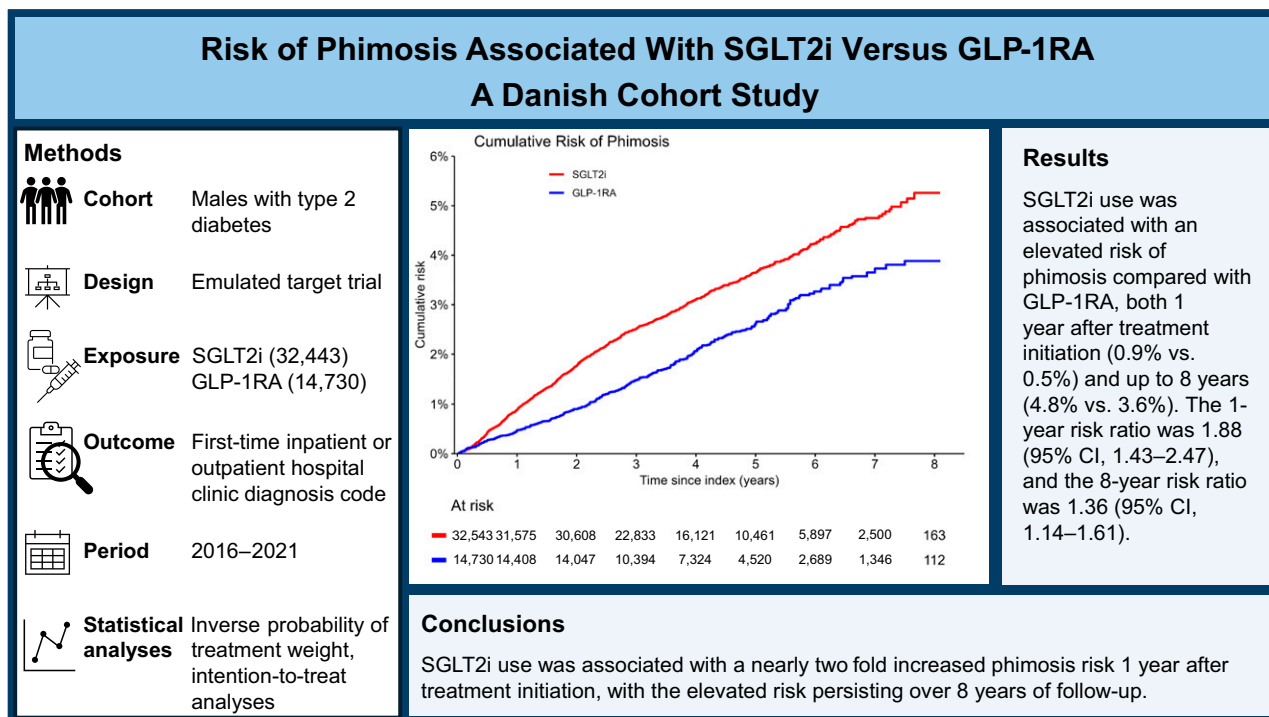


Risk of Phimosis Associated With SGLT2i Versus GLP-1RA: A Danish Cohort Study

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ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are associated with an increased risk of mycotic genital infections, potentially leading to complications like phimosis. The extent of these risks remains unclear.
- **What is the specific question we wanted to answer?**
Does initiation of SGLT2i, compared with glucagon-like peptide-1 receptor agonists (GLP-1RA), increase the risk of phimosis in men with type 2 diabetes?
- **What did we find?**
SGLT2i users had a nearly twofold higher risk of phimosis than GLP-1RA users 1 year after treatment initiation.
- **What are the implications of our findings?**
When prescribing SGLT2i, awareness of the increased risk of phimosis is important, while balancing the risk against the benefits.



Risk of Phimosis Associated With SGLT2i Versus GLP-1RA: A Danish Cohort Study

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OBJECTIVE

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) induce glucosuria, potentially leading to infection and inflammation in the preputial microenvironment, subsequently increasing the risk of phimosis. We aimed to investigate the risks of phimosis in males with type 2 diabetes initiating SGLT2i or glucagon-like peptide-1 receptor agonists (GLP-1RA).

RESEARCH DESIGN AND METHODS

In this population-based active-comparator new-user cohort study emulating a target trial, we included all adult male metformin users in Denmark initiating SGLT2i or GLP-1RA between 2016 and 2021. We used inverse probability of treatment weighting to balance the distribution of potential confounders. We estimated weighted intention-to-treat risk and risk ratios of phimosis identified from population-based medical databases.

RESULTS

In this study, we included 32,486 SGLT2i initiators and 14,793 GLP-1RA initiators with a median follow-up of 4 years (maximum 8 years). The risk of phimosis was elevated among SGLT2i users. The 1-year risk of phimosis was 0.9% among new SGLT2i users and 0.5% among new GLP-1RA users, corresponding to a 1-year risk ratio of 1.88 (95% CI, 1.43 to 2.47). During 8 years of follow-up, the risk of phimosis accumulated up to 4.8% in SGLT2i users and 3.6% in GLP-1RA users, with an 8-year risk ratio of 1.36 (95% CI, 1.14 to 1.61).

CONCLUSIONS

SGLT2i use was associated with a nearly twofold increased phimosis risk 1 year after treatment initiation in men with type 2 diabetes, compared with GLP-1RA use. Over 8 years of follow-up, the risk remained elevated, indicating a persistently higher risk associated with SGLT2i use.

