SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND THE RISK OF GOUT: A DANISH POPULATION BASED COHORT STUDY AND SYMMETRY ANALYSIS

Running title: SGLT2-inhibitors and the risk of gout

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ABSTRACT

Purpose: Sodium-glucose cotransporter-2 inhibitors (SGLT2-I) are frequently used in type 2 diabetes and have recently been associated with lower rates of gout compared to glucagon-like peptide-1 receptor agonists (GLP1-RA). Our objective was to assess the association of SGLT2-I and gout using a cohort study design and a symmetry analysis.

Methods: Using the Danish nationwide health registries, we conducted an active comparator, new user cohort study comparing the 3-year risk of gout among SGLT2-I users with propensity score matched GLP1-RA users. Individuals were followed according to the intention-to-treat, and incidence rate differences (IRD) and hazard ratios (HR) were obtained. To address unmeasured confounding that is stable over time, a corresponding symmetry analysis was performed.

Results: 11,562 pairs of SGLT2-I and GLP1-RA users were identified, contributing 43,927 person-years of follow-up. The incidence rate of gout was 4.8 and 9.1 events per 1000 person years among SGLT2-I and GLP1-RA users, yielding an IRD of 4.3 (95% confidence interval: 5.9 to -2.8) and HR of 0.52 (0.41 to 0.66). In the symmetry analysis, 118 individuals initiated SGLT2-Is after gout; 80 patients initiated treatment prior to gout. The trend adjusted SR was 0.63 (0.47 to 0.84) and the active comparator adjusted estimate was 0.67 (0.44 to 0.86).

Conclusions: Initiation of SGLT2-Is was associated with a markedly decreased risk of gout compared to initiation of GLP1-RAs. The findings are comparable to prior studies addressing this association.

Keywords: Sodium-Glucose Transporter 2 Inhibitors, Gout
KEY POINTS

- SGLT2-Is have recently been associated with lowered rates of gout, but limitations of the original study were a short mean duration of follow up and potential unmeasured confounding.
- The Danish health registries enable researchers to follow most individuals for multiple years.
- The symmetry analysis design is robust towards measured and unmeasured confounders that are stable over time.
- Using a cohort and symmetry analysis design we obtained risk estimates compatible with the original work.
- SGLT2-Is may be useful to reduce the risk of gout in individuals with type 2 diabetes.
INTRODUCTION

Sodium–glucose cotransporter-2 inhibitors (SGLT2-I) are important drugs for the treatment of type 2 diabetes\(^1\), and have been shown to reduce the incidence of cardiovascular outcomes in patients with diabetes\(^2\). SGLT2-Is block the reabsorption of glucose at the proximal convoluted tubule, conferring a hyperosmolar urine, and an increased urine output\(^3\).

In a recent paper, it was demonstrated that SGLT2-I treatment reduced the incidence of gout\(^4\), presumably because of increased excretion of uric acid\(^1\). The authors acknowledged certain limitations with the study including a mean follow-up of nine months, and the possibility of unmeasured confounding.

Our aim was to replicate the previous study on the association between SGLT2-Is and gout, as well as to apply a methodology robust towards confounders that are stable over time.

METHODS

Using the Danish health registries\(^5\), we conducted an active comparator, new user cohort study investigating the risk of incident gout among initiators of SGLT2-Is compared to a propensity score (PS) matched cohort of Glucagon-like-peptide-1 receptor agonist (GLP1-RA) initiators. We estimated incidence rates (IRs), incidence rate differences (IRDs) and hazard ratios (HRs). To address potential unmeasured confounding, we analyzed the association between SGLT2-I initiation and incident gout using a symmetry analysis\(^6\). This study is reported according to the STROBE\(^7\) guideline.

Study population and data sources

All individuals who redeemed their first prescription for an SGLT2-I or a GLP1-RA during the period Jan 1st 2013 to Dec 31st 2018 were eligible for inclusion. Individuals with a prior diagnosis of cancer, previous prescription of uric acid lowering drugs, colchicine, a prior diagnosis of gout or less than one year of residency in Denmark were excluded.

