Open Access
Volume 4 Issue 2
Mini-Review Article

International Journal of Endocrinology and Diabetes

PUBTEXTO

Perspectives of Diabetes, Heart Failure and Chronic Kidney Disease (CKD) Treating By Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i)

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Article Info

Article History:
Received: 09 October, 2021
Accepted: 14 October, 2021
Published: 17 October, 2021

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DOI: https://doi.org/10.36266/IJED/121

Abstract

Sodium-glucose cotransporter-2 inhibitor (SGLT2i) was initially applied to diabetes, successively to heart failure and recently to chronic kidney disease (CKD) with its expanding application. For decades, several cardiovascular outcome trials (CVOT) have been conducted for SGLT2i. They include mega studies of CREDENCE, CANVAS, DECLARE-TIMI 58, EMPA-REG OUTCOME, EMPA-KIDNEY, EMPEROR-Reduced, DAPA-HF, DAPA-CKD, and others. DAPA-CKD is an on-going study for non-DM cases. Recommendations for actual medical practice of SGLT2i include i) careful combined treatment of diuretics, ii) checking urinary ketones against ketosis, iii) avoiding the first-line agent, and iv) establishing basically reasonable lifestyle and nutrition in addition to medical agents.

Keywords: Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i); Cardiovascular Outcome Trials (CVOT); Heart Failure with Reduced Ejection Fraction (HFrEF); Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD)

Abbreviations: Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i), Heart Failure with Reduced Ejection Fraction (HFrEF), Cardiovascular Outcome Trials (CVOT), Canagliflozin and Renal Events in Diabetes and Established Nephropathy Clinical Evaluation (CREDENCE), Canagliflozin Cardiovascular Assessment Study (CANVAS), Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58), Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD), Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME), The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY), Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced)

Mini-Review

Historically, sodium-glucose cotransporter-2 inhibitor (SGLT2i) was initially applied to diabetes and clinically effective [1]. Later, it was reported to have an effect on heart failure because it has a positive effect on water electrolyte metabolism [2]. Subsequently, a clinical effect was also observed for chronic kidney disease (CKD). Now, the application of SGLT2i in clinical practice is expanding [3]. In this article, the perspectives of SGLT2i for heart failure and CKD are described.

Clinically adequate management of heart failure has been important. In particular, heart failure with reduced ejection fraction (HFrEF) was a problem [4]. Poor contraction of the left ventricle results in inadequate ejection, resulting in an increase in diastolic volume, an increase in diastolic pressure, and a decrease in ejection fraction. A recent topic for HFrEF is clinical application of SGLT2i [5]. In other words, the indications in SGLT2i include the case with HFrEF and Type 2 diabetes (T2D) with heart failure. However, it is not recommended in all cases. At risk of urinary tract infections, poor pubic cleanliness, low ADL, poor nutrition and CKD grade 5, and others should be used with caution. Consequently, SGLT2i is not a panacea and control of lifestyle-related improvements are essential.

For decade, several cardiovascular outcome trials (CVOTs) on the effect of oral hypoglycemic agents (OHAs) have been conducted [6]. Among them, SGLT2i has been attracted attention for beneficial efficacy on cardiovascular and renal outcomes. Several well-known mega studies have been reported so far. The Canagliflozin and Renal Events in Diabetes and Established Nephropathy Clinical Evaluation (CREDENCE) study was

performed in all Diabetic cases with eGFR 30-89 mL/min/1.73m^2 and urinary protein >300 mg/gCre [7]. In the Canagliflozin Cardiovascular Assessment Study (CANVAS) study, all Diabetes were examined with eGFR ≥30 mL/min/1.73m^2 and urinary protein ≥30 mg/gCre [8]. Dapagliflozin Effect on CardiovasculAR Events (DECLARE-TIMI 58) study included subjects of all diabetics, with eGFR >60 mL/min/1.73m^2 and evaluation of urine protein in all cases [9]. In the renal sub-analysis of Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME), subjects were all diabetic with eGFR 30-59 mL/min/1.73m^2, and urinary protein >300 mg/gCre [10]. Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study included non-DM cases with eGFR ranged approximately 20-60 mL/min/1.73m^2 and urinary protein ranged approximately >100 mg/gCre [11].