In the rapidly evolving landscape of type 2 diabetes management, sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) have emerged as prominent new drugs in recent years (1). SGLT2i effectively decrease hyperglycemia in people with type 2 diabetes by promoting glucose excretion through the kidneys, causing glucosuria (2). However, a related concern is the approximately threefold elevated risk of genital infections (3–5), which, in men, may increase inflammation in the preputial microenvironment, potentially increasing the risk of phimosis (6,7).

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Phimosis, the constriction of the prepuce (foreskin), can impede retraction over the glans penis and lead to pain and difficulties in sexual intercourse and urination (6,7). Phimosis is most common in children but has a second incidence peak after the sixth decade of life, with an estimated prevalence ranging from 0.5% to 13% (6,7). In later life, this condition is often caused by inflammation and genital infection. Men with type 2 diabetes have a threefold risk of balanitis (8) and up to a sevenfold risk of phimosis (9–11). Phimosis, in turn, is known to increase the risk of penile cancer by up to 12-fold (12). Penile cancer is a rare malignancy, with an annual incidence of ~1 per 100,000 men (13). Its risk has been linked to obesity, type 2 diabetes, and balanitis, whereas circumcision appears to have a protective effect (12,14–18).

Solid evidence supports the efficacy of SGLT-2i in type 2 diabetes, but the risks of phimosis and penile cancer among men treated in everyday clinical practice are largely unknown. To determine whether SGLT2i treatment might be associated with greater risk of phimosis than GLP-1RA treatment, we conducted a large population-based cohort study emulating a target trial. Although we anticipated that penile cancer would be rare even in our large-scale health registries, we explored this cancer as an additional outcome, given its potential link to phimosis and long-term inflammation.

RESEARCH DESIGN AND METHODS

Study Design and Data Sources

This cohort study was designed to emulate a two-arm randomized clinical trial (the target trial) comparing the associations of SGLT2i versus GLP-1RA with phimosis and penile cancer risk. We outlined the target trial protocol to address our research question, and we defined the study population, treatment exposure, outcomes, and statistical approach based on this protocol (19). The details of the target trial protocol and the emulation are provided in Supplementary Table 1.

This study was conducted in Denmark, which has a tax-funded health care system and meticulously documents all medical services in high-quality, nationwide databases. Each Danish citizen is assigned

a unique registration number at birth or immigration (20), enabling accurate individual-level data linkage across all national databases. The databases used in this study were the Danish Civil Registration System, which records data on the residence, migration, and vital status of all Danish residents since 1968 (20); the Danish National Patient Registry, which includes data on all inpatient admissions, discharges, diagnoses, and surgical procedures in Danish hospitals since 1977, and outpatient clinics and emergency department contacts since 1995 (21); the Danish National Prescription Registry, which includes data on all reimbursed prescriptions redeemed at Danish pharmacies since 1995 (22); and the Register of Laboratory Results for Research, which includes blood sample biochemistry data since 2015 (23).

Eligibility Criteria

All adult men 18 years or older were eligible for inclusion if they had initiated SGLT2i or GLP-1RA in Denmark between 1 January 2016 and 31 December 2021. During this period, GLP-1RA and SGLT2i were generally used in similar clinical situations, such as a second-line glucose-lowering treatment in patients with type 2 diabetes (24,25). Patients were included on the date of their first reimbursed SGLT2i or GLP-1RA prescription in the Danish National Prescription Register (index date; flowchart in Supplementary Fig. 1). Patients with prior use of either drug were excluded ($n = 15,305$ patients). To align with treatment guidelines during the study period (24–26), patients were required to be receiving metformin treatment at baseline, defined by filling of at least one metformin prescription in the year before the index date. This criterion also ensured that eligible SGLT2i or GLP-1RA initiators had type 2 diabetes, as dapagliflozin was temporarily approved for type 1 diabetes treatment in Denmark, and SGLT2i and GLP-1RA might have been used to treat heart failure and obesity without diabetes, respectively, toward the end of our study period. Patients prescribed the approved obesity treatment liraglutide (Saxenda) were not included in the GLP-1RA initiator group. In agreement with type 2 diabetes guideline recommendations in place during the study period (25), patients with an eGFR below 30 mL/min

per 1.73 m² at baseline were also excluded to reflect eligibility criteria for initiating SGLT2i, although these guideline recommendations have since changed toward initiation at even lower kidney function (24). Furthermore, we excluded patients with a medical history of phimosis, surgical removal of the prepuce, penile cancer, or penile carcinoma in situ. Finally, individuals who did not reside in Denmark at least 12 months before index date were excluded, to ensure accurate baseline data collection (flowchart in Supplementary Fig. 1).

Outcomes and Covariates

The primary study outcome was phimosis. As an additional prespecified outcome, we examined penile cancer. Both outcomes were identified according to a first-time inpatient or outpatient hospital clinic diagnosis code in the Danish National Patient Registry.

Potential confounders were selected according to prior knowledge and guided by directed acyclic graphs. We obtained data from nationwide databases on demographic characteristics, other glucose-lowering drugs, type 2 diabetes complications, immunomodulatory comedications, urogenital pathology, social and frailty markers, other comorbidities, and other comedications. The definitions of variables are shown in Supplementary Table 2.

