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Comparative risk of genital infections associated with SGLT2 inhibitors: A real-world retrospective cohort study

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Abstract

It is unclear the extent to which Sodium-glucose co-transporter 2 (SGLT2) inhibitors increase the risk of genital infections in routine clinical care against other antidiabetic medications, or whether the increased risk is consistent across gender or age subgroups, within individual SGLT2 agents, or it is more pronounced at a particular time after treatment initiation. We conducted a retrospective cohort study in two US commercial claims databases (2013–2017). In the primary analysis, a 1:1 propensity-score matched cohorts of female and male with type-2 diabetes mellitus initiating a SGLT2 inhibitor *vs* DPP-4 inhibitors was created. The outcome was a composite of genital candidal infections, vaginitis or vulvovaginitis in females, and genital candidal infections, balanitis, balanoposthitis, phimosis or paraphimosis in males. Among a propensity-score matched cohorts of 129,994 females and 156,074 males, the adjusted Hazard Ratio and excess-risk per 1,000 person years for SGLT2 v DPP-4 inhibitors was 2.81 (95% CI, 2.64, 2.99) and 87.4 (95% CI, 79.1, 96.2) respectively for females, and was 2.68 (95% CI, 2.31, 3.11and 11.9 (95% CI, 9.3–15.0) for males. Findings were similar in the SGLT2 inhibitor vs GLP1 agonist comparison, more pronounced in the subgroup of patients aged ≥60 (HR, 4.45 (95% CI, 3.83–5.17) in females and 3.30 (95% CI, 2.564.25) in males), and no meaningful difference across individual SGLT2 inhibitors was identified. This increase in risk was evident in the first month of treatment initiation and remained elevated throughout the course of therapy. SGLT2 inhibitors were associated with an approximately three-fold increase in risk of genital infections

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Sodium--glucose co-transporter 2 (SGLT2) inhibitors - a newer class of anti-diabetic medications - reduce plasma glucose in an insulin-independent manner by inhibiting glucose reabsorption in the proximal tubule.[1] In addition to reducing serum glucose concentration,

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SGLT2 inhibitors also exert additional beneficial effects on cardiovascular markers including blood-pressure and weight,[2] cardiovascular endpoints, and all-cause mortality.[3,4]

Because SGLT2 inhibitors increase the availability of glucose in the genitourinary tract,[5] clinical trials have linked their use to a three to five-fold increase in the risk of genital infections.[2,6–14] Since diabetes is a strong independent predictor of genital infections,[15–17] further increases in the risk of genital infections can decrease quality of life predisposing patients to therapy discontinuation and subsequently poor glycemic control.

As clinical trials (RCTs) have narrowly defined inclusion criteria that commonly exclude patients with multiple comorbidities or high frailty, it is unclear the extent to which the increased risk of genital infections observed in clinical trials among patients randomized to SGLT2 inhibitors is reflected in routine clinical care, against other antidiabetic drug-classes. Further, it is unknown whether this risk varies appreciably across subgroups of age and gender (as RCTs do not commonly report on adverse reactions by subgroups),[6,8,9] within individual SGLT2 inhibitors (prior evidence has come from indirect comparisons via network meta-analyses),[8] or is more pronounced at any particular time after treatment initiation.

Accordingly, using two large cohorts of commercially-insured patients in the US, we sought to assess the risk of genital infections in patients with diabetes mellitus type 2 (T2DM) initiating an SGLT2 inhibitor compared to Dipeptidyl peptidase-4 (DPP4) inhibitors, reporting on the subgroups of age, gender, and assessing this risk within individual SGLT2 inhibitors and duration of therapy.

METHODS

Data source and study population

This study utilized data from Truven Health MarketScan ® (April 2013 - December 2016) and Optum © Clinformatics ® Datamart (April 2013 - September 2017), both of which are US based health insurance databases that collect data on patient demographics, inpatient and outpatient medical service use, and outpatient pharmacy dispensing.

