

Increased phimosis risk with SGLT2 inhibitors versus GLP-1 RAs

Men with type 2 diabetes initiated on SGLT2 inhibitors had nearly double the risk of developing phimosis (constriction of the penile foreskin) than those initiated on GLP-1 receptor agonists, according to this population-based, active-comparator cohort study of new users, undertaken in Denmark and published in *Diabetes Care*. Risk differences were highest in the first year after initiation, with rates of 0.9% in those starting SGLT2 inhibitors compared to 0.5% in those starting a GLP-1 RA, giving a 1-year risk ratio of 1.88. Although risks attenuated, at 8 years, phimosis risk remained elevated at 4.8% with SGLT2 inhibitors and 3.6% with GLP-1 RAs, (risk ratio 1.36). Penile cancer risk may also have been higher in men using SGLT2 inhibitors versus GLP-1 RAs, but this is very rare and only a median of 4 years' follow-up was possible in this analysis. The increased risks of both conditions are postulated to be due to increased mycotic genital infections, and clinicians are encouraged to stress the importance of genital hygiene when initiating SGLT2 inhibitors, particularly in uncircumcised men.



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Phimosis is constriction of the penile foreskin, which can cause difficulties with urination and sexual intercourse. It is most common in children but is also more common in men in later life. Men with type 2 diabetes are known to have a threefold increased risk of balanitis and up to a 7-fold increased risk of phimosis. Men with phimosis have a 12-fold increased risk of penile cancer, a rare cancer which occurs in around 1 in 100 000 men and which is associated with obesity, type 2 diabetes and balanitis.

Mycotic genital infections are known to be roughly three-times as common in men and women using SGLT2 inhibitors as those using other glucose-lowering drugs, but no previous studies have explored the risk of phimosis or penile cancer in men with type 2 diabetes using these agents.

Data from the Danish Civil Registration System, Danish National Patient Registry, Danish National Prescription Registry and the Register of Laboratory Results for Research were used to identify and follow all males using metformin in Denmark who initiated an SGLT2 inhibitor ($n=32\,486$) or a GLP-1 receptor agonist ($n=14\,793$) between January 2016 and December 2021. Around 15 000 people with type 2 diabetes with prior use of these drug classes were excluded. Only people already prescribed metformin were included, as this helped identify people who were using SGLT2 inhibitors or GLP-1 RAs for type 2 diabetes rather than for other conditions such as heart failure or chronic kidney disease. During the period studied, both SGLT2 inhibitors and GLP-1 RAs were used in Denmark as second-line therapy in those with type 2 diabetes.

The present study

In this population-based, active-comparator, new-user, cohort study emulating a target trial (see *Box 1*), Ljungberg and colleagues aimed to identify whether men initiated on an SGLT2 inhibitor for diabetes would be at greater risk not just of mycotic genital infections but also of phimosis in uncircumcised men and of penile cancer.

Box 1. What is “target trial emulation”?

Target trial emulation (TTE) is an observational “research design that aims to emulate a randomized clinical trial [RCT] structure within a large set of observational data”, such as data sourced from a healthcare database or medical registry; the (hypothetical) RCT that would have ideally answered the research question is the “target trial” that is emulated.

TTE can reduce bias, improve the understanding of findings and facilitate causal inference (Andrade, 2025).



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The primary outcome was phimosis, with penile cancer also prespecified as an outcome but with a 1-year lag time, since cancers diagnosed shortly after drug initiation were deemed unrelated to the treatments. A variety of statistical tools were used to balance potential confounders between the groups in this “real-world” study.

Results

Median follow-up was 4 years, with a maximum follow-up of 8 years, during which time 61% of men treated with SGLT2 inhibitors and 54% of GLP-1 RA users discontinued therapy. During the study, 45% of SGLT2 inhibitor users started GLP-1 RAs and 40% of GLP-1 RA users started SGLT2 inhibitor therapy. Phimosis and penile cancer were mainly diagnosed in urology outpatient clinics.

Risk of phimosis diagnosis was higher in men initiating SGLT2 inhibitors than GLP-1 RAs, with cumulative risk curves starting to separate around 3 months after treatment initiation and with the greatest differences occurring by 1–2 years following initiation.

- 1-year phimosis risk was 0.9% among new users of SGLT2 inhibitors, compared with 0.5% among new users of GLP-1 RAs.
 - 1-year risk ratio was 1.88 (95% CI 1.43–2.47).
- Phimosis risk persisted but the comparative increased risk with SGLT2 inhibitors attenuated over the follow-up period:
 - 8-year risk of phimosis was 4.8% and 3.6% in SGLT2 inhibitor and GLP-1 RA users, respectively (risk ratio 1.36).

After 1 year, 0.8% of those initiating SGLT2 inhibitors underwent surgery for phimosis, which was double the rate in those initiating GLP-1 RAs.

