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ARTICLE

Sodium–glucose cotransporter 2 inhibitors and risk of nephrolithiasis

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Abstract

Aims/hypothesis Sodium–glucose cotransporter 2 inhibitors (SGLT2Is) may reduce nephrolithiasis risk by increasing urine flow. We aimed to investigate whether initiation of SGLT2I was associated with reduced nephrolithiasis risk.

Methods We conducted an active-comparator new-user cohort study using the Danish health registries in the period 11 November 2012 to 31 December 2018. Individuals aged ≥40 years initiating SGLT2Is or glucagon-like peptide-1 receptor agonists (GLP1 RAs) were followed from treatment initiation until an inpatient or outpatient diagnosis of nephrolithiasis, death, emigration or end of study. New users of SGLT2Is were matched 1:1 on propensity scores to new users of GLP1 RAs. In supplementary analyses, risk of recurrent nephrolithiasis was assessed in individuals with a history of nephrolithiasis before treatment initiation.

Results We identified 24,290 and 19,576 eligible users of SGLT2Is and GLP1 RAs, respectively. After matching, 12,325 patient pairs remained. The median age was 61 years and median follow-up was 2.0 years. The nephrolithiasis rate was 2.0 per 1000 person-years in SGLT2I initiators compared with 4.0 per 1000 person-years in GLP1 RA initiators, with a rate difference of −1.9 per 1000 person-years (95% CI −2.8, −1.0) and an HR of 0.51 (95% CI 0.37, 0.71). For recurrent nephrolithiasis (n = 731 patient pairs), the rate difference was −17 per 1000 person-years (95% CI −33, −1.5) and the HR was 0.68 (95% CI 0.48, 0.97).

Conclusions/interpretation Initiation of treatment with SGLT2Is was associated with a clinically significant reduced risk of incident and recurrent nephrolithiasis.

Keywords Cohort studies · Databases · Dipeptidyl peptidase 4 inhibitors · Glucagon–like peptide 1 receptor agonists · Nephrolithiasis · Observational studies · Sodium–glucose cotransporter 2 inhibitors · Type 2 diabetes

Abbreviations

DPP4I	Dipeptidyl peptidase 4 inhibitor
GLP1 RA	Glucagon-like peptide-1 receptor agonist
SGLT2I	Sodium–glucose cotransporter 2 inhibitor

Introduction

Sodium–glucose cotransporter 2 inhibitors (SGLT2Is) are increasingly used in the treatment of type 2 diabetes mellitus [1]. In addition to their effect on glycaemic control, SGLT2Is have been shown to reduce body weight, BP, risk of major cardiovascular events and hospitalisation for heart failure [2, 3]. SGLT2Is increase urinary glucose excretion through a reduced renal reabsorption of glucose leading to osmotic diuresis and increased urinary flow [4]. Theoretically, SGLT2Is may reduce the risk of upper urinary tract stones (nephrolithiasis) by reducing the concentration of lithogenic substances in urine [4].

Nephrolithiasis affects approximately 1 in 11 people during their lifetime and can cause renal obstruction, hydronephrosis and ultimately chronic kidney disease [5]. Since type 2 diabetes is an established risk factor for nephrolithiasis [6, 7], a preventive effect of SGLT2Is towards nephrolithiasis would be clinically important. The currently available clinical

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Research in context

What is already known about this subject?

- Sodium–glucose cotransporter 2 inhibitors (SGLT2Is) may reduce nephrolithiasis risk by several mechanisms including increased urine flow
- The currently available clinical evidence is based on secondary analyses of randomised trial data but the low number of events and resulting insufficient power in these trials preclude firm conclusions being reached

What is the key question?

- Is use of SGLT2Is associated with a decreased risk of nephrolithiasis?

What are the new findings?

- In this nationwide, active-comparator new-user cohort study, initiation of therapy with SGLT2Is was associated with an approximately 50% reduced risk of incident nephrolithiasis compared with initiation of glucagon-like peptide-1 receptor agonists

How might this impact on clinical practice in the foreseeable future?

- Awaiting replication in other populations, the possible preventive effect of SGLT2Is towards nephrolithiasis should be considered when prescribing an otherwise indicated second-line glucose-lowering treatment

evidence is based on secondary analyses of randomised trial data [8]. However, the low number of recorded nephrolithiasis events in these trials and resulting insufficient power precluded firm conclusions being reached. Using nationwide Danish registries, we conducted an observational cohort study to assess the risk of nephrolithiasis associated with initiation of therapy with SGLT2Is.

