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

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Diabetes Care 2014;37:e221–e222 | DOI: 10.2337/dc14-1380

The recent findings from the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial that insulin glargine has a neutral association with cancer outcomes are, as Bordeleau et al. (1) state, "reassuring," but we suggest that they are not yet conclusive.

Observational studies initially supported the hypothesis that glargine is linked with an increased cancer risk. Many of the earlier studies were justifiably criticized for methodological limitations and were arguably inconclusive. Results from the ORIGIN trial (2) seemed to bring a clearer picture. Although cancer was a post hoc end point, the findings were relevant: no differences between treatment arms for all cancer incidence or deaths, or for incidence of several cancer types, leading some to suggest closure on this topic (3). More recent analyses from the ORIGIN trial led Bordeleau et al. to a similar conclusion. However, it is important to remind the readership that these were analyses of observational data within a randomized trial, and thus the rules of causal inference from observational studies apply rather than inferring causality (or lack of it) to the random allocation of baseline treatment.

In the analyses of Bordeleau et al. (1), the investigators applied several good principles of causal inference from observational studies, such as using time-varying methods to estimate drug exposure. The need for these is clear—for example, at the beginning of the trial, metformin was used by 27% and 28% of the glargine and standard care arms, respectively; at the trial end, these rates were 47% and 60%, respectively. Given an outcome of cancer incidence, cumulative glargine use is the exposure of interest, yet the main finding was reported based on modeling only initial glargine allocation. Within the intervention arm, 19% of the patients stopped using glargine permanently, while 43% were ever off glargine, largely due to patient refusal. Additionally, within the standard care arm, 12% of the patients commenced insulin by the end of the study. Total daily dose of any insulin is included as a time-varying variable in secondary analyses, but because of these changes in both treatment arms, this is insufficient.

We encourage the ORIGIN investigators to fully account for glargine exposure by considering this exposure as time-varying cumulative exposure in their analyses. As glargine use postrandomization was not random, a time-varying variable for ever/never exposure should be used to address the allocation bias problems (4).

Moreover, the point estimate for breast cancer risk associated with glargine exposure and accounting for time-varying insulin use is 1.24, with a wide 95% CI (0.72–2.15) because of only 56 events. Is this a type 2 error? As previous observational analyses have demonstrated similarly elevated increased risks with prolonged glargine exposure (5), to be reassured may be premature.

In addressing the hypothesis of a link between insulin glargine use and subsequent cancer risk, the strength of the ORIGIN data is a clinically uniform observational study of new insulin users, with protocol-driven follow-up and cancer end points, not its randomization at origin.

Duality of Interest. A.G.R. has received honoraria and research funding from Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

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