Effect of Sodium–Glucose Cotransporter 2 (SGLT2) Inhibitors on Diabetic Ketoacidosis among Type 2 Diabetes Patients: A Meta-analysis of Randomized Controlled Trials

Short running title: SGLT2 inhibitors and Diabetic Ketoacidosis

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

[1] Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, Indiana, USA

[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, MD, ScD

Department of Epidemiology,

Richard M. Fairbanks School of Public Health, Indiana University,

1050 Wishard Blvd, Indianapolis, Indiana, USA

Tel: 317-274-3833; Fax: 317-274-3433

Email: yiqsong@iu.edu

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Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antidiabetic drugs for the treatment of type 2 diabetes mellitus (T2DM) (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 mellitus (2, 3). In May 2015, the U.S. Food and Drug Administration (FDA) issued an updated drug safety communication warning about SGLT2 inhibitors potentially increasing the risk of DKA (4). Since DKA is a rare adverse effect, the evidence from individual studies or simply pooling the numbers from multiple reports is generally weak. We therefore conducted a meta-analysis of randomized controlled trials (RCTs) to examine whether SGLT2 inhibitors affect the risk of DKAs in patients with T2DM.

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov from inception to January 27, 2016 to identify the published and unpublished RCTs of SGLT2 inhibitors that reported DKA events in patients with T2DM. Two reviewers independently performed the study selection, data extraction, and quality assessment. A Peto odds ratio (OR) with 95% confidence interval (CI) using a random-effects model was used due to 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. 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 the Fig.1. SGLT2 inhibitors were not associated with significantly higher risk of DKA than control group (OR, 1.71; 95%CI 0.56 to 5.20). Furthermore, our subgroup analyses showed that SGLT2 inhibitors were not significantly associated with increased risk of DKA when compared with placebo (OR 1.98; 95% CI 0.56 to 6.94) or dipeptidyl peptidase 4 (DPP-4) inhibitors (OR 1.00; 95%CI 0.09 to 11.01). No statistical heterogeneity was observed all 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 mellitus (2, 3). Some plausible mechanisms are already proposed by which SGLT2 inhibitors might trigger DKA (3, 5). Based on current evidence from RCT data, we found that SGLT2 inhibitors were not significantly associated with an increased risk of DKA among patients with T2DM. Consistent with previous report (5), the frequency of reported DKA events related to SGLT2 inhibitor treatment in T2DM patients is less than 0.1%.By synthesizing cumulative evidence from RCTs, our study, however, did not support the adverse effect on DKA among T2DM 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 non-class effect. There is some evidence indicating that the risk of euglycemic DKA related to SGLT2 inhibitors may be increased among long-standing T2DM patients with marked β-cell insufficiency, in latent autoimmune diabetes, or under other severe medical conditions (5). In this regard, further safety monitoring based on

larger number of cases and detailed clinical information on related DKA cases is warranted to resolve uncertainty about this specific drug safety issue.

ACKNOWLEDGEMENTS

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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, and all other authors (D.L., T.W., and S.Z.) critically reviewed the report.