Methods

Study design and setting We conducted a population-based active-comparator, new-user cohort study of individuals initiating SGLT2Is compared with initiators of glucagon-like peptide-1 receptor agonists (GLP1 RAs), using the Danish health registries [9]. These registries provide nationwide, individual-level data on vital status and migrations [10], hospital and ambulatory diagnoses since 1977 [11], and prescriptions filled at community pharmacies since 1995 [12]. These are routinely collected administrative data and, due to the tax-funded healthcare system in Denmark, practically all Danish residents are included [9]. The codes used to define exposures, covariates and outcomes are available in electronic supplementary material (ESM) Table 1.

Population We identified all Danish individuals initiating SGLT2I or GLP1 RA treatment from 11 November 2012 (the date of approval of the first SGLT2I in Europe) until 31 December 2018 [13]. Eligible individuals were 40 years of age or above when initiating the study medication, had not filled any prescriptions for either SGLT2Is or GLP1 RAs at any time before study entry, had resided in Denmark continuously for at least 1 year before cohort entry, and did not have a history of nephrolithiasis (ESM Fig. 1). Individuals that filled a prescription for both an SGLT2I and a GLP1 RA at the date of cohort entry were excluded.

Outcome The primary outcome was incident nephrolithiasis, recorded as an inpatient or outpatient diagnosis of calculus of the kidney and ureter (i.e. upper urinary tract stones not including bladder stones) in the Danish National Patient Registry [11]. A diagnosis of nephrolithiasis in the registry has not been validated by chart review; however, the validity and completeness of diagnosis codes are generally high in the Danish National Patient Registry [11].

Exposure and follow-up Drug exposure was based on filled prescriptions using the Danish Prescription Registry [12]. Individuals were followed from the day of the first SGLT2I/GLP1 RA prescription until a nephrolithiasis event, death, migration, or end of study period (31 December 2018). In the main analysis, we emulated an intention to treat analysis (i.e. individuals remained in the exposure group assigned at study entry throughout follow-up, irrespective of discontinuation of treatment or initiation of the comparator drug). Use of SGLT2Is included both monotherapy formulations as well as fixed-dose combinations (e.g. empagliflozin with metformin).

Propensity score matching Studied individuals were characterised at cohort entry with regards to prior diagnoses and use of medicines. To adjust for confounding, we applied a high-dimensional propensity score approach [14, 15]. In brief, a set of candidate covariates was identified from all recorded inpatient and outpatient diagnoses as well as filled

prescriptions during the year leading up to cohort entry. Variable selection was performed according to Schneeweiss et al, selecting the 100 covariates most likely to exert a confounding effect to enter into the propensity score model [14]. We used the zero-cell correction as outlined by Rassen et al [16]. In addition, we forced sex, birth year, calendar year of cohort entry and 13 prespecified variables that reflected diabetes severity or strongly affected nephrolithiasis risk (e.g. diabetic retinopathy, insulin use and use of thiazides) into the propensity score model (ESM Table 1). The propensity score was estimated in a logistic regression model with SGLT2I treatment as dependent and the above covariates as independent variables. In accordance with the asymmetrical trimming principle, we excluded individuals with propensity scores below the 2.5th percentile of the propensity score distribution for SGLT2Is or above the 97.5th percentile of the GLP1 RA propensity score distribution [17]. Individuals were then matched 1:1 on propensity scores using nearest-neighbour matching with a caliper of 0.02. Covariate balance was assessed using standardised differences, and values above 0.10 were considered as reflecting significant imbalance [18].

Statistical analysis The probability of developing nephrolithiasis during the study period for users of SGLT2Is and GLP1-RAs was plotted in 5 year cumulative incidence plots using the Kaplan–Meier method. We calculated incidence rates and incidence rate differences with 95% CIs in the unmatched cohorts and the propensity score matched cohorts using univariate analyses based on Poisson models [19]. We evaluated the assumption of constant rates during follow-up by letting event rates depend on year since treatment initiation in each exposure group. In one supplementary analysis, this assumption was not met. For that analysis, the incidence rate difference was estimated by fitting a generalised linear model using a Poisson distribution and an identity link function with stratum-specific incidence rates for each year of follow-up as dependent variables and initiation of SGLT2I and year of follow-up as independent variables. We used univariate Cox regression to estimate HR and 95% CIs. The proportional hazard assumption was checked visually in log–log and Schoenfeld residual plots. For both the Poisson-based models and the Cox regression, the competing events death and migration were handled using a cause-specific approach (i.e. individuals were censored at the time of the competing event) [20]. Statistical analyses were conducted in Stata version 16.1 (StataCorp, TX, USA).