We obtained information on prescription drug use, prior diagnoses received, and
vital status from the Danish health registries (table S1).

Follow up
Individuals were followed for up to three years and were censored upon death or migration. Individuals were assumed to be exposed from the first prescription received during follow-up (SGLT2-I or GLP1-RA) regardless of discontinuation or switching between study medication, thus emulating an intention-to-treat approach.

Outcomes
The outcome of interest was gout, as recorded by initiation of any uric acid lowering therapy (ULT), colchicine or a first hospital diagnosis of gout. Initiation of ULT is indicated in individuals with recurrent gout flares, tophi or otherwise complicated gout. ULT is also indicated in individuals with urolithiasis and increased urinary uric acid levels. To quantify any potential outcome misclassification due to urolithiasis, we identified the number of individuals who received a diagnosis of urolithiasis in the 90 days leading up to initiation of ULT.

Confounding
Measured confounding variables were addressed using PS methods. Covariate selection was performed according to the high-dimensional PS algorithm using information on in- and outpatient diagnoses, and redeemed prescriptions during the year prior to cohort entry. GLP1-RA initiators were matched to SGLT2-I initiators in a 1:1 ratio using the nearest neighbor algorithm, allowing a maximum difference in the PS of 0.02 units between pairs.
For the codes used to define exposures, covariates and the outcome see table S2.

Statistical analysis
Descriptive statistics were used to characterize cohorts at baseline. We calculated IRs and estimated IRDs with 95% confidence intervals (95% CI) using generalized linear models using a Poisson distribution and an identity link. Hazard ratios (HR) with 95% CIs were estimated using Cox regression.

Supplementary analyses
To increase comparability with risk estimates from previous studies, individuals were
followed according to a per-protocol approach and censored upon discontinuation of or switching between study medications. To evaluate the consequences of imbalance in the PS-matched cohorts, we included characteristics with a standardized mean difference greater than 0.1 as covariates in the Cox regression. To explore whether results were robust to the choice of active comparator, we repeated the cohort analysis with dipeptidyl peptidase-4 inhibitor (DPP4-I) users as the comparator.

Symmetry analysis
To address unmeasured confounding, we investigated the association between SGLT2-I initiation and incident gout using a symmetry analysis. In a symmetry analysis, the number of individuals initiating SGLT2-Is prior to initiating treatment for gout is compared to the number of individuals experiencing the reverse sequence during a symmetric observation period. The risk estimate obtained is the sequence ratio (SR = SGLT2→Gout / Gout→SGLT2). We estimated SRs for observation windows of 180, 365, and 900 days prior to and after initiation of an SGLT2-I. To adjust for temporal trends in the prevalence of the outcome, trend-adjusted SRs12 were obtained. To adjust for confounding by indication, we obtained active comparator-adjusted SRs by simple division of the trend-adjusted estimates for SGLT2-I and GLP1-RA13.

RESULTS
We identified 21,590 users of SGLT2 inhibitors and 17,071 users of GLP1-RAs (figure 1). SGLT2-I users were slightly older, more often men and had a lower use of loop-diuretics and insulin than users of GLP1-RAs (table S3). After PS trimming and matching, 11,562 pairs of SGLT2-I users and GLP1-RA users remained. Satisfactory balance was achieved for all covariates, except lipid lowering agents and recent use of metformin (table S3), and PS distributions (figure S1) overlapped sufficiently. For all covariates included in the PS, see table S4.

