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Empagliflozin and decreased risk of nephrolithiasis: A potential new role for SGLT2 inhibition?

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## ABSTRACT

**Aims:** Diabetes mellitus is a risk factor for nephrolithiasis. A recent observational study found that SGLT2 inhibitor use by type 2 diabetes (T2D) patients was associated with a 49% lower risk of nephrolithiasis, compared to GLP-1 receptor agonists. We examined the association between nephrolithiasis and the SGLT2 inhibitor empagliflozin, using existing data from randomized clinical trials.

**Methods:** We pooled data from 15,081 T2D patients randomized to empagliflozin (n=10,177) or placebo (n=4,904) from 20 phase I-IV trials including the large CV outcome trial, EMPA-REG OUTCOME. Incident urinary tract stone events were captured using a pre-defined collection of MedRA terms. A sensitivity analysis using a narrower definition was also performed. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated using the relative risk estimate, stratified by study.

**Results:** The median exposures to study drug was 543 days (placebo) and 549 days (empagliflozin). 183 patients experienced an incident urolithiasis during follow-up (placebo, 79; empagliflozin, 104), yielding annual incidence rates of 1.01 versus 0.63 events/100 patient-years in the two respective groups. The IRR was 0.64 (95% CI 0.48, 0.86), in favor of empagliflozin. In the sensitivity analysis, the results were similar (IRR, 0.62 [95% CI 0.45, 0.85]).

**Conclusion:** Compared to placebo, empagliflozin therapy was associated with an approximate 40% reduced risk of urinary tract stone events in T2D patients. The underlying mechanisms are unknown but may involve altered lithogenic profile of the urine. Dedicated randomized prospective clinical trials are warranted to confirm these initial observations in both patients with and without T2D.

**Keywords:** Nephrolithiasis, SGLT2 inhibitors, Empagliflozin, Type 2 diabetes mellitus.

**Abbreviations:** DM – Diabetes mellitus, SGLT2 Sodium-glucose cotransporter 2, CV-Cardiovascular, T2D – Type 2 diabetes mellitus, RA – receptor agonists.

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## Introduction

Nephrolithiasis is a common problem with an estimated global prevalence of up to 15% (1). Rates are increasing over the past several decades, likely the result of changes in diet and lifestyle. After an initial stone event, recurrence rates are high, with up to 50% of patients experiencing a second episode in the future. Urinary tract stones can negatively impact renal function and have been associated with increased risk of chronic kidney disease. In the United Kingdom, estimated annual expenditures may be as high as £324 million (2), whereas in the United States this figure approaches \$10 billion (3). There is therefore a growing need for effective preventive strategies.

Type 2 diabetes mellitus (T2D) is a well-known risk factor for nephrolithiasis. Although the links between these two conditions are not fully understood, hyperuricemia and hyperuricosuria in insulin resistant patients with metabolic syndrome may play a key role. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a newer class of glucose-lowering medications demonstrated to have significant cardiovascular (CV) and renal benefits in large clinical trials involving patients with T2D, and also those with heart failure and chronic kidney disease, irrespective of diabetes status. Recently, in an observational study involving 24,290 individuals with T2D taking SGLT2 inhibitors, Kristensen *et al* reported a striking hazard ratio (HR) of 0.51 (95% CI 0.37, 0.71) for incident nephrolithiasis and a HR of 0.68 (95% CI 0.48, 0.97) for recurrent nephrolithiasis, compared with individuals using GLP-1 receptor agonists (RA) (4). These data, while provocative, were entirely retrospective and therefore possibly prone to bias. We therefore sought to examine the association between renal stone disease and the use of SGLT2 inhibitors, using existing data from randomized controlled clinical trials involving one member of this class, empagliflozin.

## Methods

A total of 15,081 patients from 20 phase I-IV randomized placebo-controlled trials including the large cardiovascular outcome trial, EMPA-REG OUTCOME, were included in this analysis. The pooled data comprised T2D patients treated with empagliflozin (either 10 mg or 25 mg doses) (n = 10,177), or placebo (n = 4,904). Details and ClinicalTrial.gov identifier for all studies included were previously published (Table 1 in Schorling Kinduryte et al.). We captured incident urinary tract stone events (urolithiasis) as adverse events using a pre-defined collection of MedRA terms: nephrolithiasis, renal colic, ureterolithiasis, calculus bladder, calculus urinary, calculus urethral, and nephrocalcinosis (MedDRA version 22.1). In a sensitivity analysis we assessed a narrower definition excluding the terms, renal colic and nephrocalcinosis.

To adjust for differences in drug exposure, incidence rates and 95% confidence intervals (CI) per 100 patient-years by the Clopper Pearson method are reported. For the comparison between empagliflozin and placebo, incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated based on the Cochran–Mantel–Haenszel procedure using the relative risk estimate stratified by study. IRRs and CIs are graphically displayed in a Forest plot in the overall study population.

Descriptive statistics (continuous variables: mean, standard deviation (SD); categorical variables: absolute and relative frequencies) of baseline data for patients with and without a new urinary tract stone diagnosis during follow-up are provided per treatment (placebo vs. empagliflozin 10/25 mg).

