COMMENT ON ERONDU ET AL.

Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program. Diabetes Care 2015;38:1680–1686

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In the recent analysis of the canagliflozin trials, Erondu et al. (1) reported the incidence of acidosis, including diabetic ketoacidosis (DKA), in patients with type 2 diabetes (T2D) receiving canagliflozin treatment. Although it is highly persuasive that sodium–glucose cotransporter 2 inhibitors could increase the risk of DKA from a mechanistic standpoint (2), there are three issues that desire some comments.

In contrast to the report from the U.S. Food and Drug Administration (3) and the recent case reports by Peters et al. (4), blood glucose levels were markedly elevated in almost all 12 patients except for 2 patients, one without reported glucose levels and one within the range of 148–320 mg/dL. As all patients were treated for diabetes, the adverse incidences are likely to be triggered by acute events leading to markedly elevated hyperglycemia and acidosis. However, ketone levels were not available in 7 out of 12 cases. Thus, it is highly possible that not all the reported cases were DKA. Markedly elevated hyperglycemia with acidosis could have been the result from some acute event, and canagliflozin might not have played a role in the development of acidosis. It will be more informative if the authors could provide the events associated with severe hyperglycemia and acidosis.

From the description of the case reports by Erondu et al. (1), the clinical presentation of DKA differs from the classic ketosis-prone T2D (5), in which DKA is the initial manifestation of diabetes. In the current report, all patients had established diabetes for at least 10 years, except for 2 patients. Among 7 patients with a reported C-peptide level, all except one had fairly low C-peptide levels, suggesting significant β-cell exhaustion, which is against ketosis-prone T2D (2).

The central issue is whether canagliflozin increases the risk of DKA in patients with T2D. The authors failed to address this issue clearly in their conclusion. The true incidence of DKA in patients with T2D is difficult to estimate and largely not available. In this report, the incidence of DKA in the comparator group was provided and could serve as the reference for comparison with the treatment group. If we assumed all 12 cases had DKA, the odds ratio for DKA in the canagliflozin 100 mg group was 2.59 (95% CI 0.47–14.15), in the canagliflozin 300 mg group was 3.88 (0.78–19.22), and in the combined canagliflozin groups was 3.23 (0.71–14.77). After the exclusion of 6 cases of confirmed autoimmune diabetes, the odds ratio for DKA in the canagliflozin 100 mg group was 0.65 (0.06–7.14), in the canagliflozin 300 mg group was 1.94 (0.32–11.61), and in the combined canagliflozin groups was 1.29 (0.24–7.07). These results indicate that canagliflozin does not increase the risk of DKA in patients with T2D.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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