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

Fu, E.L.; Diepen, M. van

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

Edouard L. Fu and Merel van Diepen

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We read with interest the recent study by Kwon et al. (1) examining the long-term effects of metformin use on mortality and incident end-stage kidney disease among 10,426 patients with type 2 diabetic kidney disease. The authors report that metformin use decreased the risk of all-cause mortality by 35% and end-stage renal disease progression by 33% after applying propensity score matching to adjust for a number of measured confounders.

We are concerned by the possible influence of immortal time bias on the study results. Immortal time arises when patients are classified into treatment groups at baseline based on treatment information that is only available *after* baseline (2). Since the treatment group is based on future information, by definition no deaths can occur in the treatment group between baseline and this future point in time. After all, individuals who have an event prior to taking up treatment would be classified into the untreated group. In this study, follow-up started on the date of the first creatinine measurement, but patients were classified as metformin users if they were prescribed metformin for longer than 90 days during the follow-up period (1). Such exposure classification may lead to an unfair survival advantage for the metformin users. For example, if all individuals in the metformin group started metformin treatment only after 5 years of follow-up, no deaths would occur in the metformin group during the first 5 years. The metformin group would thus be "immortal" for this time period. Due to the long-term follow-up of this study (maximum follow-up was 16 years), immortal time may have substantially biased the study results.

Immortal time bias could have been prevented by correctly assigning the person-time between start of follow-up and treatment initiation to the untreated group, e.g., by using a Cox model with a time-varying exposure (2). Individuals will then contribute person-time to the unexposed group before metformin initiation and to the exposed group after metformin initiation. When using a time-dependent exposure, time-dependent confounding will also be present. If these time-dependent confounders play the role of both confounder and mediator, simply adjusting for them in a regression model will produce biased results. For example, HbA_{1c} is influenced by prior metformin treatment status but also influences future metformin treatment status. Therefore, HbA_{1c} will both confound and mediate the effect of metformin on mortality and a straightforward time-dependent Cox analysis may not suffice in this case (3). Instead, methods such as marginal structural models based on inverse probability weighting should be applied (3). Other methods that could have been used to avoid immortal time bias include landmarking (4) or the use of grace periods (5).

In conclusion, we feel the possibility of immortal time bias casts serious doubt on the validity of the results. Observational pharmacoepidemiologic studies must be designed and analyzed properly. Only then can the results of these studies meaningfully inform clinical practice.

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

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Department of Clinical Epidemiology, Leiden University Medical Center, the Netherlands

Corresponding author: Edouard L. Fu, e.l.fu@lumc.nl