Statistical Analyses

To balance any residual skewness in the distribution of potential confounders between treatment cohorts after the application of the active comparator design, we used inverse probability of treatment (IPT) weighting. First, logistic regression analysis was used to compute the probability of receiving SGLT2i/GLP-1RA treatment (propensity score [PS]). We then used PS to determine the stabilized IPT weights for all individuals, assigning weights of proportion SGLT2i initiators divided by PS for SGLT2i initiators and proportion of GLP-1RA initiators divided by $1 - PS$ for the GLP-1RA reference group. Covariate balance was evaluated by examination of standardized mean differences between treatment groups. Covariates with a standardized mean difference below 0.1 were considered well-balanced. Baseline characteristics were described

for both the crude and IPT-weighted cohorts.

We conducted intention-to-treat analyses, wherein participants were considered exposed from the index date throughout the entire follow-up period. Patients were followed until an outcome event, death, emigration, or the end of the study (31 January 2024), whichever came first.

We computed IPT-weighted cumulative risk curves for phimosis and penile cancer, treating death as a competing event, using the Aalen-Johansen estimator. From these cumulative risk curves, we calculated the 1-, 5-, and 8-year risks, risk differences, and risk ratios for phimosis and penile cancer associated with use of SGLT2i versus use of GLP-1RA as reference. The 95% CI were obtained through robust variance estimators. For the additional outcome, penile cancer, we introduced a 1-year lag period, as any cancer diagnosed shortly after treatment initiation would likely not be causally related to drug exposure. We thus started follow-up for penile cancer 1 year after drug initiation, excluding persons with penile cancer within the first year and those with <1 year of follow-up.

All statistical analyses were conducted in R version 4.3.

Sensitivity Analyses

To assess the robustness of our findings, we conducted several sensitivity analyses. First, we conducted on-treatment analyses, estimating treatment duration by calculating the number of days covered by each filled prescription, multiplying the number of packages by the package's numerical volume. We added a 180-day grace period, to account for suboptimal adherence and the use of lower doses than expected in new drug users. In the on-treatment analyses, participants were excluded from further follow-up at treatment discontinuation or initiation of a comparator study drug class. Second, we stratified our risk ratio analyses by various subgroup characteristics, including age, HbA_{1c}, and diabetes duration. Third, to further investigate the role of glycemic control, we modeled the association between baseline HbA_{1c} levels and the risk of phimosis using a four-knot restricted cubic spline. Fourth, we specifically examined the risk of undergoing surgery

for phimosis in both drug initiator groups. Fifth, to address potential detection bias for phimosis and penile cancer related to the known risk increase for genital infections among SGLT2i users, we conducted a negative control analysis using inguinal hernia. We used inguinal hernia as a negative control outcome, a common condition in older men that is typically detected during physical examination of the genital area and is not biologically linked to SGLT2i use. Sixth, we assessed a possible dose-response relationship with SGLT2i use by examining whether drug treatment duration for >1 year, compared with shorter duration, influenced the risk ratios of phimosis and penile cancer. Finally, we repeated our main analysis without requiring that patients were on metformin treatment at baseline.

Data and Resource Availability

Under Danish law, researchers are not permitted to share raw registry data with third parties. To protect patient privacy, the combined data set used in this study is accessible only through the National Danish Health Data Authority. Because of Danish data privacy protection laws, we are unable to report the exact number of cases observed for penile cancer. This study was registered at Aarhus University's repository (no. 2016-051-000001/810; project no. 00003734).

RESULTS

Baseline Characteristics

We identified 82,544 men initiating SGLT2i or GLP-1RA. After application of the exclusion criteria, the study cohort comprised 32,486 SGLT2i initiators and 14,793 GLP-1RA initiators (flowchart in Supplementary Fig. 1).

Before IPT weighting, the SGLT2i initiators, compared with the GLP-1RA initiators, were slightly older (63.6 years vs. 61.5 years), had a lower prevalence of hospital-diagnosed obesity (8.7% vs. 15.1%), and used insulin therapy less frequently (10.2% vs. 21.5%) (Table 1). Most of the other clinical characteristics did not differ. IPT weighting achieved good comparability between cohorts, reducing all standardized mean differences to ≤ 0.01 (Supplementary Fig. 2).

Over the 8-year follow-up, discontinuation rates were 61% for SGLT2i users and 54% for GLP-1RA users. Throughout

the follow-up, 45% of SGLT2i users initiated GLP-1RA, and 40% of GLP-1RA users initiated SGLT2i (Supplementary Fig. 3).

Phimosis was mainly diagnosed in outpatient settings (94% for both SGLT2i and GLP-1RA initiators), predominantly in urological (70% vs. 67%) and other surgical (10% vs. 12%) departments (Supplementary Table 3). Penile cancer was also primarily diagnosed in outpatient urological departments.

Phimosis

The median follow-up for phimosis was 4.0 years for SGLT2i initiators and 3.9 years for GLP-1RA initiators. The risk of phimosis based on inpatient or outpatient hospital clinic diagnoses was higher for SGLT2i initiators than GLP-1RA initiators. The cumulative risk curves began to diverge around 3 months after treatment initiation, with the greatest difference emerging in the first 1–2 years (Fig. 1A). Thereafter, the curves increased more in parallel, with a steady rise in both groups over the full 8-year follow-up. The 1-year risk of phimosis was 0.9% (95% CI, 0.8–1.9) for SGLT2i initiators and 0.5% (95% CI, 0.4–0.6) for GLP-1RA initiators, corresponding to a risk difference of 0.4% (95% CI, 0.2–0.6) and a risk ratio of 1.88 (95% CI, 1.43–2.47). After 8 years of follow-up, the cumulated risk of phimosis was 4.8% (95% CI, 4.4–5.3) for SGLT2i initiators and 3.6% (95% CI, 3.1–4.1) for GLP-1RA initiators, corresponding to an 8-year risk difference of 1.3% (95% CI, 0.6–1.9) and a risk ratio of 1.36 (95% CI, 1.14–1.61) (Fig. 1 and Table 2).

