COMMENTS AND RESPONSES

Response to 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

We kindly thank Dr. Khalangot for his comments (1). The literature contains conflicting results regarding whether an increased overall mortality (or cardiovascular mortality) risk accompanies the various sulfonylureas (2–5). The reason for this discrepancy is likely multifactorial as these reports differ in terms of their design and study populations, as well as their choice of variables for which adjustments were made, many of which can result in considerable confounding if not properly adjusted. Failure to adjust for variables such as socio-economic status, smoking status, as well as other medications (cholesterol lowering, antiplatelet, and antihypertensive) and comorbidities can result in point estimates (hazard ratios) that may not be a true reflection of the drug effect (individual sulfonylurea). Moreover, just because two drugs are the same price does not mean that a variable of socio-economic status will not impact the results; that is, socio-economic status has many effects, not just the ability to purchase medications. In our 2010 publication (2), we did not report the unadjusted results or the results adjusted for fewer variables (in order to assess/report the impact of each variable) because of space limitations.

We do not believe that the ability of glipizide and gliclazide to bind sulfonylurea receptors (SURs) is the same, as asserted by Dr. Khalangot. We estimated the hazard ratio for glipizide versus glyburide (glibenclamide) because glipizide is the SUR1-specific (pancreatic-specific) sulfonylurea that is available and commonly used in the U.S. (gliclazide is not available in the U.S.). We referred to his report in order to highlight the results, which suggested that glyburide (glibenclamide) was associated with an increased mortality risk when compared with other sulfonylureas. We did not intend to suggest glipizide and gliclazide were "equivalent" in terms of their pharmacology.

In our study, medication compliance and exposure times after baseline were unclear. These are recognized limitations that were identified in the discussion section of our manuscript. We clearly stated that the analysis was based on exposure to a medication based on the initial prescription. We reported that approximately 70% of the cohort remained on a single drug (baseline medication) throughout their time in the cohort to show that over the typical follow-up times in our study, medication changes did not appear to be a huge factor. Restricting an analysis to patients who continue the baseline drug throughout their duration in the cohort could create substantial bias, especially if patients are excluded at baseline only after finding out that the patients had switched drugs at a later date.

We hope that in the near future a randomized prospective study can be performed to determine whether the differences in pharmacologic properties inherent to individual sulfonylureas (including gliclazide) translates into differences in the risk of adverse cardiovascular outcomes and overall mortality, especially in patients with preexisting coronary artery disease.

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DOI: 10.2337/dc11-0920
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Acknowledgments—No potential conflicts of interest relevant to this article were reported.

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