Sensitivity and supplementary analyses First, to estimate the on-treatment effect, an analysis was conducted where individuals were censored at treatment discontinuation or switch to the comparator drug. Here, we assumed that the duration of a prescription, which is not recorded in the registry, corresponded to the number of defined daily doses dispensed while adding a grace period of 30 days [21]. A person who had not redeemed a new prescription within this interval was considered as having discontinued treatment.

Second, to examine whether the association varied with individual SGLT2Is, we repeated the main analyses for empagliflozin and dapagliflozin separately. These two drugs accounted for 98% of total SGLT2I sales in Denmark during the study period [22].

Third, as GLP1 RAs were approved for the treatment of obesity in individuals without type 2 diabetes in 2015 [23], we conducted analyses where users of GLP1 RAs labelled with this indication (ESM Table 1) were omitted from the GLP1 RA exposure definition.

Fourth, to evaluate the robustness of our findings with regards to our choice of active comparator, we repeated the analysis using dipeptidyl peptidase 4 inhibitors (DPP4Is) as active comparator.

Fifth, to evaluate whether the findings were robust regarding the choice of propensity score technique, we repeated the main analyses in the unmatched but asymmetrically trimmed cohort as follows: (1) adjusting for propensity scores; (2) stratifying by propensity score deciles; and (3) using inverse probability of treatment weighting based on the propensity score. Finally, the E-value [24], the minimum strength of association that an unmeasured confounder must have with both the treatment and outcome to negate the observed association, was calculated and compared with known confounders that were not measured in this study (i.e. obesity).

Nephrolithiasis recurrence To assess whether SGLT2I initiation was associated with risk of recurrent upper urinary tract stone disease, we repeated the main analysis in a separate study population of SGLT2I or GLP1 RA initiators with a diagnosis of nephrolithiasis recorded in the Danish National Patient Registry before initiation of SGLT2I or GLP1 RA treatment.

Ethics approval The study was approved by the University of Southern Denmark (reference number 10.113) and the Danish Health Data Authority. According to Danish law, ethical approval is not required for register-based studies [25].

Results

We identified 24,290 SGLT2I initiators and 19,576 GLP1 RA initiators eligible for inclusion (Fig. 1). The incidence of SGLT2I use increased during the study period while use of GLP1-RAs was stable (ESM Fig. 2). Baseline characteristics before and after matching are shown in Table 1. The incidence rate of nephrolithiasis before matching was 2.5 per 1000 person-years (95% CI 2.1, 3.0) in SGLT2I initiators and 4.2 per 1000 person-years (95% CI 3.7, 4.8) in GLP1 RA users (Table 2).

Table 1 Baseline characteristics for new users of SGLT2Is and GLP1 RAs before and after propensity score matching