Penile Cancer

For penile cancer, the median follow-up was 4.1 years for SGLT2i initiators and 3.9 years for GLP-1RA initiators. In this period, we observed ≤ 20 new cases of penile cancer in the groups combined, thus limiting the statistical precision of the estimates. The risk curves remained nearly identical during the initial years of follow-up, starting to separate after ~2–3 years, with a higher incidence for SGLT2i versus GLP-1RA, albeit driven by few penile cancer cases overall. A few cases among SGLT2i users happened late during follow-up, that is, around year 7–8 (Fig. 1B). As expected for this rare outcome, the absolute risks were

Table 1—Characteristics of SGLT2i and GLP-1RA initiators, crude and after IPT weighting

	Crude cohort			IPTW cohort*		
	SGLT2i, n (%)	GLP-1RA, n (%)	SMD	SGLT2i, n (%)	GLP-1RA, n (%)	SMD
Number of patients	32,486	14,793		32,543*	14,730*	
Age, median [Q1, Q3]	63.6 [55.3, 71.5]	61.5 [52.9, 69.9]	0.19	62.8 [54.5, 71.1]	63.1 [54.5, 71.1]	<0.01
Male	32,486 (100)	14,793 (100)	<0.01	32,543 (100)	14,730 (100)	<0.01
Index			0.10			<0.01
2016–2017	6,746 (20.8)	2,997 (20.3)		6,692 (20.6)	3,023 (20.5)	
2018–2019	11,235 (34.6)	4,450 (30.1)		10,752 (33.0)	4,828 (32.8)	
2020–2021	14,505 (44.7)	7,346 (49.7)		15,100 (46.4)	6,878 (46.7)	
Diabetes-related characteristics						
Diabetes duration, median [Q1, Q3]	7 [3, 11]	6 [3, 11]	0.03	7 [3, 11]	7 [3, 11]	<0.01
Hospital-diagnosed retinopathy	3,646 (11.2)	1,634 (11.0)	<0.01	3,657 (11.2)	1,663 (11.3)	<0.01
Hospital-diagnosed neuropathy	1,535 (4.7)	794 (5.4)	0.03	1,606 (4.9)	736 (5.0)	<0.01
Hospital-diagnosed nephropathy	1,364 (4.2)	843 (5.7)	0.07	1,550 (4.8)	721 (4.9)	<0.01
Diabetes treatment within a year before index						
Insulin therapy	3,302 (10.2)	3,188 (21.6)	0.32	4,546 (14.0)	2,064 (14.0)	<0.01
DPP4 inhibitors	10,589 (32.6)	4,597 (31.1)	0.03	10,481 (32.2)	4,788 (32.5)	<0.01
Sulfonylureas	4,543 (14.0)	1,980 (13.4)	0.02	4,483 (13.8)	2,039 (13.8)	<0.01
Other diabetes treatment	111 (0.3)	36 (0.2)	0.02	102 (0.3)	44 (0.3)	<0.01
HbA _{1c} levels			0.10			<0.01
HbA _{1c} <6.5%	1,405 (4.3)	850 (5.7)		1,556 (4.8)	701 (4.8)	
HbA _{1c} 6.5–7.4%	9,096 (27.9)	3,571 (24.1)		8,660 (26.6)	3,871 (26.3)	
HbA _{1c} ≥7.5%	21,247 (65.4)	10,027 (67.8)		21,570 (66.3)	9,824 (66.7)	
HbA _{1c} missing	765 (2.4)	345 (2.3)		757 (2.3)	333 (2.3)	
eGFR levels, mL/min			0.16			<0.01
eGFR <45	2,618 (8.1)	1,706 (11.5)		3,016 (9.3)	1,390 (9.4)	
eGFR 45–59	6,577 (20.2)	2,455 (16.6)		6,207 (19.1)	2,813 (19.1)	
eGFR 60–89	16,896 (52.0)	7,258 (49.1)		16,587 (51.0)	7,474 (50.7)	
eGFR ≥90	5,916 (18.2)	3,113 (21.0)		6,225 (19.1)	2,824 (19.2)	
eGFR missing	479 (1.5)	261 (1.8)		508 (1.6)	230 (1.6)	
Other comorbidities						
Cardiovascular disease	9,792 (30.1)	4,082 (27.6)	0.06	9,612 (29.5)	4,422 (30.0)	0.01
Solid cancer (not urogenital)	921 (2.8)	341 (2.3)	0.03	865 (2.7)	385 (2.6)	<0.01
Urogenital cancer	980 (3.0)	496 (3.4)	0.02	1,022 (3.1)	472 (3.2)	<0.01
Hematological cancer	282 (0.9)	152 (1.0)	0.02	299 (0.9)	136 (0.9)	<0.01
Chronic obstructive pulmonary disease	2,338 (7.2)	1,206 (8.2)	0.04	2,447 (7.5)	1,109 (7.5)	<0.01
Hospital-diagnosed obesity	2,828 (8.7)	2,235 (15.1)	0.20	3,506 (10.8)	1,596 (10.8)	<0.01
Urological surgery	2,221 (6.8)	1,151 (7.8)	0.04	2,323 (7.1)	1,060 (7.2)	<0.01
Genital surgery	431 (1.3)	243 (1.6)	0.02	464 (1.4)	212 (1.4)	<0.01
Genital infection	81 (0.2)	57 (0.4)	0.02	95 (0.3)	42 (0.3)	<0.01
HIV	44 (0.1)	21 (0.1)	<0.01	45 (0.1)	21 (0.1)	<0.01
Psoriasis	223 (0.7)	139 (0.9)	0.03	255 (0.8)	117 (0.8)	0.01
Lichen planus	46 (0.1)	18 (0.1)	<0.01	45 (0.1)	20 (0.1)	<0.01
Lichen sclerosis	437 (1.3)	226 (1.5)	0.02	458 (1.4)	211 (1.4)	<0.01
Dermatitis and eczema	329 (1.0)	166 (1.1)	0.01	342 (1.1)	153 (1.0)	<0.01
Other comedications						
Antihypertensive drugs	25,971 (79.9)	11,941 (80.7)	0.02	26,126 (80.3)	11,860 (80.5)	<0.01
Loop diuretics	3,686 (11.3)	2,042 (13.8)	0.07	3,979 (12.2)	1,821 (12.2)	<0.01
Statins	24,268 (74.7)	10,706 (72.4)	0.05	24,068 (74.0)	10,883 (73.9)	<0.01
Antiplatelet drugs	3,569 (11.0)	1,427 (9.6)	0.04	3,452 (10.6)	1,579 (10.7)	<0.01
Oral glucocorticoids	1,162 (5.1)	778 (5.3)	<0.01	1,687 (5.2)	770 (5.2)	<0.01
Topical glucocorticoids	6,170 (19.0)	3,235 (21.9)	<0.01	6,464 (19.9)	2,920 (19.8)	<0.01
NSAIDs	7,524 (23.2)	3,313 (22.4)	0.02	7,460 (22.9)	3,380 (22.9)	<0.01
Other immunosuppressive drugs	893 (2.7)	408 (2.8)	0.01	890 (2.7)	97 (2.7)	<0.01
Frailty markers						
Mental disorder	2,091 (6.4)	1,077 (7.3)	0.03	2,181 (6.7)	991 (6.7)	<0.01
Alcoholism	494 (1.5)	270 (1.8)	0.02	530 (1.6)	248 (1.7)	<0.01
Dementia	248 (0.8)	104 (0.7)	<0.01	243 (0.7)	109 (0.7)	<0.01

