COMMENT ON YANG ET AL.

GLP-1RAs for Ischemic Stroke Prevention in Patients With Type 2 Diabetes Without Established Atherosclerotic Cardiovascular Disease. Diabetes Care 2022;45:1184–1192

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We read with great interest the recent article in *Diabetes Care* by Yang et al. (1). The authors conducted a retrospective cohort study to evaluate the effectiveness of glucagon-like peptide 1 receptor agonists (GLP-1RAs) for ischemic stroke prevention from the Taiwan National Health Insurance Research Database. While these results are important, we would like to highlight several methodological issues and provide our perspective.

First, it is unclear whether type 2 diabetes (T2D) had been well controlled. Diabetes may increase the risk of stroke (2). National Health Insurance guidelines in Taiwan require that GLP-1RAs be used only in patients with T2D who have received the maximum tolerated dose of metformin or sulfonylurea and still do not have adequate blood glucose control. It is difficult to determine whether the risk reduction is due to better disease control with an additional drug or to the effect of GLP-1RAs.

Second, the selection of the control group for the study could cause potential bias. The comparison group is non–GLP-1RA users. However, metformin is the first-line choice for T2D, and the newer second-line choices for T2D should include GLP-1RAs, dipeptidyl peptidase 4 inhibitors, and sodium–glucose cotransporter 2 inhibitors (3). We suggest that the authors conduct a further comparison of these classes of drugs to enhance the credibility of the results. In addition, the experimental group's index date was set as the first prescription record for GLP-1RAs, while the control group's index date was a randomly generated date after T2D diagnosis. The period from study entry to the index date may be different between the experimental and control groups. Such a classification may cause potential "immortal time bias," which can overestimate the effect of treatment (4). The authors should clarify this point.

Third, there are residual confounders that should be considered. Although the authors had stratified for comorbidities and performed propensity score matching to balance possible confounders, we believe that there are still important residual confounders, such as the duration of diabetes, the severity of the kidney disease, and the patient's income and education level, that may limit the interpretation of the study results.

The authors provided us with important and valuable findings. However, we suggest that addressing the abovementioned important issues will make this study, which is based on an adequate database, more convincing.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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