The study cohort comprised of patients initiating an SGLT2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin) or a Dipeptidyl Peptidase-4 inhibitor (sitagliptin, saxagliptin, linagliptin or alogliptin) aged greater than 18 with evidence of T2DM any time prior to drug initiation. Patients entered the study on the day of a first filled prescription of any of the drugs listed above (i.e., cohort entry date). Cohort membership required patients to have no prior dispensings for either study drug class in the 6 months prior to cohort entry, and no concomitant initiation of both study drug classes on the same day. Patients with evidence of diabetes mellitus type I, end-stage renal disease, cancer, human immunodeficiency virus, pregnancy, history of mycotic infections (for e.g., dermatophytosis) or genital infections (see below) were excluded (see supplement table 1 for exclusion-criteria definitions). Analysis was stratified by gender to account for the different nature and incidence of genital infections.

Propensity score matching

To mitigate the potential for confounding, new initiators of SGLT2 inhibitors were matched to new initiators of DPP4 inhibitors according to their estimated propensity score, which modelled the probability of initiating an SGLT2 inhibitor compared to a DDP4 inhibitor on cohort entry, given 44 baseline covariates (see supplement tables 2–5) assessed 6-months prior to drug initiation, and included sociodemographic variables (e.g., age, sex), diabetes severity and diabetic drug use (e.g., complications of diabetes, insulin use), common comorbid conditions (e.g., hypertension, ischemic heart disease), and conditions related to risk of genital infections (for e.g., estrogen use, history of urinary-tract infections). We propensity-score-matched an SGLT2 initiator with a DPP4 initiator within a maximum caliper of 0.01.

Follow up and study endpoints

Patients were censored on the earliest of the following events: end of healthcare or pharmacy continuous eligibility, switching exposure class or adding therapy from the comparator class, therapy discontinuation (defined as a 30-day treatment gap after the expiration of the last prescription's supply), 365 days, or the last date of data availability.

The primary outcome was an episode of genital infections, which was defined as a composite of genital candidal infections, vaginitis or vulvovaginitis for females, and genital candidal infections, balanitis, balanoposthitis, phimosis or paraphimosis for males (see supplement table 1 for outcome definitions). As a secondary outcome, we restricted the definition of genital infections related to candidal infections only.

Statistical analysis

We assessed the performance of the propensity score by cross-tabulating the baseline covariates by exposure group before- and after - matching. Hemoglobin A1c, which was available for 10% of the pooled population, was not included in the propensity score but used to assess the glycemic control before and after matching. In the propensity-score matched cohort, we estimated the risk of genital infections for SGLT2 inhibitors compared to DPP-4 inhibitors by calculating the number of events, incidence rates, and hazard ratios with 95% confidence intervals. The adjusted excess risk for genital infections was estimated by I_0 x (HR-1) where I_0 is the crude rate of the outcome in control group per 1,000 person-years, and HR is the adjusted hazard ratio (95% CI were calculated analogously). All statistical analyses were performed with the use of the validated Aetion platform (see supplement).[18] Analysis were performed within each database, and estimates were pooled through fixed-effects meta-analysis (see supplement for more information).

Sensitivity and secondary analysis

To assess the robustness of our analysis, we created a new cohort of patients changing the active comparator from DPP-4 inhibitors to Glucagon-like peptide-1 (GLP1) receptor agonists. We also conducted two subgroup analysis. First, because older patients may have a higher risk of SGLT2 induced infections, we examined subgroup of patients over 60. Second, we ran stratified analysis comparing dapagliflozin and empagliflozin to canagliflozin (the most commonly utilized agent during the study period in the US). Within

all subgroups, the propensity score was re-estimated, and patients were re-matched based on the newly estimated PS.

RESULTS

Within the two databases, there were 174,812 patients that initiated a SGLT2 inhibitor and 336,922 patients that initiated a DPP-4 inhibitor (Table 1). Prior to matching, and for both genders, the two groups differed in several baseline covariates. Compared to their SGLT2 inhibitor counterparts, DPP-4 inhibitor initiators were older, less likely to have used insulin or GLP1 agonists during the baseline, and more likely to have a history of urinary tract infections. Within the PS-matched cohort - comprising of 286,068 total patients - the baseline covariates (including hemoglobin A1c, which was not included in the PS model) were comparable with no standardized differences exceeding 10% (see supplement tables 2–5 for baseline characteristics prior and post propensity score matching by gender and database)

Primary analysis

Prior to adjustment, the Hazard Ratio [HR] for genital infections among females and males was 3.38 (95% CI, 3.22–3.55) and 2.78 (95% CI, 2.50–3.10; see supplement table 6 for pooled and database-specific estimates).

