Letter

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Clinical Efficacy of Sodium-Glucose Cotransporter 2 Inhibitor and Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy in Type 2 Diabetes Mellitus: Real-World Study (*Diabetes Metab J* 2022;46:658-62)

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Kim et al. [1] examined the efficacy of the combination of sodium-glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) in patients with type 2 diabetes mellitus (T2DM). Glycosylated hemoglobin (HbA1c) decreased 1.5% (95% confidence interval [CI], 1.27 to 1.74) and 1.4% (95% CI, 1.19 to 1.70) after 6 months and 1 year, respectively. In addition, the bodyweight change was −2.8 kg (95% CI, −4.21 to −1.47). I present some queries regarding their study, and then discuss the advantage/efficacy of SGLT2i and GLP-1RA for lowering the risk of cardiovascular diseases.

First, the authors analyzed data from 104 patients with T2DM. A total of 67.3% and 97.1% patients had comorbidities of hypertension and dyslipidemia. In addition, a total of 98.1%, 81.7%, and 10.6% patients received metformin, sulfonylurea and insulin, respectively. I understand that the authors described the possibility of combination effect on clinical outcomes such as HbA1c and bodyweight in "Discussion" as the study limitation. Especially, bodyweight may also interact with metabolic components such as T2DM, dyslipidemia, and hypertension [2]. As lifestyle factors such as exercise, nutritional intake, would also contribute to clinical outcomes, appropriate adjustments are needed for the analysis.

Second, the mean age was 51.1 years old, and 41.3% were females. Namely, the estrogen synthesis may change in the period of menopause, and prevalence of dyslipidemia would increase in combination with obesity. I think that stratified analysis by sex may be needed for conducting multiple regression analysis.

Regarding the multiple regression analysis, the authors did not present the square value of multiple regression coefficients (R^2) or adjusted R^2, which would be a useful indicator for presenting predictive ability. Although baseline HbA1c could predict HbA1c reduction after 1 year, R^2, or adjusted R^2 should be calculated.

Next, I discuss the efficacy and safety of GLP-1RA and SGLT2i on cardiovascular disease. By setting other antidiabetic drugs as a control, Baviera et al. [3] reported that the adjusted hazard ratios (HRs) of GLP-1RA for death, cerebrovascular disease and ischemic stroke, and lower limb complications significantly decreased. In addition, the adjusted HRs of SGLT2i inhibitors for death, cerebrovascular disease and heart failure (HF) significantly decreased. The frequencies of serious adverse events were quite low, and the authors recommended the use of GLP-1RA and SGLT2i in patients with T2DM for lowering the risk of cardiovascular/cerebrovascular disease and death.

Regarding the combination effect, Wright et al. [4] examined

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the association of SGLT2i, GLP-1RA, and their combination with the risk for major adverse cardiac and cerebrovascular events (MACCE) and HF in patients with T2DM. The adjusted odds ratios (ORs) of patients with SGLT2i, GLP-1RA, and the SGLT2i/GLP-1RA combination for MACCE and HF were 0.82 (95% CI, 0.73 to 0.92), 0.93 (95% CI, 0.81 to 1.06), and 0.70 (95% CI, 0.50 to 0.98), respectively. In addition, the adjusted ORs of patients with SGLT2i, GLP-1RA, and the SGLT2i/GLP-1RA combination for HF were 0.49 (95% CI, 0.42 to 0.58), 0.82 (95% CI, 0.71 to 0.95), and 0.43 (95% CI, 0.28 to 0.64), respectively. There were larger beneficial effects of SGLT2i than those of GLP-1RA for reducing vascular events, especially for HF, and there was no synergic effect with the combination of SGLT2i and GLP-1RA on MACCE and HF. Not only fatal events, but also mild-to-moderate events could be prevented by these new antidiabetic medications.

There is a different mechanism in each antidiabetic drug for improving glucose metabolism, which may have mechanisms for contributing risk reduction in vascular events. SGLT2i and GLP-1RA have effects on cardiovascular and renal protection [5], and the efficacy and safety of these drugs should be comprehensively evaluated in combination with glucose metabolism and cardiovascular diseases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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