Characteristic	Before matching			After matching		
	SGLT2I (n=24,290)	GLP1 RA (n=19,576)	SMD	SGLT2I (n=12,325)	GLP1 RA (n=12,325)	SMD
Age, years	63 (55–70)	60 (51–68)	0.26	61 (53–69)	61 (53–68)	0.01
Male sex	15,091 (62.1)	10,579 (54.0)	0.16	6968 (56.5)	7023 (57.0)	0.01
Follow-up, years	1.5 (0.7–2.7)	2.6 (1.1–4.3)	0.57	2.1 (1.1–3.3)	1.9 (0.8–3.4)	0.06
Medical history						
Diabetic nephropathy	964 (4.0)	1438 (7.3)	0.15	658 (5.3)	629 (5.1)	0.01
Diabetic retinopathy	2332 (9.6)	2234 (11.4)	0.06	1248 (10.1)	1201 (9.7)	0.01
Diabetic neuropathy	1490 (6.1)	1454 (7.4)	0.05	843 (6.8)	757 (6.1)	0.03
Obesity	4605 (19.0)	6189 (31.6)	0.29	3120 (25.3)	3020 (24.5)	0.02
Chronic kidney disease	462 (1.9)	743 (3.8)	0.11	315 (2.6)	314 (2.5)	0.00
Upper urinary tract infection	153 (0.6)	225 (1.1)	0.06	99 (0.8)	102 (0.8)	0.00
Hypertension	18,893 (77.8)	15,212 (77.7)	0.00	9525 (77.3)	9476 (76.9)	0.01
Myocardial infarction	2104 (8.7)	1427 (7.3)	0.05	1086 (8.8)	866 (7.0)	0.07
Heart failure	1554 (6.4)	1414 (7.2)	0.03	904 (7.3)	743 (6.0)	0.05
Hyperparathyroidism	123 (0.5)	120 (0.6)	0.01	66 (0.5)	77 (0.6)	0.01
Diabetes drugs						
Insulin	3226 (13.3)	5391 (27.5)	0.36	2357 (19.1)	2262 (18.4)	0.02
Metformin	17,953 (73.9)	13,743 (70.2)	0.08	9009 (73.1)	8878 (72.0)	0.02
Sulfonylurea	5597 (23.0)	4281 (21.9)	0.03	2968 (24.1)	2803 (22.7)	0.03
DPP4I	11,245 (46.3)	6652 (34.0)	0.25	4961 (40.3)	4824 (39.1)	0.02
Other drugs						
Thiazide	3598 (14.8)	3416 (17.4)	0.07	2035 (16.5)	2003 (16.3)	0.01
Loop diuretic	2785 (11.5)	3527 (18.0)	0.19	1805 (14.6)	1719 (13.9)	0.02
Lipid-modifying agent	18,075 (74.4)	13,715 (70.1)	0.10	8970 (72.8)	8567 (69.5)	0.07
Antigout drug	1042 (4.3)	1015 (5.2)	0.04	529 (4.3)	604 (4.9)	0.03
NSAID	5519 (22.7)	5290 (27.0)	0.10	3218 (26.1)	3090 (25.1)	0.02
Glucocorticoid	1435 (5.9)	1319 (6.7)	0.03	803 (6.5)	746 (6.1)	0.02
Antibiotics for UTIs[a]	2034 (8.4)	2142 (10.9)	0.09	1228 (10.0)	1132 (9.2)	0.03

Data are presented as median (IQR) or n (%)

[a] Therapy with antibiotics that are used almost exclusively for urinary tract infections in Denmark: pivmecillinam, trimethoprim, sulfamethizole and nitrofurantoin

NSAID, non-steroidal anti-inflammatory drug; SMD, standardised mean difference; UTI, urinary tract infection

The distribution of propensity scores is shown in ESM Fig. 3 and the 100 covariates identified by the high-dimensional approach to be included in the propensity score model are shown in ESM Table 2. After propensity score trimming and matching, 12,325 patient pairs remained. Baseline characteristics were evenly distributed between the matched cohorts with standardised mean differences below 0.10 for all covariates of interest (Table 1).

Matched SGLT2I users were followed for a median of 2.1 years compared with 1.9 years in the GLP1 RA cohort. The 5 year cumulative incidence plots are shown in Fig. 2. The incidence rate of nephrolithiasis was 2.0 per 1000 person-years (95% CI 1.6, 2.6) in SGLT2I users vs 4.0 per 1000 person-years (95% CI 3.3, 4.8) in GLP1 RA users (Table 2). The resulting incidence rate difference was −1.9 per 1000 person-years (95% CI −2.8, −1.0) and the HR was 0.51 (95% CI 0.37, 0.71).

Sensitivity and supplementary analyses The as-treated analysis yielded results further away from the null, with an incidence rate difference of −2.7 per 1000 person-years (95% CI −4.2, −1.3) and an HR of 0.40 (95% CI 0.23, 0.69) (Table 2).

Associations similar to the main analysis were found for dapagliflozin (HR 0.56 [95% CI 0.39, 0.79]) and empagliflozin (HR 0.55 [95% CI 0.36, 0.86]) when these drugs were examined separately (ESM Table 3).

When restricting the comparator cohort to individuals initiating GLP1 RAs that were marketed with diabetes and not obesity as the indication, the HR was 0.63 (95% CI 0.46, 0.86).

