LETTER

Cancer risk in the EMPA-REG OUTCOME trial. Reply to Shaikh AMY [letter] and Kohler S, Lee J, George JT et al [letter]

Huilin Tang¹ · Jiali Han^{1,2} · Yiqing Song¹

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Abbreviations

FDA Food and Drug Administration
SGLT2 Sodium–glucose cotransporter 2

To the Editor: We strongly but respectfully disagree with the letter by Dr. Shaikh [1] regarding an issue with the reporting of the number of cases of bladder cancer from the EMPA-REG OUTCOME Trial [2] in our meta-analysis of sodium–glucose cotransporter 2 (SGLT2) inhibitors and risk of cancer [3]. Since 2007, Section 801 of the Food and Drug Administration (FDA) Amendments Act (FDAAA) requires the submission of summary results, including adverse events for clinical trials of FDA-regulated drugs, to the [ClinicalTrials.gov](http://www.ClinicalTrials.gov) databank (www.ClinicalTrials.gov) [4]. As stated in our article, ‘If cancer events were not reported in the manuscripts, data from regulatory submissions or the ‘Serious adverse events’ section on ClinicalTrials.gov were extracted’ [3]. Our study included only confirmed cases of bladder cancer, classified as ‘bladder cancer’, ‘bladder cancer transitional cell carcinoma’ and

‘bladder cancer recurrent’, which were identified according to the Medical Dictionary for Regulatory Activities (MedDRA) (such information was also presented in electronic supplementary material (ESM) Table 2 of our article) [3]. Hence, the number of incident cases of bladder cancer in our article was correctly extracted from ClinicalTrials.gov, with the current database for the EMPA-REG OUTCOME Trial (ClinicalTrials.gov registration no. NCT01131676, accessed 9 August 2017) still showing six cases of bladder cancer, two cases of bladder transitional cell carcinoma, and one recurrent case of bladder cancer in the empagliflozin groups, and zero cases in the placebo group (Table 1).

We appreciate the updated data from the US FDA provided by Dr. Shaikh [1], which is also highlighted in a second letter by Kohler et al [5], although the crude comparisons of case numbers made in this second letter could be misleading owing to the small sample size [5]. Even based on the intention-to-treat data or on-treatment data sets provided by Kohler and colleagues [5], we still observed a non-significant trend towards increased risk of bladder cancer in the pooled empagliflozin groups compared with the placebo groups; the relative risks were 1.20 (95% CI 0.42, 3.40) for the intention-to-treat data set and 1.83 (95% CI 0.51, 6.56) for the on-treatment data set. In addition, we feel it is important to note that the actual number of confirmed cancer cases would continue to accumulate during an extended post-trial period of the EMPA-REG OUTCOME Trial. However, given that participants in this trial were no longer receiving randomly assigned treatments, a crude comparison of accrued case numbers on an intention-to-treat basis tends to lead to a biased and incorrect estimate of drug effect owing to potential bias and confounding. Hence, we stand by our statement that ‘there is some evidence suggesting that SGLT2 inhibitors (especially empagliflozin) might increase risk of bladder cancer’, rather than conclusive evidence demonstrating a causal relationship.

✉ Jiali Han
jialhan@iu.edu

✉ Yiqing Song
yiqsong@iu.edu

¹ Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, 1050 Wishard Blvd, Indianapolis, IN 46202, USA

² Melvin and Bren Simon Cancer Center, Indiana University, Indianapolis, IN, USA

Table 1 Bladder cancer in EMPA-REG OUTCOME Trial

Classification	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
Bladder cancer <i>n/N</i> (%)	0/2333 (0.00)	1/2345 (0.04)	5/2342 (0.21)
Bladder cancer recurrent <i>n/N</i> (%)	0/2333 (0.00)	0/2345 (0.00)	1/2342 (0.04)
Bladder transitional cell carcinoma <i>n/N</i> (%)	0/2333 (0.00)	1/2345 (0.04)	1/2342 (0.04)

Data obtained from www.ClinicalTrials.gov (accessed 9 August 2017), which was last updated and verified 7 April 2016

Given the rapidly increasing use of SGLT2 inhibitors, future large long-term randomised trials, post-trial observational studies and real-world evidence are required to monitor the long-term safety of SGLT2 inhibitors regarding the risk of specific cancer types, especially bladder cancer.

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References

1. Shaikh AMY (2017) SGLT2 inhibitors and cancer: why further evidence is required. *Diabetologia* <https://doi.org/10.1007/s00125-017-4434-9>
2. Zinman B, Wanner C, Lachin JM et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 373:2117–2128
3. Tang H, Dai Q, Shi W, Zhai S, Song Y, Han J (2017) SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. *Diabetologia* <https://doi.org/10.1007/s00125-017-4370-8>
4. US Food and Drug Administration (2007) Food and Drug Administration Amendments Act of 2007. Public Law 110-85. Available from www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf. Accessed 12 August 2017
5. Kohler S, Lee J, George JT, Inzucchi SE, Zinman B (2017) Bladder cancer in the EMPA-REG OUTCOME trial. *Diabetologia* <https://doi.org/10.1007/s00125-017-4430-0>