In the main analysis (table 1), intention-to-treat with follow-up capped at 3 years, we found IRs of gout of 4.8 and 9.1 events/1000 person-years among SGLT2-I and GLP1-RA users, for an IRD of -4.3 events/1000 person-years (95% CI -5.9 to -2.8). The HR was 0.52 (0.41 to 0.66). Similar results were seen for the crude analysis (table 1, figure S2). In the per-protocol analysis (table 1), we found a similar HR as in...
the main analysis, 0.49 (0.33 to 0.71) and an IRD of -3.4 events/1000 person-years (-5.1 to -1.6). When adjusting for the observed imbalances in use of lipid lowering drugs and metformin between the PS-matched cohorts, we obtained a HR of 0.53 (0.42 to 0.67). Using DPP4-Is as the active comparator yielded similar risk estimates (table S5). Out of 420 individuals who initiated ULT, only five had received a urolithiasis diagnosis prior to treatment initiation.

In the symmetry analysis using a one-year window on either side of the index antidiabetic prescription, we found 80 persons prescribed SGLT2-Is before gout and 118 persons following the opposite order (figure S3), for a crude SR of 0.68 (0.51 to 0.91). The crude SR for GLP1-RAs was 0.98 (0.82 to 1.18). Trend adjustment had minimal effect (table S6). The active comparator-adjusted SR for SGLT2-inhibitors was 0.67 (0.44 to 0.86) for a one-year window. Sequence ratios for observation windows of 180 and 900 days were comparable in magnitude (table S6).

DISCUSSION
In this nation-wide cohort study of 38,661 adults with diabetes, we found a lower rate of gout with SGLT2-I use compared to GLP1-RA use. The risk reduction with use of SGLT2-I was approximately 50% in the matched cohort corresponding to four fewer cases per 1,000 person-years of treatment. Results from a symmetry analysis, which is unaffected by unmeasured confounders that are stable over time, were consistent with results from the cohort study.

The main strength of our analysis was the ability to follow individuals for multiple years after cohort entry using the Danish health care registers. Further, we used high-dimensional propensity scores to eliminate any measured confounding.

However, there are also important limitations: Our outcome definition mainly relied on new use of ULT or colchicine and was not able to capture gout events treated with non-steroidal anti-inflammatory drugs or glucocorticoids. Further, the outcome definition has not been validated. Still, due to the narrow indication for ULT and the low number of individuals with urolithiasis who may have been misclassified (N=5), we expect the outcome definition to be reliable. Finally, we did not have
measurements on body weight and renal function, which potentially are important confounders. To explore this potential bias, we tested the validity of our results using a symmetry analysis, as body weight can be assumed to be stable over the duration of follow up\textsuperscript{14} and henceforth does not affect a symmetry analysis. Risk estimates for the cohort study and symmetry analysis were comparable, indicating a negligible amount of confounding introduced by not having data on body weight.

Our findings align with the study we aimed to replicate\textsuperscript{4}. In this study, SGLT2-I use was associated with a HR of 0.64 and IRD of 2.9 events/1000 person-years for gout compared to use of GLP1-RAs. However, the relative- and absolute risk estimates in our study were further away from the null (HR 0.52 and IRD -4.3 events/1000 person-years). Compared to our study with a mean duration of 391 days of follow-up, the mean follow-up duration was shorter (282 days) in the previous study. We found that the reduced risk of gout associated with SGLT2-Is persisted during follow-up. Considering that two studies now independently establish that initiation of SGLT2-Is is associated with a reduced risk of gout, SGLT2-Is could be considered in patients at high risk of gout where second-line antidiabetic treatment is otherwise indicated.

In conclusion, use of SGLT2-Is was associated with a 50% reduced risk of gout and SGLT2-Is may be useful to reduce the risk of gout in patients with type-2 diabetes.
FUNDING
No specific funding was obtained for this study.

ETHICS STATEMENT
According to Danish law, studies based on registry data do not require approval from an ethics review board.

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 proposal. 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 proposal. 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 proposal. Kasper Bruun Kristensen and Daniel Pilsgaard Henriksen report no conflicts of interest.

DATA AVAILABILITY
Due to data protection regulation, data cannot be shared directly by the authors. Data is accessible to authorized researchers after application to the Danish Health Data Authority. To apply for data and help with the application process, please see https://sundhedsdatastyrelsen.dk/da/forskerservice/ansog-om-data.