Table 2 Risk of nephrolithiasis before and after propensity score matching

Analysis	Before matching		After matching	
	SGLT2I	GLP1 RA	SGLT2I	GLP1 RA
Main analysis				
Patients, *n*	24,290	19,576	12,325	12,325
Events, *n*	111	227	58	108
Person time, years	44,064	53,903	28,473	27,339
Rate per 1000 person-years (95% CI)	2.5 (2.1, 3.0)	4.2 (3.7, 4.8)	2.0 (1.6, 2.6)	4.0 (3.3, 4.8)
Rate difference per 1000 person-years (95% CI)	−1.7 (−2.4, −1.0)		−1.9 (−2.8, −1.0)	
HR (95% CI)	0.58 (0.46, 0.73)		0.51 (0.37, 0.71)	
Sensitivity analysis using an as-treated protocol				
Patients, *n*	24,290	19,576	12,325	12,325
Events, *n*	30	99	18	53
Person time, years	16,844	20,524	9944	11,640
Rate per 1000 person-years (95% CI)	1.8 (1.2, 2.5)	4.8 (4.0, 5.9)	1.8 (1.1, 2.9)	4.5 (3.5, 6.0)
Rate difference per 1000 person-years (95% CI)	−3.0 (−4.2, −1.9)		−2.7 (−4.2, −1.3)	
HR (95% CI)	0.38 (0.25, 0.57)		0.40 (0.23, 0.69)	
Sensitivity analysis with DPP4I as active comparator				
Patients, *n*	17,000	44,369	10,908	10,908
Events (*n*)	63	482	43	71
Person time, years	31,229	126,755	19,050	19,079
Rate per 1000 person-years (95% CI)	2.0 (1.6, 2.6)	3.8 (3.5, 4.2)	2.3 (1.7, 3.0)	3.7 (2.9, 4.7)
Rate difference per 1000 person-years (95% CI)	−1.8 (−2.4, −1.2)		−1.5 (−2.6, −0.4)	
HR (95% CI)	0.51 (0.39, 0.67)		0.61 (0.41, 0.88)	
Sensitivity analysis with recurrent nephrolithiasis as outcome				
Patients, *n*	1418	1181	731	731
Events (*n*)	86	132	54	74
Person time, years	2350	2738	1485	1386
Rate per 1000 person-years (95% CI)	36.6 (29.6, 45.2)	48.2 (40.6, 57.2)	36.4 (27.8, 47.5)	53.4 (42.5, 67.0)
Rate difference per 1000 person-years (95% CI)	−13.8 (−25.4, −2.3)[a]		−17.0 (−32.6, −1.5)	
HR (95% CI)	0.67 (0.51, 0.88)		0.68 (0.48, 0.97)	

[a] Since the event rate with GLP1 RA exposure could not be assumed to be constant during follow-up, the rate difference was estimated using generalised linear models as described in the section on statistical analysis

Repeating the cohort identification and analysis using DPP4Is as active comparator, the incidence rate difference was −1.5 per 1000 person-years (95% CI −2.6, −0.4) and the HR was 0.61 (95% CI 0.41, 0.88) (Table 2; cohort characteristics are shown in ESM Table 4 and ESM Fig. 4).

Applying the following alternatives to propensity score matching yielded results comparable with the main analysis: adjusting for propensity score (HR 0.56 [95% CI 0.42, 0.73]); stratifying on propensity score decile (HR 0.56 [95% CI 0.42, 0.74]); and applying inverse probability of treatment weighting (HR 0.57 [95% CI 0.43, 0.75]).

The calculated E-value was 3.33 for the point estimate and 2.17 for the upper boundary of the 95% CI of the HR.

Nephrolithiasis recurrence We identified 1418 initiators of SGLT2Is and 1181 GLP1 RA initiators with a history of nephrolithiasis before study drug initiation, of whom 731 patient pairs remained after matching and trimming. Baseline characteristics were similar after matching except for a slightly longer duration of follow-up among SGLT2I users (ESM Table 5). The incidence rate for recurrent nephrolithiasis was 36 per 1000 person-years in the SGLT2I cohort and 53 per 1000 person-years in the GLP1 RA cohort, yielding an incidence rate difference of −17 (95% CI −33, −1.5) and an HR of 0.68 (95% CI 0.48, 0.97) (Table 2 and ESM Fig. 5).