Continued on p. 5

Table 1—Continued

	Crude cohort			IPTW cohort*		
	SGLT2i, n (%)	GLP-1RA, n (%)	SMD	SGLT2i, n (%)	GLP-1RA, n (%)	SMD
Hospital admissions 1 year prior to index			0.02			<0.01
None	28,442 (87.5)	12,869 (87.0)		28,394 (87.3)	12,823 (87.1)	
1–2	3,544 (10.9)	1,710 (11.6)		3,647 (11.2)	1,669 (11.3)	
≥3	500 (1.5)	214 (1.4)		503 (1.5)	237 (1.6)	
Hospital outpatient contacts 1 year prior to index			0.11			<0.01
None	20,537 (63.2)	8,564 (57.9)		19,957 (61.3)	8,991 (61.0)	
1–4	9,609 (29.6)	5,032 (34.0)		10,122 (31.1)	4,594 (31.2)	
≥5	2,340 (7.2)	1,197 (8.1)		2,463 (7.6)	1,133 (7.8)	

Categorical data are shown as *n* (%), and continuous data are shown as median [interquartile range]. Look-back period for reimbursed prescriptions is 1 year, and 10 years for hospital diagnoses. *Population size may shift after IPTW balancing because of the reweighting process. DPP-4, dipeptidyl-peptidase 4; NSAIDs, nonsteroidal anti-inflammatory drugs; SMD, standardized mean difference.

low (Fig. 1) (note the compressed y-axis scale in Fig. 1B compared with Fig. 1A). Our results suggested elevated penile cancer risk in men initiating SGLT2i, with a cumulated 8-year risk of 0.09% (95% CI, 0.03–0.22) for SGLT2i initiators and 0.01% (95% CI, 0.00–0.06) for GLP-1RA initiators, corresponding to a risk difference of 0.07% (95% CI, –0.01 to 0.05) and a risk ratio of 6.34 (95% CI, 1.16–34.52) (Fig. 1 and Table 2).

Sensitivity Analyses

In the on-treatment analyses (Supplementary Table 4 and Supplementary Fig. 4), the median follow-up was 2.2–2.4 years, and results were consistent with the intention-to-treat findings. The 1-year risk of phimosis was 0.9% (95% CI, 0.8–1.0) for SGLT2i initiators and 0.4% (95% CI, 0.3–0.5) for GLP-1RA initiators, corresponding to a risk ratio of 2.25 (95% CI, 1.66–3.05). After a maximum of 8 years, the risk ratio for phimosis was 1.88 (95% CI, 1.36–2.61). For penile cancer, the cumulative 8-year risk was 0.20% (95% CI, 0.06–0.75) for SGLT2i initiators and 0.01% (95% CI, 0.00–0.07) for GLP-1RA initiators, corresponding to a risk ratio of 20.14 (95% CI, 1.91–212.14).