Table 2 reports pooled PS-matched estimates (see supplement table 7 for database specific estimates). Among PS-matched females, there were 3,599 cases of genital infections in the SGLT2 inhibitor group compared to 1,247 in the DPP-4 inhibitor group, corresponding to an adjusted incidence of 135.5 v 48.5 per 1,000 person-years (Appendix Table 6). The adjusted HR for the SGLT2 inhibitor group was 2.80 (95% CI, 2.63–2.99), translating to an excess risk per 1,000 person-years [ER] of 87.6 (95% CI, 79.1–96.7). Among PS-matched males, the HR was similar to females in magnitude of the effect [2.66 (95% CI, 2.30–3.08), but owing to a lower incidence of genital infections in males, the ER was significantly lower, ER 11.9 (95% CI, 9.4, 15.0). The association between SGLT2 inhibitor use and candidal infections was more pronounced, with a HR of 3.35 (95% CI, 3.05– 3.67) corresponding to an ER of 53.1 (95% CI, 46.4–60.4) among females, and a HR of 3.35 (95% CI, 2.28–4.91) corresponding to an ER of 2.4 (95% CI, 1.3–4.1) among males.

Supplement Figure 1 shows the pooled 1:1 propensity score matched Kaplan-Meier curves describing the cumulative incidence of genital infections among males and females; the increase in risk was apparent within the first month of SGLT2 inhibitor initiation and remained elevated through the course of therapy.

Sensitivity and secondary analysis

Changing the active comparator from DPP-4 inhibitor to GLP1-agonists did not appreciably alter the risk, HR 2.91 (95% CI, 2.73 −3.10) in females and 2.85 (95% CI, 2.42–3.35) in males. In the subgroup of patients ≥60, the HR for genital infections was higher, HR 4.45 (95% CI, 3.83–5.17) in females and 3.30 (95% CI, 2.56–4.25) in males. Using canagliflozin as reference, the risk of genital infections was similar with empagliflozin [HR 0.97 (95% CI,

0.89–1.05) among females and 0.97 (95% CI, 0.80–1.15) among males], and dapagliflozin [HR 0.90 (95% CI, 0.83, 0.97) among females and 0.99 (95% CI, 0.83–1.17) among males].

DISCUSSION

In a large population-based study, we found that SGLT2 inhibitor use was associated with an approximately three-fold increase in the risk of genital infections compared with other diabetes treatment. This association was consistent across genders and databases, robust to change of active comparator, and larger in magnitude in the subgroup of patients ≥ 60 years old. Within individual SGLT2 inhibitors, the risk appeared similar across agents, and remained elevated throughout the duration of therapy.

Our primary findings are consistent with previous randomized controlled trials which found a three-to-five-fold increase in the risk of genital infections.[2,8,9] However, previous clinical trials on SGLT2 inhibitors neither evaluated the incidence of genital infections by age or sex, nor performed direct comparisons across individual SGLT2 inhibitors or examined duration of therapy. A network meta-analysis that indirectly compared the risk of genital infections among individual SGLT2 inhibitors found canagliflozin had a slightly higher risk of genital infections, followed by dapagliflozin and empagliflozin.[6] However, because network meta-analyses use clinical trial estimates to indirectly compare individual SGLT2 inhibitors, the heterogeneity in characteristics of clinical trials (e.g., inclusion criteria, outcome definitions and choice of active comparator) can make it difficult to elucidate estimates of risk for the individual agents. By contrast, this study utilized a standardized design to directly compare the individual SGLT2 inhibitors.

Additional strengths of the current investigation include its large size, which allowed for the investigation of the risk of genital infections among older patients and within individual SGLT2 inhibitors, in a real-world setting, allowing for better generalizability of our findings to routine care patients. Study limitations are noted. First, although we utilized propensity score matching to mitigate concern for bias by characteristics associated with SGLT2 inhibitor use and genital infections, some potential confounders were not available in our data (for e.g. circumcision status or behavioral risk factors[19]); however, given the magnitude of the effect size, this association is unlikely to be fully explained by the presence of residual confounding. Second, by requiring a medical encounter related to genital infections, we may have systematically excluded cases of genital infections with a milder underlying symptomatology. However, the choice of a more specific outcome definition maximizes study validity. Third, our findings are generalizable to commercially-insured patients. However, it is unlikely that the risk of genital infections would vary among patients with different insurance types. Fourth, because this was a claim based study, the analysis did not control for some important variables like duration of diabetes or body mass index; however, claims based proxies have been shown to be good surrogates for these characteristics.[20]

