COMMENTS AND RESPONSES

Comment on: Pantalone et al. The Risk of Overall Mortality in Patients With Type 2 Diabetes Receiving Glipizide, Glyburide, or Glimepiride Monotherapy: A Retrospective Analysis. Diabetes Care 2010;33: 1224–1229

In the article by Pantalone et al. (1), the authors did not identify an increased total mortality risk among individual sulfonylureas (SUs)—glibenclamide versus glimepiride or glipizide—but did suggest that glimepiride may be the preferred SU in patients with history of coronary artery disease (CAD). The authors found that in a retrospective cohort of patients with CAD, the hazard ratio (HR) for mortality in the subgroup of glibenclamide versus glimepiride was 1.36 (95% CI 0.96–1.91); $P = 0.081$.

Pantalone et al. refer to our assessment of total and cardiovascular mortality HRs in patients treated with gliclazide versus glibenclamide (0.33 [95% CI 0.26–0.41] and 0.29 [0.21–0.38], respectively; $P < 0.001$) and total mortality HRs in patients receiving glimepiride versus glibenclamide (0.60 [0.41–0.89]; $P = 0.01$) (2), considering them based on incorrect adjusting for variables.

Pantalone et al. believe that the ability of glipizide and gliclazide to bind SU receptors does not differ, and that is why they estimated HR for glipizide versus glibenclamide. Meanwhile, the interaction of these molecules with the SU receptors is different; for example, their half-maximal inhibitory concentration on chanel activity differs by more than 10 times, whereas the corresponding differences between glibenclamide, glipizide, and glimepiride could be significantly lower (3). According to a recent nationwide register-based study in Denmark, monotherapy with glibenclamide, glimepiride, or glipizide—but not with gliclazide—is associated with increased mortality and CAD risk compared with metformin (4). It is even speculated that differences between SUs may underpin the different outcomes observed in the ACCORD and ADVANCE trials (4,5).

In our study of 119,570 patients who had originally been assigned to monotherapy with glibenclamide, glimepiride, or gliclazide, the unchangeableness of received treatment has been confirmed in only 64,288 cases after a minimum of two follow-up checks. We managed to avoid bias in risk assessments that have arisen due to changes in treatment. This is why we have obtained gliclazide versus glibenclamide totals and cardiovascular disease mortality HRs that were so high that they have sustained adjustments for seven variables. Glimepiride versus glibenclamide HR was not as high and was significant only for total mortality, without adjusting.

We were unable to consider the influence of socio-economic differences on the risk of SU-related mortality, but in the case of the glimepiride versus gliclazide comparison (HR 1.8 [95% CI 1.2–2.9]; $P = 0.006$), this factor was not significant since the cost of these drugs in the Ukraine is the same (2).

It seems that Pantalone et al. did not perform the verification of treatment unchangeableness during the observation period and did not mention the nonadjusted HRs. The authors only gave HRs, simultaneously adjusted for 22 variables, which greatly complicates the impact assessment of each variable.

Finally, Pantalone et al. indicate the need for prospective studies to assess the risk of individual SUs, but if gliclazide will not be included in such assessment, the truth will remain unrevealed.

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