Effect of Sodium–Glucose Cotransporter 2 Inhibitors on Diabetic Ketoacidosis Among Patients With Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials

Huilin Tang,[1,2] Dandan Li,[3] Tiansheng Wang,[4] Suodi Zhai,[2] and Yiqing Song[1]

Diabetes Care 2016;39:e123–e124 | DOI: 10.2337/dc16-0885

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antidiabetes drugs for the treatment of type 2 diabetes (T2D) (1). In addition to their hypoglycemic effect, SGLT2 inhibitors also offer several beneficial effects, such as weight loss and blood pressure reduction (1). However, the overall health benefits of these drugs needed to outweigh their possible side effects. Recently, cumulative evidence suggests that SGLT2 inhibitors may lead to diabetic ketoacidosis (DKA), which is a serious acute complication of diabetes (2,3). In May 2015, the U.S. Food and Drug Administration issued an updated drug safety communication warning about SGLT2 inhibitors potentially increasing the risk of DKA (4). As DKA is a rare adverse effect, the evidence from individual studies or simply pooling the numbers from multiple reports is generally weak. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) to examine whether SGLT2 inhibitors affect the risk of DKA in patients with T2D.

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov from inception to 27 January 2016 to identify the published and unpublished RCTs of SGLT2 inhibitors that reported DKA events in patients with T2D. Two reviewers (H.T. and D.L.) independently performed the study selection, data extraction, and quality assessment. A Peto odds ratio (OR) with 95% CI was used due to a very low event rate. The I^2 statistic was used to detect the possible between-study heterogeneity. All statistical analyses were performed with STATA version 14.

A total of 10 eligible RCTs involving 13,134 patients and 14 DKA events were identified from 1,268 citations (5–14). Overall, the event rates were 0.1% in the group of SGLT2 inhibitor users versus 0.06% in the control groups. The meta-analysis results are shown in Fig. 1. Overall, SGLT2 inhibitor groups were not associated with a significantly higher risk of DKA compared with the control groups (OR 1.71 [95% CI 0.56, 5.20]). Furthermore, our subgroup analyses showed that SGLT2 inhibitors were not significantly associated with an increased risk of DKA when compared with placebo (1.98 [0.56, 6.94]) or dipeptidyl peptidase 4 (DPP-4) inhibitors (1.00 [0.09, 11.01]). No statistical heterogeneity was observed in the analyses, except for the subgroup analysis of SGLT2 inhibitors versus DPP-4 inhibitors ($I^2 = 66.7\%$).

Previous trials reported increased DKA cases with the use of SGLT2 inhibitors, especially when they were used off-label in patients with type 1 diabetes (2,3). Some plausible mechanisms are already proposed by which SGLT2 inhibitors might trigger DKA (3,15). Given the current evidence from RCT data, we found that SGLT2 inhibitors were not significantly associated with an increased risk of DKA among patients with T2D. Consistent with a previous report (15), the frequency of reported DKA events related to SGLT2 inhibitor treatment in T2D patients is less than 0.1%. By synthesizing cumulative evidence from RCTs, our study did not support the adverse effect on DKA among T2D patients. Although the null results presented the highest strength of evidence from available RCT data, we cannot rule out the possibilities of a modest effect on DKA by SGLT2 inhibitors, an effect on a specific clinical phenotype of DKA (e.g., euglycemic DKA), or a nonclass effect. There is some evidence indicating that the risk of euglycemic DKA related to SGLT2 inhibitors may be increased among long-standing T2D patients with marked β-cell insufficiency, in latent autoimmune diabetes in adults, or under other severe medical conditions (15). In this regard, further safety monitoring based on a larger number of cases and detailed clinical information on related DKA cases is warranted to resolve the

[1]*Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University–Purdue University Indianapolis, Indianapolis, IN*
[2]*Department of Pharmacy, Peking University Third Hospital, Beijing, China*
[3]*Department of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, China*
[4]*Department of Pharmacy Administration and Clinical Pharmacy, Peking University Health Science Center, Beijing, China*

Corresponding author: Yiqing Song, yiqsong@iu.edu.

Received 24 April 2016 and accepted 11 May 2016.