The use of SGLT2 inhibitors was associated with an approximately three-fold increased risk of genital infections when compared to two other classes of anti-diabetic medications. The risk of genital infections should be evaluated against the glycemic and cardiovascular benefits when prescribing these agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1:

Select baseline patient characteristics for patients initiating an SGLT2 or a DPP4 inhibitor[a]

	Female				Male			
	Pre-matching		Post-matching		Pre-matching		Post-matching	
	DPP4 (n=153,736)	SGLT2 (n=78,814)	DPP4 (n=64,997)	SGLT2 (n=64,997)	DPP4 (n= 183,186)	SGLT2 (n=95,998)	DPP4 (n=78,037)	SGLT2 (n=78,037)
Age								
<30	1191 (0.8)	848 (1.0)	683 (1.1)	691 (1.1)	1171 (0.6)	703 (0.8)	621 (0.8)	606 (0.8)
30–45[b]	1467 (9.5)	1181 (14.9)	9267 (14.2)	9295 (14.3)	2188 (11.9)	1439 (14.9)	1167 (14.9)	1176 (15.0)
45–60[b,c]	5696 (37.0)	4062 (51.5)	3226 (49.6)	3219 (49.5)	7714 (42.1)	5061 (52.7)	3949 (50.6)	3970 (50.8)
>=60[b,c]	8089 (52.6)	2552 (32.3)	2278 (35.0)	2281 (35.1)	8298 (45.2)	3028 (31.5)	2624 (33.6)	2597 (33.2)
Diabetic complications								
Renal	1099 (7.2)	3592 (4.6)	2802 (4.3)	2920 (4.5)	1253 (6.8)	5306 (5.5)	3948 (5.1)	4019 (5.2)
Neurological	1372 (8.9)	7637 (9.7)	5665 (8.7)	5738 (8.8)	1449 (7.9)	9542 (9.9)	6729 (8.6)	6914 (8.9)
Ocular	6285 (4.1)	3114 (4.0)	2213 (3.4)	2331 (3.6)	6667 (3.6)	3726 (3.9)	2614 (3.3)	2699 (3.5)
Peripheral circulation	3115 (2.0)	1005 (1.3)	768 (1.2)	839 (1.4)	3634 (2.0)	1476 (1.5)	1027 (1.3)	1133 (1.5)
Anti-diabetic drug use								
GLP1 agonist[b,c]	6207 (4.0)	1705 (21.6)	5795 (8.9)	6521 (10.0)	5247 (2.9)	1885 (19.6)	5016 (6.4)	5614 (7.2)
Sulfonyl ureas	5096 (33.1)	2371 (30.0)	2007 (30.8)	1985 (30.5)	6420 (35.0)	3341 (34.8)	2785(35.6)	2736 (35.0)
Metformin[b,c]	9629 (62.6)	5378 (68.2)	4397 (67.6)	4380 (67.3)	1193 (65.1)	7076 (73.7)	5624 (72.0)	5645 (72.3)
Insulin[b,c]	2109 (13.7)	2125 (26.9)	1348 (20.7)	1357 (20.8)	2214 (12.0)	2553 (26.5)	1527 (19.5)	1545 (19.8)
Hemoglobin A1c[b,c,d]	8.6 (1.6)	8.3 (1.8)	8.5 (1.9)	8.5 (1.9)	8.8 (1.8)	8.5 (1.9)	8.8 (1.8)	8.8 (1.9)
Risk factors for genital infections								
Broad spectrum antibiotics	4032 (26.2)	2149 (27.2)	1750 (26.9)	1757 (27.0)	3526 (19.2)	1926 (20.0)	1533 (19.6)	1534 (19.6)
Oral steroid use	1770 (11.5)	9239 (11.7)	7473 (11.4)	7627 (11.7)	1475 (8.1)	7572 (7.9)	5983 (7.7)	6144 (7.9)
Estrogen use[b,e]	9324 (6.1)	6499 (8.2)	4959 (7.6)	4935 (7.6)				
Urinary tract infection	1522 (9.9)	5937 (7.5)	4988 (7.6)	5052 (7.77)	5058 (2.8)	1664 (1.7)	1362 (1.7)	1424 (1.8)

