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The Reply

I appreciate the authors' comments. Safiri raises a valid statistical point, namely, the use of a composite cardiovascular end point as a primary end point in our article.[1] The problem is well known, but it has been done in many (almost all) clinical trials in an attempt to limit the number of patients needed and the duration of follow-up to prevent beta errors.

Making single cardiovascular end points (eg, myocardial infarction, stroke, or cardiovascular mortality) the primary end point would increase the number of patients and events needed, and the duration of follow-up by several fold. Thus, the composite end point has been accepted in the literature as a legitimate end point in clinical trials.

Hierarchical regression models have their own limitations, that is, they cannot rely on statistically significant results if in the hierarchy a nonsignificant outcome occurs. If, for example, the model includes 10 outcomes and the second happens to be nonstatistically significant, any subsequent results that may be statistically significant are only considered hypothesis-generating and not final.

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Reference

1. Papademetriou V, Nylen ES, Doumas M, et al. Chronic kidney disease, basal insulin glargine, and health outcomes in people with dysglycemia: the ORIGIN Study. *Am J Med*. 2017;130(12):e1427-e1465, e39.

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