RE: Gout and sodium-glucose cotransporter-2 inhibitors

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We have read the comments by Dr Lai (1) regarding our study “Sodium-glucose cotransporter-2 inhibitors and the risk of gout: A Danish population based cohort study and symmetry analysis” with great interest (2). The author raises the following concerns regarding our study:

1) That we did not include measurements of glycated haemoglobin A1c (HbA1c), which would have allowed us to assess the effect of each treatment on HbA1c levels. Although the above is an interesting question, the intent of our study was not to compare the effectiveness of the two antidiabetic agents on HbA1c levels. The purported mechanism whereby sodium-glucose cotransporter-2 inhibitors (SGLT2-I) prevent gout is independent of their glycaemic effect, and it is not clear to us how data on HbA1c levels would aid in the interpretation of our findings.

2) We did not investigate the biochemical effect of SGLT2-Is or GLP1 receptor agonists (GLP1-RA) on blood uric acid levels. There are several reasons not to use serum uric acid levels as an outcome: The clinically relevant outcome is gout attacks and not serum levels of a given biomarker. Our study adds to existing trial evidence of SGLT2-Is lowering effect on uric acid levels (3) by providing a clinical endpoint instead of a surrogate endpoint.

3) Dr Lai has calculated the number needed to treat for one additional patient to benefit (333, 95% confidence interval 227 to 667) based on the reported incidence rate difference and interprets this number as being too high to have a clinically meaningful effect. In an unselected population like in our study (all patients initiating SGLT2-Is and GLP1-RAs without prior gout), the absolute risk of gout is low (5.4 events/1000 person years, which is higher than the 0.58 to 2.89 events/1000 person years reported by a recent review (4)). Since gout is an uncommon disease, the incidence rate difference will necessarily be small and the number needed to treat for one additional patient to benefit will be high, even for a highly gout preventing drug. We therefore do not recommend SGLT2-Is for prophylaxis of gout attacks to all individuals in a low-risk population, and neither would we recommend other uric acid lowering therapy.

4) Finally, Dr Lai argues that it would be of interest to compare SGLT2-I users to users of metformin. We chose to compare SGLT2-Is and GLP1-RAs as both drugs are recommended as second line antidiabetic agents in Denmark and are mainly prescribed if metformin therapy fails to achieve the desired level of glycaemic control. Comparing a
first line treatment (metformin) to a second line treatment (SGLT2-Is) will most likely induce confounding by disease severity.

We thank Dr Lai for his constructive comments. The suggestions and concerns ask for a comprehensive risk-benefit assessment between SGLT2-Is and GLP1-RAs which is outside the scope of our work. Still, we think that our results could potentially be useful when choosing between SGLT2-Is and GLP1-RAs for patients at a high risk of gout attacks. Further, we hope that future studies will investigate the effect of SGLT2-Is on flares in patients with manifest gout, something which was not possible in this study.

**Conflicts of interest**
Lars Christian Lund reports participation in research projects funded by Menarini Pharmaceuticals and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current work. Mikkel Højlund reports participation in a research project funded by Menarini Pharmaceuticals with funds paid to the institution where he was employed (no personal fees) and with no relation to the current work. Jesper Hallas reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current work. Kasper Bruun Kristensen and Daniel Pilsgaard Henriksen report no conflicts of interest.
References