Most subgroup analyses of phimosis revealed results consistent with the main findings (Fig. 2 and Supplementary Figs. 5 and 6). SGLT2i initiators had an elevated risk of phimosis in all subgroups regardless of age, HbA_{1c} level, and diabetes duration. Given the low number of penile cancers, subgroup analyses were not possible for this outcome.

When examining the risk of phimosis according to baseline HbA_{1c} levels using a restricted spline, we found that the

risk increased with higher HbA_{1c} levels in both SGLT2i and GLP-1RA initiators. Across HbA_{1c} levels, SGLT2i initiators consistently had a higher risk of phimosis (Supplementary Fig. 7).

The absolute and relative risks of surgery for phimosis closely aligned with the risk of inpatient and outpatient diagnoses of phimosis (main analysis). After 1 year, 0.8% (95% CI, 0.7–0.9) of SGLT2i initiators and 0.4% (95% CI, 0.3–0.5) of GLP-1RA initiators underwent surgery (risk ratio, 2.00; 95% CI, 1.5–2.68) (Supplementary Table 5 and Supplementary Fig. 8).

In our negative control analysis using inguinal hernia as the outcome, we found very similar risks in both groups (Supplementary Fig. 9). The weighted risk ratio for inguinal hernia after 8 years of follow-up was 0.98 (95% CI, 0.74–1.31), showing no association with SGLT2i initiation compared with GLP-1RA initiation.

Stratified by treatment duration, the risk of phimosis and penile cancer was highest among SGLT2i users with longer treatment durations (Supplementary Table 6 and Supplementary Fig. 10). For phimosis, the 1-year risk ratio was 1.55 (95% CI, 1.08–2.22) for SGLT2i users treated <1 year and 2.01 (95% CI, 1.55–2.66) for those treated ≥1 year, compared with GLP-1RA users. For penile cancer, the 8-year risk ratio was 2.45 (95% CI, 0.40–14.99) for SGLT2i users treated <1 year and 7.64 (95% CI, 1.32–44.13) for ≥1 year of treatment, compared with GLP-1RA users.

In the analysis excluding the requirement of baseline metformin use, we included 5,961 additional SGLT2i initiators and 2,538 GLP-1RA initiators. Initiators not on metformin differed markedly

from the main study population, for example, on HbA_{1c} (37% having HbA_{1c} below 6.5% in non-metformin vs. 4.7% in metformin users) and cardiovascular disease (54% in non-metformin vs. 30% in metformin users). Despite these differences, the relative risk of phimosis remained almost unchanged, with a 1-year risk ratio of 1.88 (95% CI, 1.44–2.46) in the SGLT2i users compared with the GLP-1RA users. There were no events of penile cancer in the non-metformin users, and the penile cancer risk remained elevated in the extended analysis at 6.65 (95% CI, 1.26–35.09) in SGLT2i users compared with GLP-1RA users (Supplementary Figs. 11 and 12).

CONCLUSIONS

In this large population-based cohort study designed to emulate a target trial, phimosis risk doubled among men with type 2 diabetes who initiated SGLT2i compared with those who started GLP-1RA. This elevated risk was consistent across all subgroups and analytical approaches. The elevated risk of phimosis among SGLT2i users attenuated over time but remained consistently higher throughout follow-up. Although the absolute risk of penile cancer was low, our findings suggest that SGLT2i users had a higher risk of penile cancer than GLP-1RA users.

Mechanistically, the elevated risk of both phimosis and penile cancer in SGLT2i initiators might be attributable to a higher incidence of genital infections with SGLT2i use (3–5). SGLT2i prevent glucose reabsorption in the kidneys, leading to glucosuria. Glucosuria, in turn, fosters bacterial and fungal growth, which might affect the microenvironment