Penile cancer was identified in less than 20 men over 4 years, and more cases were identified in those initiating SGLT2 inhibitors versus GLP-1 RAs, with curves separating after 2–3 years. However, since numbers were so small, it was difficult to ascertain the significance of this.

Results were similar when on-treatment data (duration 2.2–2.4 years) were compared with intention-to-treat data. Increased phimosis risk with SGLT2 inhibitor versus GLP-1 RA initiation

was identified irrespective of age, HbA_{1c} and diabetes duration. Risk of phimosis increased with higher HbA_{1c} in both treatment groups.

To help rule out confounding, a negative control analysis was carried out using inguinal hernia as the outcome, and this found no difference between those initiating SGLT2 inhibitors versus GLP-1 RAs. An analysis was also undertaken in men without the requirement for metformin use, and this allowed an additional 5961 men initiated on SGLT2 inhibitors and 2538 initiated on a GLP-1 RA to be added to the cohort. As expected, this study population differed markedly, with a higher proportion having HbA_{1c} <48 mmol/mol and higher numbers with established cardiovascular disease, but there was no change in the ratio of SGLT2 inhibitor users to GLP-1 RA initiators who developed phimosis compared with the main study.

Discussion

The authors postulate that the mechanism behind both the increased risk of phimosis and the possible small increase in penile cancer seen with SGLT2 inhibitor initiation could be due to a higher risk of genital infections. However, as this was an observational study, an association is all that can be ascertained.

The main study strength was the use of population-based registries, ensuring identification and follow-up of those initiating SGLT2 inhibitors and GLP-1 RAs across Denmark during the study period. Limitations included possible misclassifications of those with phimosis (unlikely since these were mainly urological specialist diagnoses); detection bias due to increased surveillance (but there was no increased risk of inguinal hernia in SGLT2 inhibitor users); lack of precision in penile cancer rates due to small numbers over only 4 years of follow-up; lack of information on BMI, circumcision, ethnic diversity, and socioeconomic and lifestyle factors; and the intention-to-treat and on-treatment analyses having different limitations. Since no other studies have looked specifically at phimosis and penile cancer risk in people using SGLT2 inhibitors, the authors call for further studies to confirm these findings.



Circumcision removes the risk of phimosis and reduces the rate of penile cancer; therefore, amongst populations with high rates of circumcision, phimosis and penile cancer rates would be expected to be lower than those identified in this study, as circumcision rates are low in Denmark, at less than 20%.

Implications for practice

An update to the NICE type 2 diabetes guideline is expected to be published in February 2026, and the draft update recommends use of SGLT2 inhibitors for everyone with type 2 diabetes unless contraindicated. Therefore, a significant increase in our use of this class of drugs is anticipated. Any risks, such as the increased risk of diabetic ketoacidosis or the phimosis risk discussed here, must be weighed against the significant benefits of SGLT2 inhibitors on cardiovascular risk and mortality for our patients.

This study highlights the importance of explaining genital hygiene to both men and women who are initiating SGLT2 inhibitors, and of reiterating and reminding of this at each consultation to reduce the risk. This is important while using SGLT2 inhibitors and also at any time when the person has high glucose levels, both of which will increase the risk of infections.

Alongside our comprehensive counselling in both men and women about sick day rules and the risks and benefits associated with

SGLT2 inhibitor use, we should now discuss the increased risk of phimosis with men and continue to encourage prompt management of genital infections, and encourage men to seek advice early if phimosis is suspected. However, these discussions need to be carefully balanced by stressing the huge benefits offered by this class of drugs for people with type 2 diabetes or with heart failure or chronic kidney disease.

It will also be very important to actively encourage people to continue treatment even if one or two bouts of mycotic genital infection occur, since men are more likely to discontinue treatment in such circumstances. We already undertake detailed counselling before initiating SGLT2 inhibitors, including discussing risk of mycotic genital infections, so it should be easy to add phimosis to our discussions until this association is confirmed or refuted by future studies. ■

Andrade C (2025) Target trial emulation: A concept simply explained. *J Clin Psychiatry* **86**: 25f15796

Ljungberg C, Nørgaard M, Vandenbroucke-Grauls C et al (2025) Risk of phimosis associated with SGLT2i versus GLP-1RA: A Danish cohort study. *Diabetes Care* **48**: 1774–82

Risk of phimosis associated with SGLT2i versus GLP-1RA: A Danish cohort study

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Practice points

1. Risks associated with SGLT2 inhibitor use, including the risk of phimosis in men identified here, should be weighed against the significant cardiovascular and renal benefits of these agents.
2. Counselling on appropriate genital hygiene is important for both men and women when initiating SGLT2 inhibitors and regularly thereafter.