COMMENTS AND RESPONSES

Response to Comment on: The ORIGIN Trial Investigators. Characteristics Associated With Maintenance of Mean A1C <6.5% in People With Dysglycemia in the ORIGIN Trial. Diabetes Care 2013; 36:2915–2922

We thank Drs. Esposito and Giugliano for their interest in the glycemic control results from ORIGIN (Outcome Reduction with Initial Glargine Intervention) (1), and their recognition of the potential importance of our findings. Citing their own systematic reviews of literature, they point out that the ability of insulin treatment to attain good control of A1C levels is strongly related to the level of glycemic control at which the intervention begins (2). We agree that starting treatment with insulin glargine for study participants with overt diabetes at entry in ORIGIN was able to keep A1C below 7.0% for 88% of participants at 1 year and 77% at 5 years, in large part because median A1C was 6.55% when treatment was started. This assumption is supported by a previously reported analysis of patient-level data from 2,193 participants who completed 24 weeks of treatment in 12 randomized studies of initiating insulin glargine (3). The mean A1C value at baseline in this glargine-treated population was 8.8%, and after 24 weeks of treatment the mean was 7.05%, with 57% of participants attaining ≤7.0%. For those with A1C <8.0% at baseline (mean 7.6%), the mean A1C at 24 weeks was 6.7% and 75% attained ≤7.0%.

Both the results of ORIGIN and analyses of prior studies, such as described here, argue that starting basal insulin before A1C has reached high levels can routinely restore control to ≤7.0%. Two important questions remain. One is whether preventing exposure to significant hyperglycemia preceding initiation of effective antihyperglycemic therapies in type 2 diabetes will substantially improve later medical outcomes. Although early use of insulin glargine in ORIGIN had a neutral effect on cardiovascular disease and cancer and seldom caused severe hypoglycemia, the long-term benefits versus risks are as yet unknown. Another question is whether earlier use of insulin can, by "resting" β-cells, delay the decline of their function as was suggested by initial analysis of progression from impaired fasting glucose or impaired glucose tolerance to overt diabetes in ORIGIN (4). Further analyses from ORIGIN and its passive follow-up study (ORIGINALE [ORIGIN And Legacy Effects]) may address these questions.

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