COMMENTS AND RESPONSES

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

In their recently published Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial (1), the investigators found that basal insulin glargine started early in the natural history of dysglycemia can maintain glycemic control near baseline levels for the whole study length. This trial is important for the size (12,537 individuals), geography (40 countries), and follow-up (up to 5 years). During glargine treatment, the percentage of diabetic patients achieving A1C <7.0% (53 mmol/mol) was 88% at 1 year and 77% at 5 years, and the percentage achieving A1C <6.5% (48 mmol/mol) was 74% at 1 year and 60% after 5 years. These percentages of success in achieving prespecified A1C targets with glargine need to be compared with the results of randomized controlled trials (RCTs) assessing the effectiveness of basal insulin analogs to reach the A1C target of <7% in patients with type 2 diabetes failing previous treatments. Our systematic review (2) of RCTs with basal insulin analogs (glargine, detemir, insulin lispro protamine suspension) included 29 trials with 38 arms and 17,588 patients; study length ranged between 16 and 104 weeks (median 24 weeks). The proportion of patients at A1C target <7% was 41.4% (95% CI 35.6–47.4), but this varied considerably between studies (I^2 = 95.7%). The comparison between the 1-year results of ORIGIN and other RCTs with a median length of 24 weeks favors ORIGIN (88 vs. 41.4%). The achievement of A1C target <6.5% has been estimated using mean and SD of A1C at the end of treatment in each RCT (3). The analysis of data coming from 43 arms and 18,976 people with type 2 diabetes gave an estimate of success of 20.8% (95% CI 18–23.7) (I^2 = 99%), which is about four times lower of that recorded in ORIGIN (A1C <6.5% at 1 year = 74%).

One main difference between ORIGIN and all other RCTs of basal insulin analogs is the starting A1C level. Baseline A1C in the diabetic groups of ORIGIN was 6.55% on the average; on the contrary, the median baseline A1C value was 8.7% (72 mmol/mol) (interquartile range 8.47–8.86%) (69–73 mmol/mol) in the 43 arms of RCTs (3). Intuitively, the closer the distance of baseline A1C from the target, the higher the likelihood to reach the target. This was what exactly happened in ORIGIN: lower A1C at baseline was a predictor of success in maintaining mean A1C <6.5%, in both univariate and multivariate analyses. Interestingly, in our systematic review (2) the lowest baseline A1C level (<8% [64 mmol/mol]) was associated with the highest success rate in achieving A1C <7% (55%, 95% CI 22.9–84.8), but this was not significant (P = 0.10), probably due to the small numbers of trials (only three trials with a mean baseline A1C <8%). Keeping A1C at any personalized target is more likely in type 2 diabetic people with lower baseline A1C.

KATHERINE ESPOSITO, MD, PHD[1]
DARIO GIUGLIANO, MD, PHD[2]

From the [1]Department of Clinical and Experimental Medicine and Surgery, Second University of Naples, Naples, Italy; and the [2]Department of Medical, Surgical, Neurological, Metabolic Sciences, and Geriatrics, Second University of Naples, Naples, Italy.

Corresponding author: Dario Giugliano, dario.giugliano@unina2.it.

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