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Review Article

Sodium-glucose co-transporter-2 inhibitor (SGLT2i) may contribute late-aging and longevity

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ABSTRACT

Recently, sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been a topic for oral hypoglycemic agents (OHAs) for diabetes. It suggested positive effects on the heart and kidneys from EMPAREG-OUTCOME study, CANVAS program, and DECLARE-TIMI 58 study. SGLT2i are expected to become the useful agents that transcend OHAs, from three recent reports. They are i) Dapagliflozin in Patients with Heart Failure and Reduced Ejection trial (DAPA-HF), ii) the Empagliflozin outcome trial in Patients with chronic heart Failure with Reduced Ejection Fraction trial (EMPEROR-Reduced), and iii) dapagliflozin-chronic kidney disease trial (DAPA-CKD). SGLT2i may become an agent for late-aging and longevity in the future.

Keywords: sodium-glucose co-transporter-2 inhibitors (SGLT2i), Dapagliflozin in Patients with Heart Failure and Reduced Ejection trial (DAPA-HF) Empagliflozin outcome trial in Patients with chronic heart Failure with Reduced Ejection Fraction trial (EMPEROR-Reduced), dapagliflozin-chronic kidney disease trial (DAPA-CKD), the evaluation of Ertugliflozin efficacy and Safety Cardiovascular outcomes trial (VERTIS-CV).

Abbreviation: Oral hypoglycemic agents (OHAs), left ventricular ejection fraction (LVEF), Hazard ratio (HR) chronic kidney disease (CKD), cardiovascular outcomes safety trials (CVOTs), major adverse cardiovascular events (MACE)

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Currently, sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been of particular interest among the oral hypoglycemic agents (OHAs) for diabetes. It seems to be rather rare drug which medical evaluation has been changed drastically. Initially, it was not accepted as a first- or second-line drug in diabetic practice, and it was advised that administration to the elderly and women should be cautioned and limited to obese young men. However, the EMPAREG-OUTCOME study [1], CANVAS program [2], and DECLARE-TIMI 58 study [3] suggested positive effects on the heart and kidneys. As it is called "Pump, pipes, & filter" [4], the primary preventive effects on heart failure (pump), renal function (filter) and on arteriosclerosis (pipes) were observed. Furthermore, the secondary preventive effect was also confirmed. Recently, it has been recommended for prescription as a first-line treatment for diabetic patients who have a high cardiovascular risk [5].

During the development of SGLT2i, large-scale randomized controlled trials (RCTs) have shown beneficial positive effects for heart failure and renal function from 2019 to 2020. They include three papers from N Eng J Med. In the future, SGLT2i are expected to become the useful agents that transcend the category of antidiabetic drugs. In this article, current topics concerning SGLT2i will be described. The first report is

concerning the "Dapagliflozin in Patients with Heart Failure and Reduced Ejection (DAPA-HF) trial. The subjects were >18 years old, with <40% of left ventricular ejection fraction (LVEF), II-IV degrees of NYHA classification (n=4744, 410 centers, 20 countries) [6]. The primary outcome included composite of worsening heart failure or cardiovascular death. As a result, Hazard ratio (HR) was significantly decreased as 0.74 ($p<0.001$). The same suppressed effects were observed, even if this result was analyzed by the presence or absence of diabetes, <60mL/min/1.73m^2, race and registered area [7].

The second is the Empagliflozin outcome trial in Patients with chronic heart Failure with Reduced Ejection Fraction trial (EMPEROR-Reduced) [8]. Subjects were 3730 patients with class II-IV heart failure with <40% of LVEF. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure. HR was 0.75 for cardiovascular death or hospitalization, 0.70 for total number of hospitalizations. The annual rate of eGFR decline was slower in empagliflozin group vs placebo group (-0.28 vs. -0.55 mL/min/1.73 m^2, $P<0.001$).

