RESPONSE TO COMMENT ON HONG ET AL.

Effects of Metformin Versus Glipizide on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Coronary Artery Disease. Diabetes Care 2013;36:1304–1311

Jie Hong,[1] Yifei Zhang,[1] Shenghan Lai,[2] and Guang Ning[1]

Diabetes Care 2014;37:e21 | DOI: 10.2337/dc13-2003

We thank Lund and Gong (1) for their letter and for taking an interest in our recent article (2). The following are responses to specific inquiries on the details of the trial. First, we respond to the statement that although our randomized clinical trial (RCT) is probably the first report of cardiovascular (CV) outcomes comparing the long-term effects of glipizide and metformin on the major CV events in type 2 diabetic patients who had a history of coronary artery disease, "several previous larger-scale RCTs in [type 2 diabetic] patients, including dedicated CV trials, do not necessarily support metformin as cardioprotective—maybe the contrary" (1). Our trial had different design, end points, and study populations than the clinical trials cited by Lund and Gong (1). Even with the same study design, clinical trials conducted in different patient populations could produce very different, even contradictory, results. Heterogeneity in clinical trials is not uncommon. Second, our trial had no placebo group. Our trial was not a phase III trial and may not need a placebo arm. Third, our trial was extended for about 2 years. Contrary to what Lund and Gong described, we state in the randomization and study medication section of the article that the study participants were randomly assigned to receive medications for 3 years. Due to staggered patient enrollment, the trial lasted 6 years since each patient must have taken medications for 3 years and have been followed up for 3 years. We provided a clear statement in this regard in our registration on ClinicalTrials.gov (3). We did not present Kaplan-Meier plots. Since we performed multiple-event analysis with the use of the proportional means regression model (3), Kaplan-Meier plots could not provide useful information for multiple-event analysis. Fourth, we failed to provide additional CV (and mortality) risk estimates for the 3-year treatment period and Kaplan-Meier plots for the whole study period. The trial was designed to follow participants for 3 years. Thus, according to time-to-event analysis, the trial should provide CV (and mortality) risk estimates for the whole study period. Since our primary end point dealt with multiple events, Kaplan-Meier plots estimating the survivor functions for events that can only occur once (such as death) would not be useful.

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

References

1. Lund SS, Gong Y. Comment on Hong et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care 2013;36:1304–1311 (Letter). Diabetes Care 2014;37:e19–e20. DOI: 10.2337/dc13-1806
2. Hong J, Zhang Y, Lai S, et al.; SPREAD-DIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care 2013;36:1304–1311
3. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J R Stat Soc Series B Stat Methodol 2000;62:711–730

[1]*Rui-jin Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China*
[2]*Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD*

Corresponding author: Guang Ning, guangning@medmail.com.cn.