



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)

Tae Jung Oh

Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea


There are numerous reasons for clinical inertia to insulin, such as fear of injection, negative appraisals of insulin, and side effects [1]. From the data of Diabetes Fact Sheets in Korea 2020 [2], the percentage of patients with type 2 diabetes mellitus using insulin is only 4.1%, much lower than the 15% estimated in UK data in 2010 [3]. Instead, many physicians prescribe quadruple oral hypoglycemic agents, which are not approved by the Korea Food and Drug Administration. Therefore, the efficacy and safety of this regimen must be analyzed.

In this article entitled, “Efficacy and safety of treatment with quadruple oral hypoglycemic agents in uncontrolled type 2 diabetes mellitus: a multi-center, retrospective, observational study,” Moon et al. [4] reported clinical data of efficacy and safety of quadruple oral hypoglycemic agents in the Yeongnam and Honam regions of Korea. This multicenter study showed a 75.6% adherence rate to quadruple oral hypoglycemic agents for 12 months, producing a $-1.1\% \pm 1.2\%$ reduction of glycosylated hemoglobin (HbA1c) without any significant safety issue. The HbA1c-lowering efficacy was similar when including patients who did not continue the quadruple regimen despite no reported reason for discontinuation. As a higher baseline HbA1c ($\geq 9.0\%$) represents better glycemic lowering effect after quadruple therapy [5], a good response is expected in the current study because the baseline HbA1c was $9.0\% \pm 1.3\%$. Even though observational studies [4,5] have shown the effec-

tiveness of the quadruple regimen, further randomized clinical trials are needed to compare this regimen with placebo or injection therapy.

There is doubt about the short- and long-term safety of the quadruple regimen. The hypoglycemia in this study was captured only by electronic records from an emergency room visit. However, most hypoglycemic events occur outside of the healthcare system [6]. The present study did not report any hypoglycemic events, even though 94.4% of patients were treated with sulfonylurea. Therefore, underestimation of hypoglycemia is suspected, and the safety of quadruple oral hypoglycemic agents regarding hypoglycemia remains unknown. Furthermore, 74.8% of patients had not achieved the treatment target (HbA1c $< 7.0\%$). Therefore, diabetic vascular complications might not be effectively prevented in the majority of patients under quadruple regimen. In addition, baseline renal function was relatively well-preserved, with mean estimated glomerular filtration rate of 90.0 mL/min/1.73 m². The indications of metformin and sodium-glucose co-transporter 2 inhibitor for renal impairment are broadening, and the quadruple regimen must be studied in patients with renal impairment. The current study did not involve clinical data of quadruple regimen use in patients with renal impairment.

In my opinion, the authors have reported valuable results about real clinical data of quadruple regimens. However, as the

Corresponding author: Tae Jung Oh  <https://orcid.org/0000-0002-5078-6123>
Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
E-mail: ohtjmd@gmail.com

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authors mentioned in the last sentence in their article, these data do not rule out the need for insulin therapy.

CONFLICTS OF INTEREST

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

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