RESPONSE TO COMMENT ON CUROVIC ET AL.

Optimization of Albuminuria-Lowering Treatment in Diabetes by Crossover Rotation to Four Different Drug Classes: A Randomized Crossover Trial. Diabetes Care 2023;46:593–601

Viktor Rotbain Curovic,[1] Frederik Persson,[1] Niels Jongs,[2] and Hiddo J.L. Heerspink[2]

Diabetes Care 2024;47:e21 | https://doi.org/10.2337/dci23-0046

The letter by Dr. Zelnik (1) about our article (2) expresses concerns around the selection of the "individual best-performing drug," subsequent reexposure to the same drug, and, most importantly, the lack of reexposure to the three ineffective drugs. We agree that including a second exposure for all drugs would reduce potential bias in selecting the right drug for each patient. In fact, the original protocol was designed to reexpose participants to one of the nonpreferred agents. However, ethics committees did not allow us to reexpose participants to one of the nonpreferred agents.

Although we were unable to reexpose patients to the nonpreferred agents, the results remain valid from a clinical point of view. Clinical trials should be designed to inform clinical practice, thus trial design should mimic clinical practice. Our trial was therefore designed in accord with clinical practice guidelines, in which treatment targeting a specific diabetic complication, in our case chronic kidney disease in diabetes, is recommended to be discontinued if no, or little, effect is seen (3). Thus, the methodology aligns with the challenge clinicians face in their daily practice, namely, selecting the right drug for the right patient. That the change in albuminuria in each treatment period was patient specific and reproducible, thus reflecting a true pharmacological response rather than a random change, is supported by several findings. First, albuminuria was substantially reduced during the treatment period with the individual's preferred drug, whereas the response to the other three drugs was poor. This was true for all drugs used in the rotation schedule. Second, there was no correlation in albuminuria response among the different agents. Third, the individual albuminuria response was also reproducible, as the change in albuminuria during the treatment period strongly correlated with the change during the washout period and the change during the confirmation period. These data thus support that the individual change in albuminuria reflects a true drug response and varies per patient.

Finally, we note the simulation analysis presented in the comment from Dr. Zelik. By sampling from five independent normal distributions, this simulation ignores the most important aspect of our trial, namely, the repeated measures within subjects and the within-subject correlations. This correlation assumes that the response during a confirmation exposure to the same drug at the same dose is not completely random within subjects, in accord with the concept of personalized medicine and our study findings.

In conclusion, we acknowledge the comments and concerns raised by Dr. Zelik from a statistical point of view. We submit that designing a similar trial reconfirming all responses is clinically unfeasible at best and unethical at worst. We welcome, however, novel trial designs and approaches to study individual drug responses in a feasible, ethical, and clinically implementable way.

Duality of Interest. F.P. has served as a consultant, on advisory boards, or as an educator for AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Sanofi, Mundipharma, MSD, Novartis, and Amgen and has received research grants to institution from Novo Nordisk, Boehringer Ingelheim, Amgen, and AstraZeneca. H.J.L.H. is a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, CSL Behring, Dimerix, Eli Lilly, Gilead Sciences, Janssen, Novartis, Novo Nordisk, and Travere Therapeutics. He received research support from AbbVie, AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

References

1. Zelnick LR. Comment on Curovic et al. Optimization of albuminuria-lowering treatment in diabetes by crossover rotation to four different drug classes: a randomized crossover trial. Diabetes Care 2023;46:593–601 (Letter). Diabetes Care 2024;47:e20
2. Curovic VR, Jongs N, Kroonen MYAM, et al. Optimization of albuminuria-lowering treatment in diabetes by crossover rotation to four different drug classes: a randomized crossover trial. Diabetes Care 2023;46:593–601
3. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753–2786

[1]*Steno Diabetes Center Copenhagen, Herlev, Denmark*
[2]*Department of Clinical Pharmacy and Pharmacology, University of Groningen, Groningen, the Netherlands*
Corresponding author: Hiddo J.L. Heerspink, h.j.lambers.heerspink@umcg.nl