Discussion

In this nationwide cohort study, initiation of SGLT2Is was associated with an approximately 50% RR reduction of

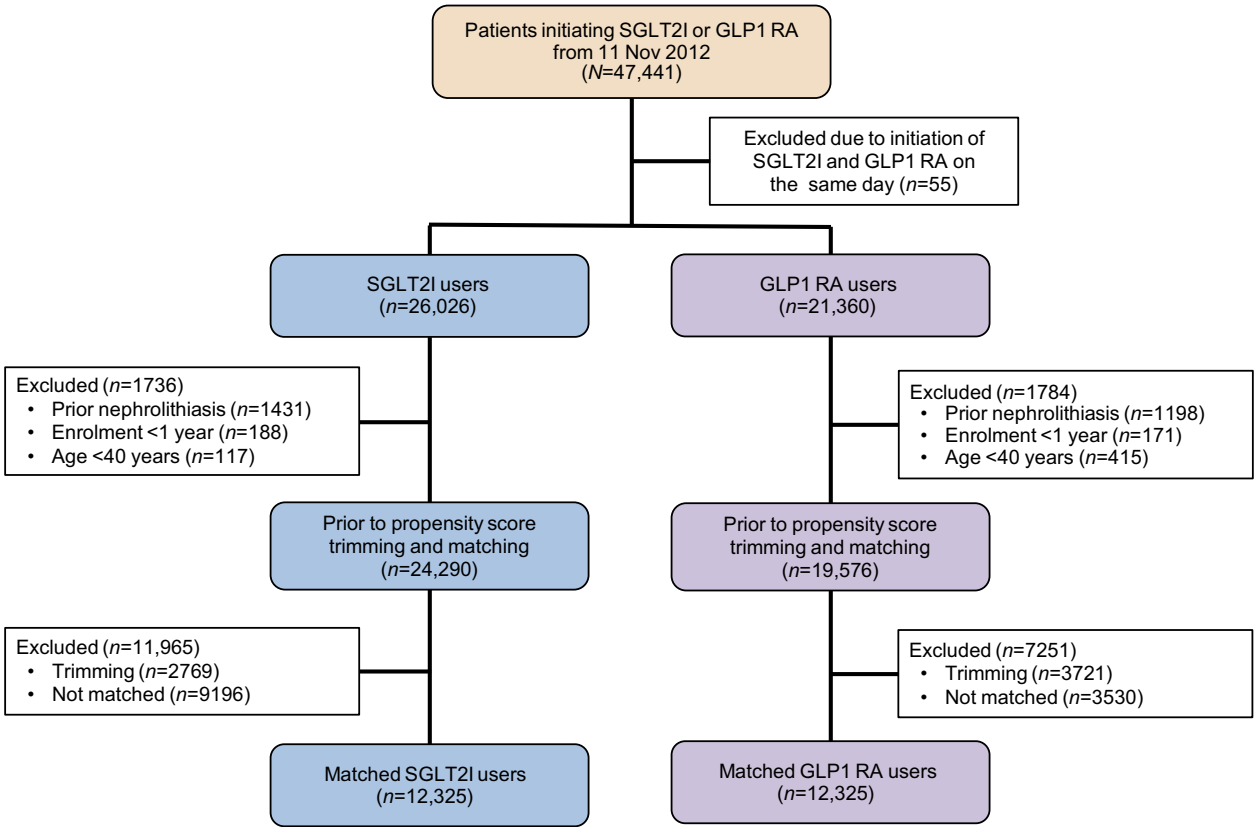

Fig. 1 Flow chart of cohort entry

nephrolithiasis compared with initiation of GLP1 RAs. This corresponded to an absolute rate reduction of −1.9 events per 1000 person-years. For recurrent nephrolithiasis, the absolute rate difference was estimated as −17 per 1000 person-years. The results were robust in a range of supplementary analyses including analyses of individual SGLT2Is and analyses using DPP4Is as a comparator.