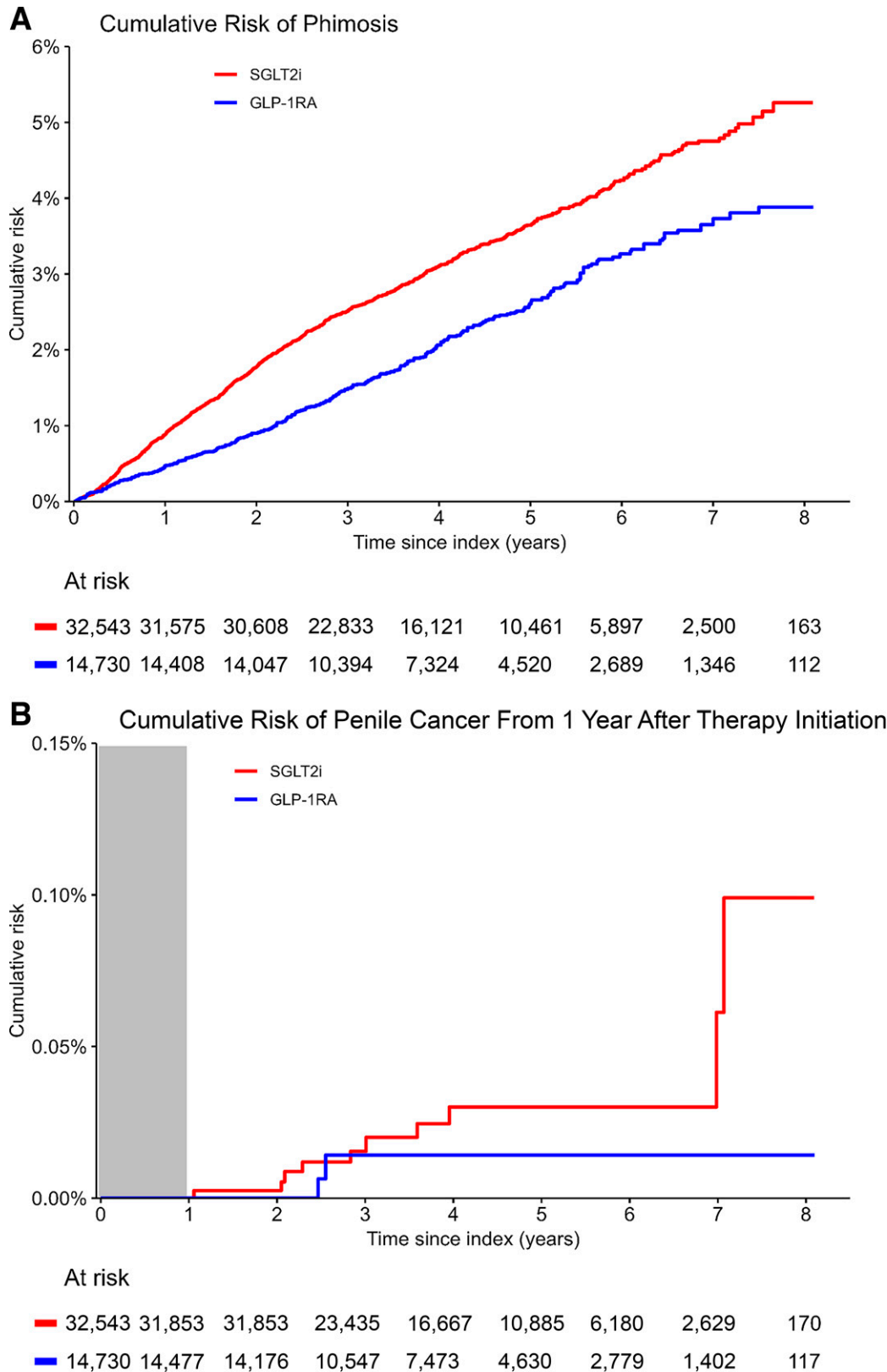


Figure 1—IPT-weighted intention-to-treat cumulative risk of phimosis and penile cancer with initiation of SGLT2i and GLP-1RA. (A) Phimosis. (B) Penile cancer.

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in the preputial space and cause inflammation, hyperplasia, and dysplasia. This could eventually lead to precursor lesions

(27,28). Phimosis creates an environment conducive to persistent infections, which further exacerbates the risk of developing

penile cancer (7,29–31). Increased genital infections due to glucosuria in SGLT2i users might therefore contribute to the

Table 2—IPT-weighted intention-to-treat 1-, 5-, and 8-year risk of phimosis and penile cancer in males initiating SGLT2i compared with GLP-1RA

Phimosis	SGLT2i initiators (n = 32,543)			GLP-1RA initiators (n = 14,730)			Risk difference, % (95% CI)	Risk ratio (95% CI)
	Events*	Events per 10,000 py	Cumulative risk, % (95% CI)	Events	Events per 10,000 py	Cumulative risk, % (95% CI)		
1 year	284	89	0.9 (0.8–1.0)	69	47	0.5 (0.4–0.6)	0.4 (0.3–0.6)	1.88 (1.43–2.47)
5 years	963	78	3.5 (3.2–3.7)	287	51	2.5 (2.2–2.8)	1.0 (0.6–1.4)	1.40 (1.21–1.62)
8 years	1045	77	4.8 (4.4–5.3)	322	52	3.6 (3.1–4.1)	1.3 (0.6–1.9)	1.36 (1.14–1.61)
Penile cancer								
1 year [†]	—	—	—	—	—	—	—	—
5 years	—	0.6	0.03 (0.01–0.06)	—	0.3	0.01 (0.00–0.05)	0.01 (–0.01 to 0.05)	2.08 (0.43–9.94)
8 years	—	0.7	0.09 (0.03–0.22)	—	0.3	0.01 (0.00–0.06)	0.07 (–0.01 to 0.16)	6.34 (1.16–34.52)

*Events are not shown for penile cancer to protect patient privacy because of a low number of events. [†]A 1-year lag period is introduced for penile cancer. py, patient-years.

elevated risks of both phimosis and penile cancer. Of note, any such risk must be weighed against the clear beneficial effects of SGLT2i on cardiovascular risk and overall mortality (32–38). Further, this study is, to the best of our knowledge, the first to examine the association between SGLT2i treatment and the risks of phimosis and penile cancer. Phimosis has only been included as part of a composite outcome of genital infections in a single study based on U.S. commercial claims databases of 156,074 men (3). Therefore, confirmatory studies are needed.

