2 diabetes (T2D). Among SGLT2-i, empagliflozin and dapagliflozin were compared for clinical effect, with empagliflozin showing a lower composite of all-cause mortality or hospitalization with a hazard ratio (HR) of 0.90. In the EMPA-ELDERLY clinical trial, empagliflozin demonstrated better HbA1c reduction and weight reduction without affecting muscle strength or mass in elderly patients with T2D. The American College of Physicians (ACP) published "Newer Pharmacologic Treatments in Adults with Type 2 Diabetes" in April 2024. The potential mechanisms for the anti-inflammatory effects of SGLT2-i will be clarified in the future.

Keywords

Empagliflozin, DAPA-HF, EMPA-ELDERLY, American College of Physicians (ACP), Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Abbreviations

ACP: American College of Physicians; GRADE: Grading of Recommendations Assessment, Development and Evaluation

Editorial

Recently, sodium-glucose cotransporter-2 inhibitors (SGLT2-i) have been effective for heart failure (HF), cardiovascular disease (CVD), chronic kidney disease (CKD), and type 2 diabetes (T2D) [1]. Several pieces of evidence concerning SGLT2-i have been shown until now, and the latest novel reports will be introduced in this article. SGLT2-i has shown cardiovascular benefits regardless of the existence of diabetes, and therefore, SGLT2-i has been recommended for HF patients. For elderly people, the risk of weight loss and other adverse effects may exist, which has not yet been resolved. By the DAPA-HF and DELIVER trials, clinical efficacy and safety have been found for HF patients with frailty or sarcopenia [2].

Among SGLT2-i, empagliflozin and dapagliflozin have revealed beneficial efficacy in HF, but the detailed

differences have not yet been compared. A recent report presented a comparison of them by a multicenter retrospective study [3]. The protocol included a total of 745,914 eligible cases, in which empagliflozin and dapagliflozin groups were compared. Empagliflozin showed a lower incidence of the composite of all-cause mortality or hospitalization with a hazard ratio (HR) of 0.90 [0.86-0.94]. No difference was found in mean HbA1c or adverse events between both groups. Consequently, cases that began empagliflozin seemed to show lower clinical events compared to those of dapagliflozin.

For the study of SGLT2-i/GLP-1RA for T2D/CVD, the CORDIALLY non-interventional study has been conducted for Central and Eastern Europe (CEE) [4]. In the protocol of 4055 applicants, the most prescribed agent was empagliflozin (48.5%) among DPP4-i, SGLT2-i, and GLP-1RA. Empagliflozin was frequently prescribed more than 10 times by cardiologists. Overall, 36.6% of cases showed CVD. Although the guideline recommended SGLT2-i or GLP-1RA, 26.8% of cases received DPP4-i. Cases starting DPP4-i showed higher age (66.4 years old, yo) than SGLT2-i (62.4 yo) and GLP-1RA (58.3 yo). CORDIALLY is a non-interventional and retrospective cross-sectional study that evaluates cardiorenal comorbidities of T2D patients under certain clinical situations. It was investigated in five CEE countries, including Bulgaria, the Czech Republic, Hungary, Poland, and Russia.

From the clinical trial of EMPA-ELDERLY, which is a randomized, double-blind, placebo-controlled, 52-week protocol, a sub-analysis of elderly Japanese adults was performed. For elderly T2D patients, SGLT2-i would decrease body weight, which may develop sarcopenia and frailty. Then, 129 T2D cases participated in the study for a comparative study in empagliflozin and placebo groups for 1 year [5]. As a result, obtained data were HbA1c -0.57% for the empagliflozin group, and weight reduction was 3.26 kg vs. 0.90 kg, respectively, as -2.37 kg. The placebo-adjusted change showed muscle mass -0.61 kg, fat mass -1.84 kg, and grip strength -0.3 kg of difference, respectively. Consequently, empagliflozin showed better HbA1c reduction and weight reduction without problems of muscle strength or mass for elderly T2D patients.

