Response

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Efficacy and Safety of Treatment with Quadruple Oral Hypoglycemic Agents in Uncontrolled Type 2 Diabetes Mellitus: A Multi-Center, Retrospective, Observational Study (*Diabetes Metab J* 2021;45:675-83)

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We are grateful for the opportunity to respond to Professor Tae Jung Oh's letter concerning our recent article, "Efficacy and safety of treatment with quadruple oral hypoglycemic agents in uncontrolled type 2 diabetes mellitus: a multi-center, retrospective, observational study" [1]. We would also like to thank Professor Oh for their valuable comments on our article.

We fully agree with the limitations of this study raised by Professor Oh. Our study demonstrated a meaningful glucose lowering effect of 1.1% after the introduction of a quadruple combination. However, the relatively good effect was likely influenced by the high glycosylated hemoglobin (HbA1c) level at baseline. In our study, the proportion of people with HbA1c <7% increased significantly to 25% after treatment with the quadruple combination for 1 year (from 2% at baseline). Thus, three out of four patients failed to reach the target of less than 7% and still had poor blood sugar control. Meanwhile, the glycemic-lowering effect of this quadruple therapy was similar (1.0% to 1.5% in HbA1c) in other observational studies [2-4].

In addition, it is reasonable to assume that reports of side effects including hypoglycemia may have been underestimated due to the retrospective nature of this study. Sulfonylurea accounted for a significant portion of the composition of triple therapy at baseline, but most oral hypoglycemic agents (OHAs) newly added to the quadruple combination were sodium-glucose co-transporter 2 inhibitors, thiazolidinediones or alpha glucosidase inhibitors, which rarely cause hypoglycemia. When dapagliflozin was introduced as the fourth drug in people with poor glycemic control, hypoglycemic events were significantly lower than seen with insulin glargine (1.6% vs. 15.1%) [5].

Although our study was not designed study for comparison with insulin or placebo treatment in triple OHA failure, it reveals the natural course and current status of quadruple OHA therapy in real clinical practice. Most of the current guidelines recommend injection therapy after triple combination; OHA add-on to the triple combination is not covered by health insurance. However, physicians are considering quadruple com-

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bination as another option in clinical practice, as noted in our study. When glycemic control is poor on two or more OHAs, treatment intensification, including insulin injection, is often delayed. The higher the number of OHAs used, the slower treatment intensification tends to be [6]. The initiation of insulin was reported to be delayed in Korean patients with type 2 diabetes mellitus uncontrolled by two or more OHAs due to various patient- and physician-related factors [7]. Nevertheless, physicians should not delay the proper use of injection therapy including insulin due to quadruple OHA therapy.

CONFLICTS OF INTEREST

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

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