Abbreviations: GLP1: Glucagon-like peptide-1 agonist; SGLT2: sodium-glucose cotransporter 2 inhibitors; DPP-4: Dipeptidyl peptidase-4 inhibitors

[a]Pooled characteristic are shown. See appendix Tables 3–6 for baseline characteristics by gender and database prior to and post propensity score matching

[b] Standardized difference > 10%, pre-matched cohort; females

[c] Standardized difference > 10%, pre-matched cohort; males

[d] Hemoglobin A1c (available for 10% of the pooled population; not included in the propensity score) was utilized to assess the presence of adequate therapeutic equipoise between the SGLT2 and their non-gliflozin counterparts prior to propensity score matching and to assess potential residual confounding after propensity score matching; mean (SD) are shown

[e] Estrogen use defined as oral contraceptives containing estrogen and hormone replacement therapy

Table 2:

Propensity score matched results[a]

	No. of patients[b]	HR (95%CI)	Excess risk (95% CI)[c]
SGLT2 inhibitors *v* DPP4 inhibitors (primary analysis)			
Female			
Genital infections (composite)	129,994	2.80 (2.63, 2.99)	87.6 (79.1, 96.7)
Canclidal genital infections		3.35 (3.05, 3.67)	53.1 (46.4, 60.4)
Male			
Genital infections (composite)	156,074	2.66 (2.30, 3.08)	11.9 (9.4, 15.0)
Canclidal genital infections		3.35 (2.28, 4.91)	2.4 (1.3, 4.1)
SGLT2 inhibitors *v* GLP1 agonists			
Female			
Genital infections (composite)	142,992	2.91 (2.73, 3.10)	91.0 (82.4, 100.3)
Candidal genital infections		3.60 (3.28, 3.95)	55.5 (48.7, 62.9)
Male			
Genital infections (composite)	139,398	2.85 (2.42, 3.35)	12.9 (9.9, 16.4)
Candidal genital infections		3.28 (2.18, 4.94)	2.5 (1.3, 4.2)
SGLT2 inhibitors *v* DPP4 inhibitors; Age ≥ 60			
Female			
Genital infections (composite)	37,764	4.45 (3.83, 5.17)	90.0 (73.9, 108.7)
Candidal genital infections		5.28 (4.28, 6.52)	54.6 (41.8, 70.4)
Male			
Genital infections (composite)	43,078	3.30 (2.56, 4.25)	18.5 (12.6, 26.2)
Candidal genital infections		4.31 (2.16, 8.59)	3.4 (1.2, 7.8)
Canagliflozin *v* Dapagliflozin			
Female			
Genital infections (composite)	49,764	0.90 (0.83, 0.97)	−12.0 (−20.3, −1.1)
Candidal genital infections		0.93 (0.84, 1.03)	−4.5 (−10.7, 2.3)
Male			
Genital infections (composite)	63,352	0.99 (0.83, 1.17)	−0.1 (−2.8, 3.0)
Candidal genital infections		1.01 (0.69, 1.46)	0.0 (−1.0, 1.7)
Canagliflozin *v* Empagliflozin			
Female			
Genital infections (composite)	40,336	0.97 (0.89, 1.05)	−4.0 (−14.9, 7.9)
Candidal genital infections		0.96 (0.86, 1.07)	−2.9 (−11.1, 6.3)
Male			
Genital infections (composite)	51,678	0.97 (0.80, 1.16)	−0.6 (−4.0, 3.4)
Candidal genital infections		0.70 (0.42, 1.15)	−0.9 (−1.7, 0.5)

Abbreviations: GLP1: Glucagon-like peptide-1 agonist; SGLT2: sodium-glucose cotransporter 2 inhibitors; DPP-4: Dipeptidyl peptidase-4 inhibitors

[a]Pooled result are reported, see supplement for database specific estimates

[b] in both the SGLT2 and comparator group

[c] Represents the number of additional cases of genital infections due to SGLT2 inhibitors initiations per 1,000 person years of follow-up