RESPONSE TO ZANDERS ET AL.

# The Association of Basal Insulin Glargine and/or n-3 Fatty Acids With Incident Cancers in Patients With Dysglycemia. Diabetes Care 2014;37:1360–1366

*Louise Bordeleau*[1] *and Hertzel C. Gerstein*[2]

*Diabetes Care 2014;37:e223 | DOI: 10.2337/dc14-1567*

Zanders et al. (1) provided a number of comments on our recently published article detailing the cancer outcomes of the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial (2). They question the reported methodology in more detail. More specifically, they feel that the cancer outcome is a post hoc end point, that total daily dose of glargine should be used as opposed to total daily dose of any insulin, and that the confidence interval for specific cancer subtype remains wide.

A properly conducted randomized clinical trial remains the most robust study methodology to assess causality, whereas epidemiologic studies can only help generate hypotheses about potential causal link due to an inability to account for unmeasured or unanticipated confounders. The ORIGIN trial (a large, multicenter, international randomized clinical trial of titrated basal insulin glargine or standard care) is therefore well positioned to address the question of potential causality. It is important to note that the analyses of cancer outcomes were prespecified in the ORIGIN statistical analysis plan that was completed well before the study database was closed and analyzed. Moreover, all cancers requiring hospitalization were ascertained from the time of randomization until the end of the trial; starting January 2010, all participants were asked to report any cancer events (including those not requiring hospitalization) since the time of randomization and at each subsequent visit; and all cancer cases were sent for blinded adjudication. Strengths of the cancer analyses include the prospective randomized nature of the trial and the large number of cancer cases. As specified in our article, a limitation of the study is the low incidence of specific types of cancer, which translate into wide confidence intervals for each specific cancer. Nevertheless, there is no signal for increased cancer risk/mortality with the use of basal insulin glargine. Further study on specific cancer subtypes will be difficult to achieve in the context of a randomized clinical trial of sufficient sample size to provide tight confidence intervals.

The total daily dose of any insulin was used in the time-varying analyses of the ORIGIN trial for the following reasons: *1*) the risk of malignancy with insulin glargine versus other types of insulin does not appear to differ (3); *2*) insulin glargine is partially degraded at the injection site, yielding products closely similar to human insulin with low mitogenic potential (4,5); and *3*) the analysis by subtypes of insulin would significantly reduce the power to detect a relationship as only 5% of patients in the standard care arm received short-acting insulin.

**Duality of Interest.** The ORIGIN trial was funded by Sanofi. H.C.G. received consulting fees from Sanofi, Novo Nordisk, Lilly, Bristol-Myers Squibb, Roche, AstraZeneca, Novartis, GlaxoSmithKline, and Bayer; lecture fees from Sanofi and Bayer; and support for research or continuing education through his institution from Sanofi, Lilly, Merck, Novo Nordisk, Boehringer Ingelheim, Bristol-Myers Squibb, and AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

## References

1. Zanders MMJ, Renehan AG, Bowker SL, et al. Comment on Bordeleau et al. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. Diabetes Care 2014;37:1360–1366 (Letter). Diabetes Care 2014;37:e221–e222. DOI: 10.2337/dc14-1380
2. Bordeleau L, Yakubovich N, Dagenais GR, et al.; ORIGIN Trial Investigators. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. Diabetes Care 2014;37:1360–1366
3. Rosenstock J, Fonseca V, McGill JB, et al. Similar risk of malignancy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: findings from a 5 year randomised, open-label study. Diabetologia 2009;52:1971–1973
4. Kuerzel GU, Shukla U, Scholtz HE, et al. Biotransformation of insulin glargine after subcutaneous injection in healthy subjects. Curr Med Res Opin 2003;19:34–40
5. Agin A, Jeandidier N, Gasser F, Grucker D, Sapin R. Glargine blood biotransformation: in vitro appraisal with human insulin immunoassay. Diabetes Metab 2007;33:205–212



[1]*Department of Oncology, Population Health Research Institute, McMaster University, Hamilton Health Sciences, Hamilton, Ontario, Canada*
[2]*Department of Medicine, Population Health Research Institute, McMaster University, Hamilton Health Sciences, Hamilton, Ontario, Canada*

*Corresponding author: Louise Bordeleau, louise.bordeleau@jcc.hhsc.ca.*