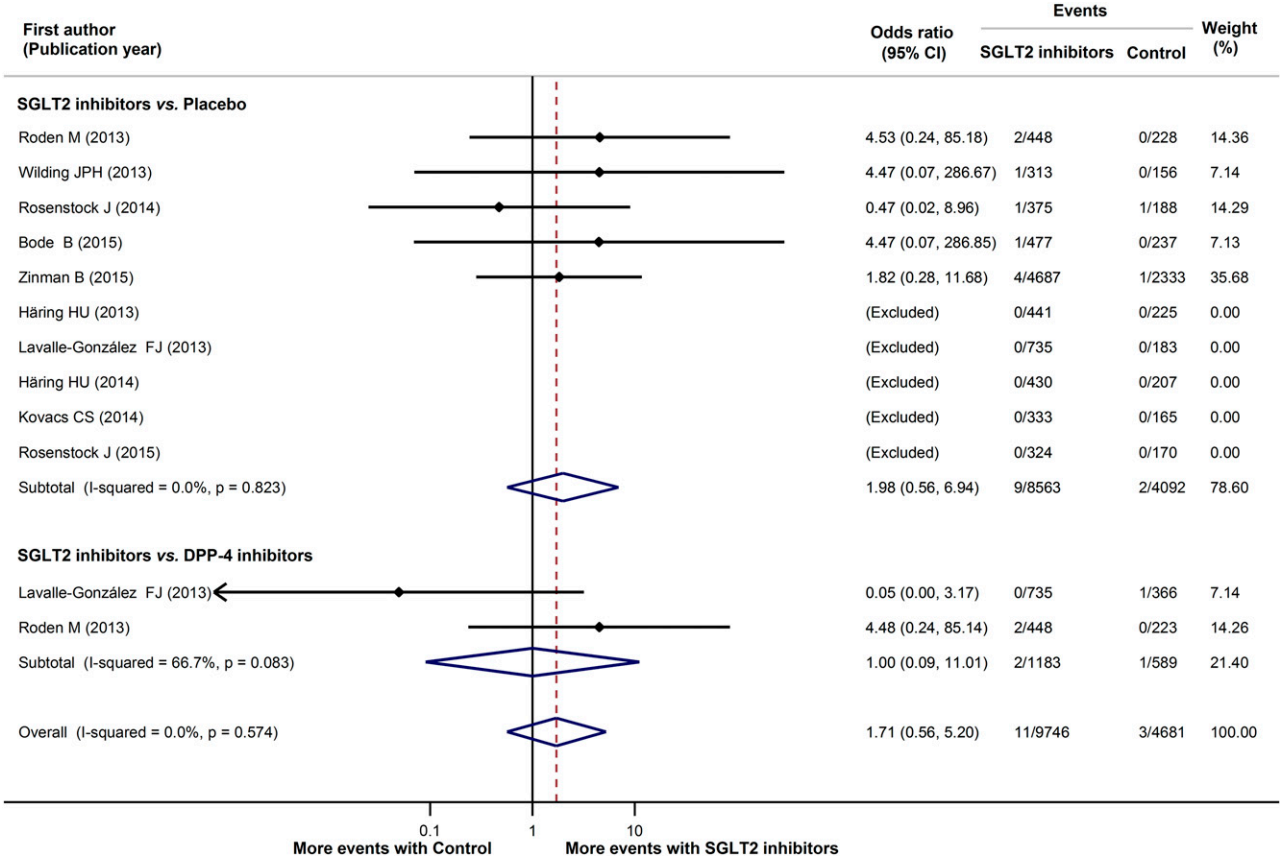

Figure 1—Meta-analysis of SGLT2 inhibitors on the risk of DKA.

uncertainty about this specific drug safety issue.

Funding. This project was supported by the Indiana University Health–Indiana University School of Medicine Strategic Research Initiative.
Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. H.T. and Y.S. had the idea for the study and led the study design. H.T. and D.L. identified and selected trials and extracted data. H.T. and D.L. performed all data analyses, checked for statistical consistency, and interpreted results. H.T. and Y.S. contributed to data interpretation. H.T. and Y.S. drafted the report. D.L., T.W., and S.Z. critically reviewed the report.

References

1. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495–502
2. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015;38:1687–1693
3. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig 2016;7:135–138
4. U.S. Food and Drug Administration. FDA drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood [Internet], 15 May 2015. Available from http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm. Accessed 13 April 2016
5. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2013;1:208–219
6. Wilding JPH, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract 2013;67:1267–1282
7. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014;37:1815–1823
8. Bode B, Stenlof K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. Diabetes Obes Metab 2015;17:294–303
9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
10. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2013;36:3396–3404
11. Lavalle-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013;56:2582–2592
12. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014;37:1650–1659
13. Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab 2014;16:147–158
14. Rosenstock J, Jelaska A, Zeller C, Kim G, Broedl UC, Woerle HJ. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 2015;17:936–948
15. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38:1638–1642