Discussion has been continued from some results of CREDENCE, DAPA-CKD and The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) [6]. EMPA-KIDNEY has been a randomized double-blind placebo-controlled trial of empagliflozin versus matching placebo. It includes about 6,000 participants with CKD, with/without diabetes. The study continues for approximately 3-4 years and can evaluate whether empagliflozin decreases the risk of renal disease progression and/or cardiovascular deaths. SGLT2i has been recognized for hypoglycemic effect as well as both of renal and cardiovascular outcomes. Some recent experiments showed different pathways, which can contribute to the cardiovascular and renal benefits. It may include the modulation of urinary potassium, chloride, phosphate, calcium and magnesium excretion [12].

As to long-term outcome, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) showed apparently the improvement of results for cases with heart failure, even if the lack of diabetic states [13]. From the result of EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure with Reduced Ejection Fraction (EMPEROR-Reduced) trial, it showed the reduction of heart failure in patients with no diabetic states. According to systematic review and meta-analysis including DAPA-HF and EMPEROR-Reduced trial, the improvements of composite renal endpoint were found. These results were not influenced by the baseline eGFR and/or presence of diabetes. DAPA-CKD trial has evaluated patients, which had CKD with/without T2DM for both group of with/without SGLT2i dapagliflozin [13].

There is an on-going mega study, which is DAPA-CKD. DAPA-CKD includes 4304 cases associated with eGFR between 25-75 mL/min/1.73m^2 and urinary albumin/creatinine ratio (UACR) ≥200 mg/gCr [14]. They were randomly divided into dapagliflozin and placebo group. They showed mean eGFR 43.1 mL/min/1.73m^2 and median UACR 949 mg/g. Among them, 68% (n=2906) showed T2DM. Their medical treatments were found as follows: ACEi and ARB 97%, diuretics 43.7%, mineralocorticoid receptor antagonists (MRAs) 5.3% and GLP1RA 2.8%. Consequently, DAPA-CKD trial enrolls various cases underlying renal diseases with renin-aldosterone (RA) system blocking therapy. The trial will show the effect of dapagliflozin associated with CKD stages 2-4 and albuminuria and with/without diabetes.

From these mega-studies, most cases are patients referred to nephrologists. What is the reason of SGLT2i for protecting renal function? Some possible effects were considered including i) simply lowering blood pressure slows down blood pressure, ii) decreased BP reduces eGFR [15], iii) weight reduction is usually observed, iv) blood glucose becomes lower and v) general clinical improvement can be obtained. For the protection of renal function, the ideal situation is for eGFR to recover above 60 mL/min/1.73m^2 and for urinary protein to drop below 30 mg/gCr. To aim for this state, it is important to improve BP, blood glucose and lipids in well-balanced manner.

In the actual medical practice, several recommendations will be described for SGLT2i [16]. They are i) Be careful about lowering blood pressure and using it combined with diuretics, ii) Check urinary ketones for avoiding possible causing ketosis [17], iii) Make the patient be sure every day that proper taking of SGLT2i may change your urine, iv) Start half dose of SGLT2i for diabetic patients, which are advised from the author's experience, v) Note that SGLT2i is not the first-line agent for all patients with diabetes, heart failure or CKD and vi) Before providing SGLT2i, improve the lifestyle and carry out some exams, education and treatments.

In summary, approved medical indications for agents may vary for countries. The standard indication for dapagliflozin for CKD is T2DM, T1DM, CKD excluding chronic heart failure, end-stage renal disease or dialysis [18]. In other words, it has been a big step forward and a topic that SGLT2i can be used even in non-diabetes [19]. Since clinical trials have not been conducted with eGFR <25, it is the challenge matter in the future. This article becomes hopefully a useful reference for daily practice.

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