A likely mechanism to explain the reduced risk of nephrolithiasis with SGLT2I use is increased urinary flow and dilution of urine due to osmotic diuresis [4]. An increase in urinary volume decreases the concentration of lithogenic substances in urine and risk of stone precipitation, and a high fluid intake has been shown to prevent recurrent stone disease in randomised trials [26]. Based on this mechanism, AstraZeneca, the manufacturer of the first SGLT2I to be marketed (dapagliflozin), filed a patent application for use of this drug to treat and prevent kidney stones in 2009 [27]. Available clinical evidence shows a 1.2-fold to twofold increase in urinary volume with SGLT2Is, although the diuretic effect may be most marked at treatment initiation and then

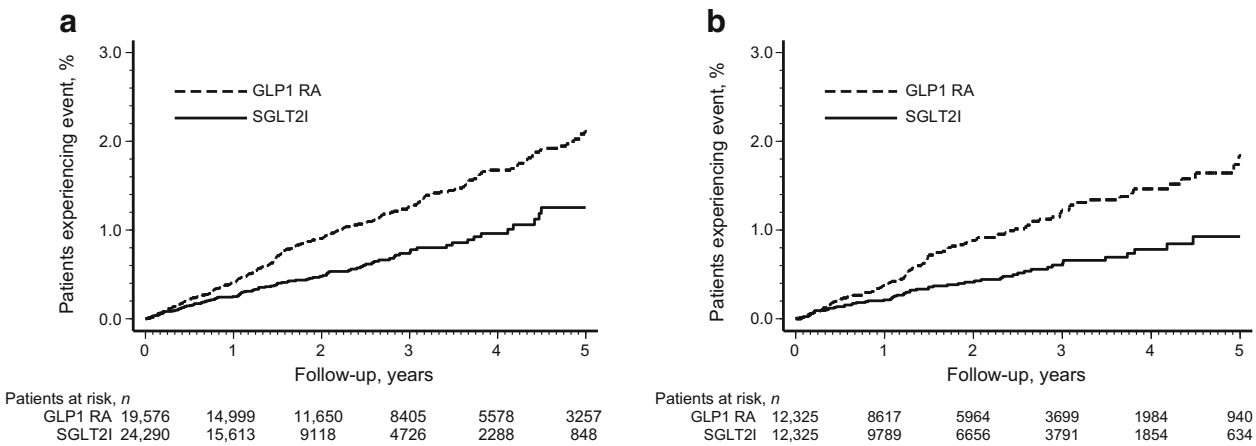

Fig. 2 Five year cumulative incidence plots for nephrolithiasis in the unmatched (**a**) and propensity score matched cohort (**b**) of SGLT2I and GLP1 RA users

decline [28]. Individuals treated with SGLT2Is may be advised to increase their fluid intake, which reduces the risk of stone precipitation [26]. Hence, the effect of increased fluid intake due to health advice cannot be disentangled from the effect of forced diuresis by SGLT2Is with this study design.

In addition to increasing urinary flow, SGLT2Is reduce serum uric acid levels and are associated with a decreased risk of gout [29, 30]. The decrease in serum uric acid is likely mediated by uricosuric pathways related to GLUT9 resulting in an increased excretion of uric acid in urine [31]. The role of increased uric acid excretion with regards to kidney stone formation is unclear. While hyperuricosuria potentially increases the risk of uric acid stones, these stones frequently form in individuals with normal urine uric acid levels and the main driver is low urine pH rather than high urine uric acid levels [32]. Interestingly, in a population of 2464 individuals with nephrolithiasis, the proportion of urate-containing stones was higher in people with diabetes (36%) than in those without (11%), presumably due to low urine pH levels in diabetic individuals [33]. We were not able to examine whether the association differed with kidney stone composition (i.e. whether the risks of calcium stones and uric acid stones were equally affected). Such results could have provided clues to the mechanisms underlying a preventive effect against stone formation.

This is the first study to examine the risk of nephrolithiasis associated with SGLT2Is in a routine clinical setting. A meta-analysis based on secondary analyses of 16 randomised clinical trials reported a pooled OR of 0.85 (95% CI 0.57, 1.26) for risk of nephrolithiasis with SGLT2Is compared with placebo or other glucose-lowering drugs [8]. The meta-analysis was, however, limited by few events in the included trials and by the fact that nephrolithiasis was not a prespecified outcome in the trials and hence not systematically recorded. We report an HR of 0.51 (95% CI 0.37, 0.71) for nephrolithiasis associated with SGLT2I use and, although the existing clinical trial data are compatible with a preventive effect of SGLT2Is, our data suggest a larger risk reduction. This may partially be explained by outcome misclassification due to underreporting of nephrolithiasis in the clinical trials and partly by differences in the studied patient populations, as we studied the effect of SGLT2Is in a routine clinical care setting with a more heterogeneous population and higher baseline risk of nephrolithiasis.

