Response

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Risk of Diabetic Retinopathy between Sodium-Glucose Cotransporter-2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists (*Diabetes Metab J* 2023;47:394-404)

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We appreciate the valuable insights from Dr. Ko and Dr. Moon regarding our recently published study, "Risk of diabetic retinopathy between sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists" [1]. Also, we are grateful for the editor's opportunity to discuss this article further.

First, we thank the authors for mentioning the heterogeneity in baseline demographics, which might affect the risk of diabetic retinopathy (DR). Sodium-glucose cotransporter-2 inhibitor (SGLT2i) new users had lower severity of diabetes mellitus (DM), including lower glycosylated hemoglobin (HbA1c), shorter duration of DM, and lower prevalence of diabetic nephropathy and diabetic neuropathy, compared to those with glucagon-like peptide-1 receptor agonist new users. We were thankful for highlighting our use of inverse probability of treatment weighting (IPTW) and target trial design to achieve a similar probability of treatment assignment and homogeneity of baseline demographics between the two groups [2]. Notably, patients' HbA1c was collected to determine the severity of DM, which was often unable to be acquired from conventional health insurance declaration databases. As the nature of the retrospective study design, we could not account for some unknown residual confounding factors. IPTW with propensity score approach could only adjust the measurable covariables, so we calculated the E-value for quantitative analysis of residual confounders. The E-values for proliferative DR and composite surgical outcome were 3.18 and 2.84, respectively, indicating our outcomes' reliability [3]. Other unmeasured confounders might be less likely to affect our observed results.

Second, we were grateful that the authors raised a concern about the generalizability of our result. The main population diagnosed with type 2 DM in Taiwan was older than 40, so we excluded patients younger than 40 years to focus on our targeted population [4]. Although we have excluded the patients with diagnoses of type 1 DM, which share different pathogenesis and treatment strategies with type 2 DM, some patients with type 1 DM may not be coded accurately [5]. Adding a cut-off age of 40 could help filter the patients and make the study population more consistent with the diagnosis of type 2 DM. We thanked the author for highlighting the elevating concern of DR in younger patients with age <40 years and further study was valuable to focus on this population.

Third, we also appreciate the authors bringing up the concern about the DR outcomes utilized in our study. The difference in the definition of DR outcome would affect the risk estimate of DR between the two groups. Macular edema, vitreous

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hemorrhage, retinal detachment, and blindness represented significant DR-related complications, but the above diagnoses could also be derived from other ocular diseases, such as retinal vein occlusion [6]. In addition, the vitreoretinal interventions in our study included intravitreal injection, retinal laser, and vitrectomy, which served as the leading therapies for vision-threatening DR. The utilization of the intervention code was able to confirm the diagnosis of advanced DR further and increased the internal validity of our outcomes. Moreover, this study classified DR outcomes as nonproliferative and proliferative DR, which aimed to estimate the risk of DR at different stages.

Fourth, we were thankful that the authors pointed out the question regarding the possible mechanism in which SGLT2i users reported a significantly lower incidence of proliferative DR and receiving vitreoretinal interventions, but no significant difference was found in nonproliferative DR in this study. This outcome was suggested to be associated with a steadier glucose-lowering effect in the short term from SGLT2i. SGLT2i users had a smaller decline of HbA1c in the early phase of our study (Fig. 3A), which may be able to alleviate the rapid progression to advanced DR and correspond to the lower cumulative incidence of proliferative DR in the early phase of our study (Fig. 2A) [1]. The renal protection effect of SGLT2i may also be related to the lower incidence of vision-threatening DR. Although we have suggested some possible pharmacotherapeutic mechanisms of the protective association between DR and SGLT2i, we agree that more research is needed to clarify the biological mechanism of SGLT2i and the association of DR at different stages.

We thank the authors' comments on this article, and we believe further investigation may be necessary and worthy in figuring out the association of SGLT2i in a younger population and the pharmacotherapeutic mechanism.

CONFLICTS OF INTEREST

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

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