In a previous meta-analysis of Japanese subjects, SGLT2-i significantly reduced skeletal muscle mass by 1.01 kg [6]. However, the study included both young and severely obese people. Therefore, clinical effects for only elderly Japanese people were not known. From the results, muscle mass did not decrease remarkably. This may be due to the elevated energy intake in the empagliflozin group and the fact that elevated ketone bodies (KB) could suppress skeletal muscle catabolism [7].

Diabetes has been a systemic, chronic, low-grade inflammatory disease and has a relationship with the development of target-organ damage (TOD). From several high-quality investigations, a close association with inflammatory status and SGLT2-i has been suggested [8]. The potential mechanisms related to the anti-inflammatory effect of SGLT2-i are expected to be clarified in the future. Concerning SGLT2-i therapy for T2D, the benefit-risk ratio has been studied [9]. The protocol included large prospective placebo-controlled trials for cardiovascular outcomes and observational cohort studies. As a result, similar relative risk reduction was found in cardiovascular mortality and hospitalization for heart failure (hHF). The absolute risk reduction was greater in elderly than in younger patients.

In April 2024, the American College of Physicians (ACP) published "Newer Pharmacologic Treatments in Adults with Type 2 Diabetes" [10]. It is a guideline for pharmacotherapy for T2D adults, excluding pregnant women. The previous version was released in 2017, and this is the successive revision in seven years. The Clinical Guidelines Committee has prioritized the evaluating measures. They applied Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The detailed factors for this approach include major adverse cardiovascular events (MACE), myocardial infarction, all-cause mortality, stroke, CKD progression, severe hypoglycemia, serious adverse events, and hospitalization for HF.

In the guidelines, there are two main recommendations. Recommendation 1 (Rec-1) is similar to the American Diabetes Association (ADA) 2024 algorithm. On the other hand, some debate exists among diabetes specialists regarding recommendation

2 (Rec-2).

Rec-1: When a T2D patient is already provided lifestyle modification and metformin, adding SGLT2-i or GLP-1RA would be adequate if necessary. This measure has high evidence with a strong recommendation. For these reasons, SGLT2-i reduces MACE, all-cause mortality, hospitalization for heart failure, and the progression of CKD.

Rec-2: Some T2D adults maintain higher blood glucose values despite lifestyle interventions and metformin. In such cases, DPP4-i is not recommended for reducing the risk of developing CKD and MACE. This is also a strong recommendation with high evidence.

Several cardiologists agree with Rec-1 but disagree with Rec-2 for the following reasons: i) This guideline seems to be strictly for US T2D patients, but it cannot apply to Japanese or Asian patients. As major reasons, the degree of obesity is different in the two countries, with an average BMI of 32 kg/m^2 vs. 25 kg/m^2, respectively. Therefore, weight reduction is smaller in Japanese people. ii) The causes of death are different in both countries. The leading cause of death in the US is cardiovascular disease. In Japan, the top three causes of death are malignant tumors, infections, and cardiovascular disease. iii) DPP4-i improves mainly blood glucose variability but does not reduce MACE, all-cause mortality, or stroke. This would be why this guideline did not recommend DPP4-i. In Japan, glucose control is always crucial for preventing infectious diseases. iv) In East Asians, DPP-4i can lower blood glucose to a greater extent than in Americans and Europeans. In actual practice, metformin and SGLT2-i cannot be used for thin sarcopenic older adults with severe renal impairment [11]. In such cases, biliary-excreted DPP4-i, such as linagliptin (Trajenta) or teneligliptin (Tenelia), has often been the first choice.

In summary, the latest topics of SGLT2-i treatment for HF, CKD, and T2D were discussed [12]. Diabetic comorbidities and macroangiopathy may differ in Western and Eastern countries, leading to different mortality and morbidity. These matters would have certain associations with various related regions. Consequently, we manage to follow up on the developments with close attention.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

Funding

There was no funding received for this paper.