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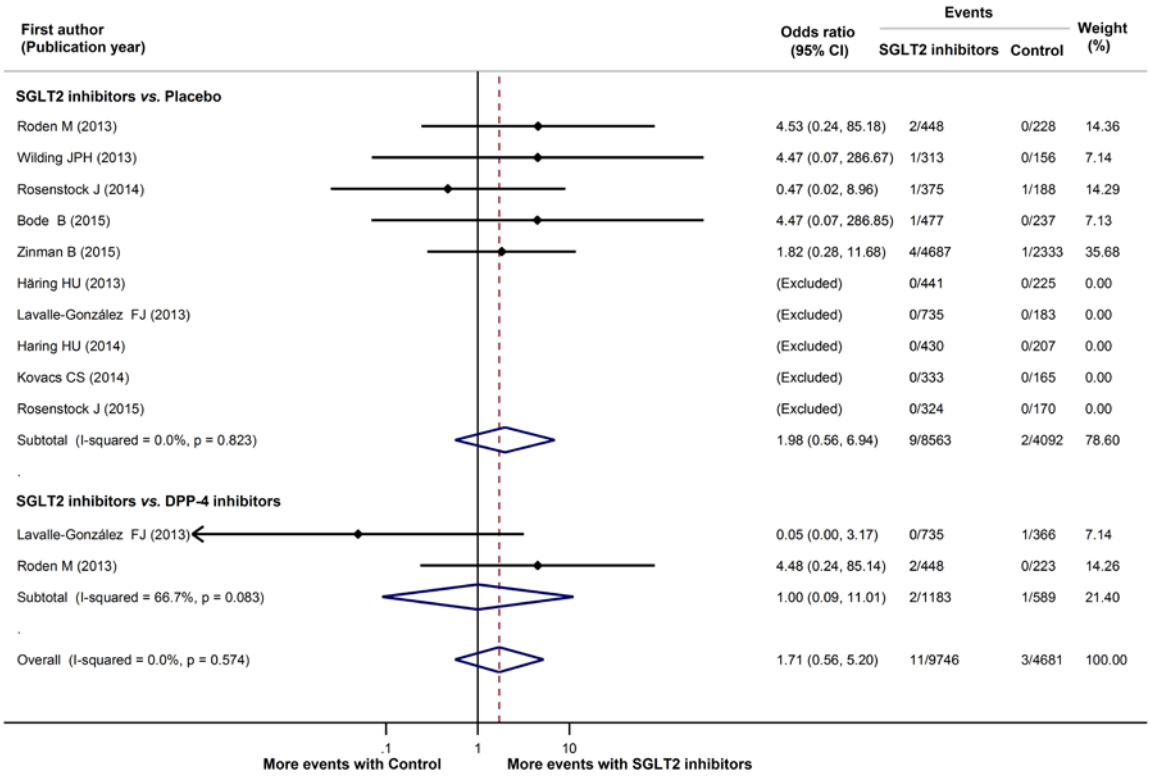
Figure Legend:

Figure 1- Meta-analysis of SGLT2 inhibitors on the risk of diabetic ketoacidosis. SGLT2 inhibitors, Sodium glucose cotransporter 2 inhibitors; DPP-4 inhibitors, dipeptidyl peptidase 4 inhibitors.

Figure 1


First author
(Publication year)
Odds ratio
(95% CI)
Events
SGLT2 inhibitors
Control
Weight
(%)
SGLT2 inhibitors vs. Placebo
Roden M (2013) 4.53 (0.24, 85.18) 2/448 0/228 14.36
Wilding JPH (2013) 4.47 (0.07, 286.67) 1/313 0/156 7.14
Rosenstock J (2014) 0.47 (0.02, 8.96) 1/375 1/188 14.29
Bode B (2015) 4.47 (0.07, 286.85) 1/477 0/237 7.13
Zinman B (2015) 1.82 (0.28, 11.68) 4/4687 1/2333 35.68
Häring HU (2013) (Excluded) 0/441 0/225 0.00
Lavalle-González FJ (2013) (Excluded) 0/735 0/183 0.00
Haring HU (2014) (Excluded) 0/430 0/207 0.00
Kovacs CS (2014) (Excluded) 0/333 0/165 0.00
Rosenstock J (2015) (Excluded) 0/324 0/170 0.00
Subtotal (I-squared = 0.0%, p = 0.823) 1.98 (0.56, 6.94) 9/8563 2/4092 78.60
SGLT2 inhibitors vs. DPP-4 inhibitors
Lavalle-González FJ (2013) 0.05 (0.00, 3.17) 0/735 1/366 7.14
Roden M (2013) 4.48 (0.24, 85.14) 2/448 0/223 14.26
Subtotal (I-squared = 66.7%, p = 0.083) 1.00 (0.09, 11.01) 2/1183 1/589 21.40
Overall (I-squared = 0.0%, p = 0.574) 1.71 (0.56, 5.20) 11/9746 3/4681 100.00
.1
1
10
More events with Control
More events with SGLT2 inhibitors