RESPONSE TO COMMENT ON LAITEERAPONG ET AL.

The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study). Diabetes Care 2019;42:416–426

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We appreciate the opportunity to discuss our work (1) further in response to Hulman et al. (2). While we understand and appreciate their four concerns, we respectfully disagree with their interpretation of our work and stand by our analytic approach and conclusions. One major concern was that the results were biased because we conditioned study inclusion on survival of 10 years. While we agree that conditioning on survival would be a concern if we were generalizing results to all patients with diabetes, we clearly specified that our results only apply to patients who survive a minimum of 10 years. It was necessary to condition the study population on some minimum years of survival because one must have adequate follow-up time in order to study the long-term effects of glycemic control. Based on the UK Prospective Diabetes Study (UKPDS), a minimum of 9 years was necessary to perceive the effects of intensive glycemic control on retinopathy and at least 20 years of follow-up were necessary to see effects on mortality (3,4). Therefore, a minimum of 10 years survival was a reasonable study inclusion criterion. Another concern expressed by Hulman et al. (2) was that the models have different follow-up periods, with the consequence that this difference in follow-up periods explains our finding that increasing durations with HbA_{1c} >8% were associated with increased complications. We agree and therefore reported a sensitivity analysis that explored the effects of a fixed 5-year follow-up period for all models. This sensitivity analysis corroborated the pattern of increasing risk of microvascular complications (Supplementary Fig. 2*A* [1]). Another concern was that the models have overlapping samples and thus should include some statistical accommodation for multiple comparisons. While we agree that the hazard ratios should be used cautiously as independent estimates of effects, our intent avoided this limitation. Rather, we defined the qualitative relationship between early glycemic control and complications in patients who survive 10 years after diagnosis. As such, this analysis does not require adjustment for multiple comparisons (5). Their last concern was that the mean HbA_{1c} value may be too crude to capture differences between exposure periods, especially if some periods may have more frequent measures than others. We recognize that this issue could be a concern for glycemic values that vary greatly over short periods of time; however, HbA_{1c} values are consistent over 3-month periods because of their dependence on the red blood cell life span (6,7). The model that Hulman et al. (2) have proposed (Poisson model with split follow-up times) is an interesting alternative to our modeling approach that could be explored in future studies.

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