AUTHOR CONTRIBUTIONS
LCL is the guarantor, had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LCL, MH, DPH, JH and KBK conceived the study. LCL performed the data analysis. LCL, MH and JH drafted the initial manuscript. All authors reviewed and revised the manuscript.
REFERENCES


Table 1. Risk of gout prior to and after propensity score matching.

<table>
<thead>
<tr>
<th></th>
<th>Unmatched SGLT2-I</th>
<th>GLP1-RA</th>
<th>Matched SGLT2-I</th>
<th>GLP1-RA</th>
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</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals (N)</td>
<td>21590</td>
<td>17071</td>
<td>11562</td>
<td>11562</td>
</tr>
<tr>
<td>Diabetes events (N)</td>
<td>174</td>
<td>316</td>
<td>108</td>
<td>193</td>
</tr>
<tr>
<td>Person time (years)</td>
<td>34,829</td>
<td>35,286</td>
<td>22,681</td>
<td>21,246</td>
</tr>
<tr>
<td>Incidence rate / 1000 PY (95% CI)</td>
<td>5.0 (4.3 to 5.8)</td>
<td>9.0 (8.0 to 10.0)</td>
<td>4.8 (3.9 to 5.8)</td>
<td>9.1 (7.9 to 10.5)</td>
</tr>
<tr>
<td>Incidence rate difference (95% CI)</td>
<td>-4.0 (-5.2 to -2.7)</td>
<td>(ref.)</td>
<td>-4.3 (-5.9 to -2.8)</td>
<td>(ref.)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.56 (0.46 to 0.67)</td>
<td>(ref.)</td>
<td>0.52 (0.41 to 0.66)</td>
<td>(ref.)</td>
</tr>
</tbody>
</table>

|                          | Per-protocol      |         |                |         |
|--------------------------|-------------------|---------|                |         |
| Individuals (N)          | 21590             | 17071   | 11562          | 11562   |
| Diabetes events (N)      | 63                | 137     | 40             | 81      |
| Person time (years)      | 20,198            | 19,812  | 12,490         | 12,302  |
| Incidence rate / 1000 PY (95% CI) | 3.1 (2.4 to 4.0) | 6.9 (5.8 to 8.2) | 3.2 (2.3 to 4.4) | 6.6 (5.3 to 8.2) |
| Incidence rate difference (95% CI) | -3.8 (-5.2 to -2.4) | (ref.) | -3.4 (-5.1 to -1.6) | (ref.) |
| Hazard ratio (95% CI)    | 0.45 (0.33 to 0.61) | (ref.) | 0.49 (0.33 to 0.71) | (ref.) |

SGLT2-I = Sodium-glucose cotransporter 2 inhibitors, GLP1-RA = Glucagon-like-peptide-1 receptor agonist, CI = 95% confidence interval
FIGURES

Figure 1. Flowchart detailing cohort selection.

SGLT2I = Sodium-glucose cotransporter 2 inhibitors, GLP1-RA = Glucagon-like-peptide-1 receptor agonists
Patients initiating SGLT2I or GLP1-RA (N=46801)

Excluded due to initiation of SGLT2I and GLP1-RA on the same day (N=55)

SGLT2I users (N=26014)

Excluded:
- Prior Gout (N=2118)
- Cancer (N=2118)
- Residency < 1 year (N=188)

Prior to propensity score trimming and matching (N=21590)

Excluded:
- Trimming (N=2561)
- Not matched (N=7467)

Matched SGLT2I users (N=11562)

GLP1-RA users (N=20732)

Excluded:
- Prior Gout (N=1943)
- Cancer (N=1556)
- Residency < 1 year (N=162)

Prior to propensity score trimming and matching (N=17071)

Excluded:
- Trimming (N=3053)
- Not matched (N=2456)

Matched GLP1-RA users (N=11562)