Both GLP1 RAs and DPP4Is are used at a similar diabetes stage and duration to SGLT2Is. As comparable alternatives to SGLT2Is with regards to indications and glycaemic regulation, use of these as active comparators aimed to leverage clinical equipoise between the comparator groups [34]. A potential limitation of using GLP1 RA as the active comparator is that GLP1 RAs may increase the risk of nephrolithiasis; however, there is no evidence to suggest this and we found similar results when using DPP4Is as reference. Besides using active comparators, we accounted for baseline differences in patient characteristics by matching on propensity scores. However, we cannot exclude residual confounding by unmeasured covariates. Most importantly, we did not have data on lifestyle factors including body weight. Being overweight is an established risk factor for nephrolithiasis, with an up to twofold increased risk of nephrolithiasis for individuals with a BMI >30 kg/m^2 compared with individuals with a BMI in the range 21–23 kg/m^2 [5], which is lower than the calculated E-value for the upper boundary of the confidence interval. Confounding by obesity is therefore unlikely to fully explain the observed results. We lacked detailed data on renal function, such as creatinine levels. However, reduced renal function is not a known cause of nephrolithiasis [35, 36]. Since diabetes is a risk factor for nephrolithiasis, it is not possible to rule out confounding by indication. We used two different active comparators and accounted for measured confounders using propensity scores. Further, the strength of the observed association and resulting large E-values suggest that confounders would have to be strongly imbalanced between exposure groups and strong risk factors for nephrolithiasis in order to explain away the observed association. The fact that residual confounding by measured confounders may be negligible is supported by the fact that the results from the adjusted analyses did not differ markedly from the crude analyses. A limitation of propensity score matching is that the external validity may be influenced by excluding individuals that could not be matched on propensity scores. However, similar incidence rates and HRs were obtained before trimming and matching, indicating that the results were unaffected by excluding these unmatched individuals. Further, the supplementary analyses without matching on propensity scores (e.g. using inverse probability of treatment weighting) yielded similar results. Because the diagnosis codes used to identify nephrolithiasis events have not been validated in the Danish registries, we cannot exclude outcome misclassification. This misclassification is likely to be non-differential between exposure groups. Further, we may have underestimated the rate of nephrolithiasis because only hospital diagnoses are recorded in the Danish National Patient Registry. Hence, smaller, less symptomatic kidney stones treated in the primary care setting would not be identified.

Current strategies for treating recurrent nephrolithiasis include maintaining a fluid intake of at least 2 l/day [26, 37, 38]. If increased fluid intake fails to prevent formation of stones, or if an individual is at high risk of recurrence, treatment with thiazides, citrate or allopurinol is recommended based on findings from randomised trials involving individuals with calcium stones [37]. We found a similar risk reduction with use of SGLT2Is for preventing recurrent nephrolithiasis as the randomised trials of thiazides. A meta-analysis reported a pooled RR of 0.52 (95% CI 0.39, 0.69) for a composite outcome of recurrence of radiographic or symptomatic nephrolithiasis with use of thiazides compared with placebo or control in six

randomised clinical trials [39]. For symptomatic nephrolithiasis alone, there was no significant difference but this endpoint was limited by a small number of events [39].

With the high prevalence of nephrolithiasis in individuals with type 2 diabetes, a preventive effect of SGLT2Is towards nephrolithiasis is clinically relevant. Further research is needed to fully elucidate the clinical impact of our findings. First, replication of these findings in other populations is warranted. If SGLT2Is are to be prescribed to treat nephrolithiasis specifically, a prospective clinical trial specifying nephrolithiasis as outcome is needed. Pending replication in other studies, the possible preventive effect of SGLT2Is towards nephrolithiasis should be considered when choosing between second-line glucose-lowering drugs that are otherwise indicated (e.g. because of poor glycaemic regulation), particularly if the individual has a history of nephrolithiasis.

In conclusion, we observed a lower rate of nephrolithiasis in individuals initiating SGLT2Is compared with GLP1 RAs or DPP4Is. These findings indicate that SGLT2I treatment may be useful to prevent nephrolithiasis in individuals with type 2 diabetes.

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Data availability The authors are not allowed to share individual-level data. Access can be granted to licensed institutions by the Danish Health Data Authority.

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