References

[1] Gragnano F, Terracciano F, Calabrò P. SGLT2 Inhibitors as the Backbone of Therapy for Cardiovascular and Renal Protection. J Cardiovasc Transl Res. 2024 Feb;17(1):227-29. [**PMID**: 37460916]

[2] Naito A, Nagatomo Y, Kawai A, Yukino-Iwashita M, Nakazawa R, Taruoka A, Takefuji A, Yasuda R, Toya T, Ikegami Y, Masaki N, Ido Y, Adachi T. The Safety and Efficacy of Sodium-Glucose Cotransporter-2 Inhibitors for Patients with Sarcopenia or Frailty: Double Edged Sword? J Pers Med. 2024 Jan 26;14(2):141. [**PMID**: 38392575]

[3] Modzelewski KL, Pipilas A, Bosch NA. Comparative Outcomes of Empagliflozin to Dapagliflozin in Patients With Heart Failure. JAMA Netw Open. 2024 May 1;7(5):e249305. [**PMID**: 38696170]

[4] Prázný M, Suplotova L, Gumprecht J, Kamenov Z, Fülöp T, Medvedchikov A, Rosenzweig D, Aleksandric M. Real-world characteristics, modern antidiabetic treatment patterns, and comorbidities of patients with type 2 diabetes in central and Eastern Europe: retrospective cross-sectional and longitudinal evaluations in the CORDIALLY® study. Cardiovasc Diabetol. 2022 Oct 8;21(1):203. [**PMID**: 36209118]

[5] Yabe D, Shiki K, Homma G, Meinicke T, Ogura Y, Seino Y; EMPA-ELDERLY Investigators. Efficacy and safety of the sodium-glucose co-transporter-2 inhibitor empagliflozin in elderly Japanese adults (≥65years) with type 2 diabetes: A randomized, double-blind, placebo-controlled, 52-week clinical trial (EMPA-ELDERLY). Diabetes Obes Metab. 2023 Dec;25(12):3538-48. [**PMID**: 37622398]

[6] Pan R, Zhang Y, Wang R, Xu Y, Ji H, Zhao Y. Effect of SGLT-2 inhibitors on body composition in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. PLoS One. 2022 Dec

30;17(12):e0279889. [**PMID**: 36584211]

[7] Koutnik AP, D'Agostino DP, Egan B. Anticatabolic Effects of Ketone Bodies in Skeletal Muscle. Trends Endocrinol Metab. 2019 Apr;30(4):227-29. [**PMID**: 30712977]

[8] Zhang R, Xie Q, Lu X, Fan R, Tong N. Research advances in the anti-inflammatory effects of SGLT inhibitors in type 2 diabetes mellitus. Diabetol Metab Syndr. 2024 May 12;16(1):99. [**PMID**: 38735956]

[9] Scheen AJ, Bonnet F. Efficacy and safety profile of SGLT2 inhibitors in the elderly: How is the benefit/risk balance? Diabetes Metab. 2023 Mar;49(2):101419. [**PMID**: 36640828]

[10] Qaseem A, Obley AJ, Shamliyan T, Hicks LA, Harrod CS, Crandall CJ; Clinical Guidelines Committee of the American College of Physicians; Balk EM, Cooney TG, Cross JT Jr, Fitterman N, Lin JS, Maroto M, Miller MC, Shekelle P, Tice JA, Tufte JE, Etxeandia-Ikobaltzeta I, Yost J. Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: A Clinical Guideline From the American College of Physicians. Ann Intern Med. 2024 May;177(5):658-66. [**PMID**: 38639546]

[11] Takahashi Y, Seino Y, Yabe D. Long-term safety and efficacy of SGLT2 inhibitor use in older east Asians with type 2 diabetes. J Diabetes Investig. 2024 Jan;15(1):63-66. [**PMID**: 37814592]

[12] Kovesdy C, Schmedt N, Folkerts K, Bowrin K, Raad H, Batech M, Fried L. Predictors of cardio-kidney complications and treatment failure in patients with chronic kidney disease and type 2 diabetes treated with SGLT2 inhibitors. BMC Med. 2022 Jan 10;20(1):2. [**PMID**: 35000594]