RESPONSE TO COMMENT ON KWON ET AL.

The Long-term Effects of Metformin on Patients With Type 2 Diabetic Kidney Disease. Diabetes Care 2020;43:948–955

Soie Kwon,[1,2] Clara Tammy Kim,[3] and Jung Pyo Lee[2,4]

Diabetes Care 2020;43:e191 | https://doi.org/10.2337/dci20-0040

We appreciate the comments by Fu and van Diepen (1) on our recent study (2) about the advantage of metformin use in patients with advanced chronic kidney disease in terms of decreasing the risk of all-cause mortality and incident end-stage renal disease. As metformin users had better baseline characteristics than nonmetformin users, we used propensity score matching for covariate balancing.

Due to the limitations of randomized controlled trials, such as extensive resource requirements and difficulties in long-term follow-up, and introduction of electronic health record system, many observational studies based on real-world data have been conducted recently (3). The prevalence of diabetic kidney disease, one of the microvascular complications, increases in patients with prolonged diabetes or poor glycemic control (HbA_{1c} >6.5%) (4). This suggests that patients with diabetic kidney disease are more likely to be prescribed multiple diabetes medications over a long period of time, which is the reason we conducted this observational study.

When performing an observational cohort study, immortal time bias and imbalanced baseline characteristics should be considered and methodologically overcome (5). For the latter, we used propensity score matching to balance the differences in baseline characteristics. As for the former, we concluded upon internal discussion that considering immortal time bias for metformin prescription, as suggested by Fu and van Diepen, is not suitable in the current study.

Most of the cases for which immortal time bias was considered, including the examples from Fu and van Diepen, simply compared two groups of patients who did or did not receive a specific treatment. In this situation, only the treatment group benefits from the immortal time bias from the time span between enrollment and treatment initiation. However, the current study population was prescribed multiple antidiabetes drugs during the study period. The prescription rate for drugs other than metformin, such as sulfonylurea and insulin, was also high (described in detail in Table 1 of the original article) (2). Also, as a first-line treatment for type 2 diabetes, metformin has more chance to be prescribed earlier than other antidiabetes drugs.

We compared the period between the earliest prescription date of antidiabetes drugs (metformin, sulfonylurea, and insulin) and patient enrollment. In the entire population, there were no statistical differences between metformin and nonmetformin groups (median days [interquartile range]; metformin group, 11.0 days [0; 611]; nonmetformin group, 12.0 days [0; 386]; $P = 0.304$). Moreover, in our main interest group (30 mL/min/1.73 m^2 < eGFR ≤ 60 mL/min/1.73 m^2), metformin had a shorter lag time (metformin group, 6.0 days [0; 73]; nonmetformin group, 10.0 days [0; 161]; $P < 0.001$). Lastly, the purpose for considering HbA_{1c} as a time-varying covariate was not to avoid immortal time bias but to consider the effect of glycemic control on the outcomes. (Better the glycemic control, better the outcome.)

Of course, we agree that more delicate statistical approaches and better-organized randomized controlled trials are needed to change the practice. We will also continue to consider immortal time bias and time-varying covariates in subsequent studies.

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

References

1. Fu EL, van Diepen M. Comment on Kwon et al. The long-term effects of metformin on patients with type 2 diabetic kidney disease. Diabetes Care 2020;43:948–955 (Letter). Diabetes Care 2020;43:e190. DOI: 10.2337/dc20-1591
2. Kwon S, Kim YC, Park JY, et al. The long-term effects of metformin on patients with type 2 diabetic kidney disease. Diabetes Care 2020;43:948–955
3. Corrigan-Curay J, Sacks L, Woodcock J. Real-world evidence and real-world data for evaluating drug safety and effectiveness. JAMA 2018; 320:867–868
4. Kim MK. Treatment of diabetic kidney disease: current and future targets. Korean J Intern Med (Korean Assoc Intern Med) 2017;32:622–630
5. Stürmer T, Wang T, Golightly YM, Keil A, Lund JL, Jonsson Funk M. Methodological considerations when analysing and interpreting real-world data. Rheumatology (Oxford) 2020;59:14–25

[1]*Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea*
[2]*Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, Korea*
[3]*Institute of Life and Death Studies, Hallym University, Chuncheon, Korea*
[4]*Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea*

Corresponding author: Jung Pyo Lee, nephrolee@gmail.com