One strength of our study was the use of population-based registries with comprehensive follow-up, thereby enabling the inclusion of all SGLT2i and GLP-1RA initiators in Denmark. However, our study has limitations. First, some misclassification of outcomes may have happened, although our outcome is based on inpatient and outpatient hospital clinic diagnoses and surgical procedures from high-quality Danish registries (20–22). Strengthening the validity of the outcomes, we confirmed that both phimosis and penile cancer were mainly diagnosed in specialized urological departments. Findings for undergoing surgery for phimosis closely aligned with those from our main analysis based on diagnoses of phimosis, further supporting the validity and robustness of our outcomes. Second, differential surveillance, that is, detection bias, may have affected our findings. SGLT2i users are more likely to develop urogenital symptoms, which may have resulted in more frequent assessment by urologists, and clinicians might have had greater vigilance for genital adverse effects in general in SGLT2i initiators compared with GLP-1RA initiators. Still, surveillance bias would probably increase mainly the proportion with less severe phimosis symptoms. Our finding that the relative risk increase of phimosis surgery aligned with the increased occurrence of phimosis diagnoses speaks against substantial surveillance bias. Additionally, the total absence of any association between SGLT2i use and inguinal hernia supports that differential surveillance alone is unlikely to explain the observed increased risk of phimosis.

Third, penile cancer is a rare malignancy, and, because we identified few cases, our estimates lacked statistical precision. Additionally, the median follow-up

Phimosis Subgroup Analyses

Subgroups	SGLT2i		GLP-1RA		1-year relative risk (95% CI)
	Patients (%)	1-year risk, % (95% CI)	Patients (%)	1-year risk, % (95% CI)	
Entire population	32,543 (100.0)	0.9 (0.8, 1.0)	14,730 (100.0)	0.5 (0.4, 0.6)	1.9 (1.4, 2.5)
Age <65	18,528 (56.6)	1.0 (0.8, 1.1)	8,292 (55.7)	0.5 (0.3, 0.6)	2.0 (1.4, 2.8)
Age ≥65	14,015 (42.8)	0.8 (0.6, 0.9)	6,438 (43.3)	0.5 (0.3, 0.7)	1.7 (1.1, 2.6)
HbA _{1c} <7.5%	10,216 (31.2)	0.6 (0.5, 0.8)	4,572 (30.7)	0.4 (0.2, 0.6)	1.6 (0.9, 2.8)
HbA _{1c} ≥7.5%	21,570 (65.9)	1.0 (0.9, 1.1)	9,824 (66.0)	0.5 (0.4, 0.7)	2.0 (1.4, 2.7)
Diabetes duration ≤6 years	15,881 (48.5)	0.9 (0.8, 1.1)	7,223 (48.5)	0.6 (0.4, 0.8)	1.6 (1.1, 2.3)
Diabetes duration >6 years	16,662 (50.9)	0.8 (0.7, 1.0)	7,506 (50.4)	0.4 (0.2, 0.6)	2.3 (1.5, 3.6)



Figure 2—Phimosis subgroup analyses. IPT weighted 1-year risk of phimosis in SGLT2i initiators compared with GLP-1RA initiators.

time for cancer was only 4 years, with a maximum of 8 years. A longer follow-up would have been ideal for examining the risk of penile cancer. However, SGLT2i were only widely used in Denmark since 2016 (1), which limited the available follow-up. Of note, the observation that fewer than 10% of individuals remained under observation by the seventh year of follow-up primarily reflects the relatively recent large-scale uptake of SGLT2i in our population, resulting in still limited available follow-up for the many individuals who initiated treatment late in the study period, rather than discontinuation. Fourth, we lacked information on factors such as BMI, circumcision, ethnic diversity, social economic factors, and lifestyle behaviors. BMI is an important risk factor for both phimosis and penile cancer (7,12); however, given that BMI is usually higher in GLP-1RA than SGLT2i users in clinical practice, corroborated by hospital-diagnosed obesity being more prevalent among GLP-1RA users in our study, any uncontrolled confounding would likely have led to an underestimation of both phimosis and penile cancer risk ratios associated with SGLT2i use, not changing our conclusions. Additionally, circumcision prevalence varies substantially between populations, with an estimated prevalence below 20% in Denmark and many other European countries, compared with ~75% in the U.S. (39). In Denmark, circumcision prevalence in adults is poorly captured in national health registries, both because many therapeutic and most nontherapeutic

ritual circumcisions are performed outside the public health care system and therefore not registered and because available database history would not cover childhood procedures for individuals with a median age of >60 years. Because circumcision prevents phimosis and lowers the risk of penile cancer (6,17,18), the absolute risk of these conditions among SGLT2i initiators would likely be lower in populations with higher circumcision rates than those reported in this study. Finally, the intention-to-treat and on-treatment analyses each have inherent limitations (40). The intention-to-treat method might have underestimated associations because of exposure misclassification related to discontinuation and switching of medications during follow-up. In contrast, the on-treatment method might have introduced bias from informative censoring because the reasons for discontinuing treatment were uncertain. The higher risk of phimosis observed during the first year of follow-up may reflect a depletion of vulnerable people, where persons predisposed to develop phimosis experience the outcome early after treatment initiation. In addition, the high rate of treatment discontinuation and switching over time may have further contributed to the lower long-term risk estimates in the intention-to-treat analyses. However, our findings were consistent across both analytical approaches, thus supporting our results' robustness.

In conclusion, men with type 2 diabetes initiating SGLT2i were found to have

a higher risk of phimosis than GLP-1RA initiators. Our findings also suggest an elevated risk of penile cancer, although the absolute risks of penile cancer were low.

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