The third is DAPA-CKD trial, in which dapagliflozin was provided to patients with chronic kidney disease (CKD) [9]. The subjects included 4303 cases from 386 centers, 21 countries, in which approximately two-thirds of them were diabetic. They showed the renal function of eGFR 25-75 mL/min/1.73m^2. The primary outcome included sustained eGFR decline at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. About 15% of the subjects showed 15 mL/min/1.73m^2 as eGFR. HR was 0.61 for primary outcome. When this result was stratified with diabetes, the similar suppression was observed regardless of the presence or absence of diabetes (HR 0.64 in diabetic patients, HR 0.50 in non-diabetic patients). Similar results were also obtained by race, gender and eGFR at 45 mL/min/1.73m^2.

From these three papers, SGLT2i showed an organ-protective effect with or without diabetes. Therefore, the features of SGLT2i can be summarized as follows: i) excrete a lot of urinary sugar to lower blood sugar, ii) protect kidney function, iii) show positive effects on cardiovascular diseases, hypertension, and heart failure, iv) has the effect of preventing age-related diseases for multiple organs. From mentioned above, SGLT2i may have various positive beneficial possibilities for actual medical practice and research.

There were originally some medical weak points for SGLT2i. As eGFR decreases, urinary glucose excretion also decreases. As a result, its use in diabetic patients with low eGFR was restricted because of decreased hypoglycemic effect and concern about acute renal failure. However, the CREDENCE trial [10] has shown the usefulness of canagliflozin in diabetic patients who already have DKD. All patients had T2DM with eGFR (56.2 ± 18.2 mL/min/1.73 m2 on average, 30-45 mL/min/1.73 m^2 in 29.8%, and <30 mL/min/1.73 m^2 excluded). Furthermore, current DAPA-CKD study showed [9] renal protective effect, where patients with <30 mL/min/1.73 m^2 were included in 15% of subjects. In the DAPA-HF study [9] and EMPEROR-Reduced study [6], a cardio protective effect was observed even in patients with heart failure with LVEF of 40% or less. From mentioned above, it can be said that the clinical efficacy of SGLT2i was shown even in severe DKD.

How will SGLT2i develop in the future? Attention has been paid to its effects on dementia, sarcopenia, and heart failure with preserved LVEF. It has been reported that some trials have already begun in this area [11-14]. At the moment, no significant positive results have been confirmed yet. However, if the effect is significantly proved in the future studies, SGLT2i will become a rare beneficial agent for wide region. Even if there is no significant difference, three papers presented in this article all show a positive tendency enough to reduce mortality.

The fourth paper would be the evaluation of Ertugliflozin efficacy and Safety Cardiovascular outcomes trial (VERTIS-CV), which investigated the cardiovascular effects of ertugliflozin [15]. The primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome and major adverse cardiovascular events (MACE). Hazard ratio were 0.97 in MACE, 0.88 in cardiovascular death, 0.81 in renal death and doubling of the serum creatinine level. Consequently, ertugliflozin was noninferior to placebo among patients with T2DM and atherosclerotic cardiovascular disease (ASCVD).

As the Food and Drug Administration (FDA) summarized the reports on the evaluation of new OHAs for T2DM, several cardiovascular outcomes safety trials (CVOTs) on SGLT2i have been performed. They are 4 kinds of CVOTs so far, and there was an investigation to compare the generalizability of SGLT2i studies for

Italian T2DM adults [16]. These studies were conducted from 222 Italian diabetes clinics with 455,662 T2DM adult patients. These included EMPA-REG OUTCOME (empagliflozin), CANVAS (canagliflozin), DECLARE-TIMI 58 (dapagliflozin), and VERTIS-CV (ertugliflozin) studies. In the strict sense, the result of each CVOT showed 11.75, 29.4%, 55.9%, and 12.8%, respectively. The fourth VERTIS-CV showed non-inferior but did not give a significant positive result [15]. This may be due to the characteristic of the protocol that was not necessarily exact.

In summary, current topics of four SGLT2i were mainly introduced in this article. They can reduce glucose toxicity to the body and are effective in clinical settings for diabetes and cardiovascular diseases [17]. These agents may be close to the immortality and longevity that human beings have pursued for thousands of years. In other words, it may be an "agent for late-aging and longevity."

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