## Results

The median exposure to study drug was 543 days (placebo) and 549 days (empagliflozin 10/25 mg); 46.5% of patients (n = 7020) were from the EMPA-REG OUTCOME trial, which had the longest median treatment exposure of 2.6 years. The baseline characteristics of the study participants and clinical features of patients with/without incident urolithiasis during the trial is shown in the Table. Among affected patients, there were more of Asian heritage, with a diagnosis of hypertension, and using anti-gout medications, whereas the use of diuretics appeared comparable. In total, 9 patients (3 in placebo, 6 in empagliflozin 10/25 mg) had a reported history of kidney stones at the baseline visit, and only one of these had a recurrent event during follow-up. In total, 183 patients experienced an incident urolithiasis during follow-up (79 in placebo, 104 in pooled empagliflozin) yielding annual incidence rates of 1.01 versus 0.63 events per 100 patient years in placebo and empagliflozin, respectively (Figure). The IRR was 0.64 (95% CI 0.48, 0.86), in favor of empagliflozin. In a sensitivity analysis, restricting the adverse event reports solely to the following 5 adverse event terms: nephrolithiasis, ureterolithiasis, calculus bladder, calculus urinary, calculus urethral, the results were similar (IRR, empagliflozin vs. placebo 0.62 [95% CI 0.45, 0.85]).

## Discussion

Recently published data indicate that SGLT2 inhibitor therapy is associated with a reduced risk of nephrolithiasis, at least in comparison to GLP-1 RA therapy. We confirm these findings in a large dataset encompassing more than 15,000 T2D patients randomized to either empagliflozin or placebo, usually on a backdrop of a variety of glucose-lowering therapies.



About 75-80% of all renal stones are composed of calcium salts, commonly calcium oxalate and less frequently calcium phosphate, and the remaining 20-25% stones of uric acid, struvite or cystine. Abnormal urinary concentrations of lithogenic substances along with decreased urinary flow promotes crystallization of stone-forming salts. One proposed mechanism for decreased stone risk with SGLT2 inhibitors is increased urinary flow rate due to osmotic diuresis from glucosuria and natriuresis and consequent changes in urinary concentrations of lithogenic substances. Urine volume increases by 200-400 ml/day at the initiation of treatment with SGLT2 inhibitors (5) and is most likely accompanied by a commensurate increase in oral fluid intake. While natriuresis appears to be transient and quickly reversed by compensatory mechanisms, glucosuria, and therefore an osmotic diuresis, persists while on treatment even when the blood glucose concentrations are in the normal range.

SGLT2 inhibition may also have indirect effects on bone and mineral metabolism, and some of these are not intuitively linked to decreased risk of urolithiasis. For example, increased sodium availability in the renal tubule modulates both nephron calcium and phosphate handling. Decreased renal calcium absorption and increased phosphate absorption results in increased urinary calcium excretion (6) and low urinary phosphate concentrations (6). High urinary calcium in the setting of hypocitraturia and low urinary volume promotes supersaturation and crystallization of calcium oxalate and less frequently calcium phosphate leading to renal stone formation. SGLT2 inhibitors are also associated with decreased serum uric acid levels from increased urate excretion (7). However, hyperuricosuria *per se* is not associated with increased risk of nephrolithiasis. The principal determinant of uric acid crystallization and precipitation (which may also serve as a nidus for calcium-oxalate stone

formation) is low urine pH. The uric acid crystals are more soluble in an alkaline milieu, thus preventing stone formation even in patients with high urinary urate (8). Animal experiments have in fact demonstrated increased urinary bicarbonate excretion and higher urine pH after SGLT2 inhibition (9). Finally, hypocitraturia is another common metabolic abnormality seen in 20-60% patients with nephrolithiasis. Urinary citrate serves to inhibit supersaturation and crystallization of calcium salts. In addition, citrate increases urine pH and reduces calcium concentration in the urine by forming complexes with calcium ion in the urine, rendering it overall less lithogenic. Recent studies have also shown that therapy with dapagliflozin, another SGLT2 inhibitor leads to a significant increase in urinary citrate excretion (10).

So, the effects of SGLT2 inhibitors on the predisposition to urinary tract stones appear complex. While any increase in urine flow due to osmotic diuresis could prevent urolithiasis, this could be counterbalanced by effects on urinary calcium and urate handling, which might promote stone formation. The possible benefits mediated through changes in urinary citrate and bicarbonate handling would also need to be considered.

While this study included a large number of patients with relatively long follow-up, our analysis has some limitations. It was *post hoc* and the definition applied for urolithiasis was based on adverse events reported by site investigators and not confirmed by chart review. Furthermore, since only one patient experienced a recurrent event of urolithiasis, we cannot draw any firm conclusion on the prevention of events in patients with a prior history. Finally, urine samples were not available from any study and, therefore, metabolic analyses regarding changes in stone risk profiles could not be performed.

In summary, we demonstrate that the use of empagliflozin was associated with an approximate 40% reduced risk of renal stone disease as compared with placebo. Even when we applied a more stringent definition, excluding renal colic (which is subjective) and nephrocalcinosis (which is a tubulointerstitial disease with a different pathophysiology), the results persisted. These data extend the preliminary observations of Kristensen *et al.* This potential additional benefit of SGLT2 inhibition is identifiable vs. placebo across a wide background of glucose-lowering therapies used in the trials included herein and not just vs. GLP-1 RA therapy as in Hallas *et al.* report. Dedicated randomized prospective clinical trials would now appear to be warranted in order to confirm these initial observations in both patients with and without T2D. Moreover, further studies of the lithogenic profile of the urine in stone formers after SGLT2 inhibition should now be conducted, in order to provide insights into the precise underlying mechanisms involved.

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## **Data availability**

The sponsor of the clinical trials (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. The datasets analyzed during the current study are available in the Boehringer Ingelheim repository (<https://trials.boehringer-ingelheim.com/>). Researchers are invited to submit inquiries via the Boehringer Ingelheim website.

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## **Contribution statement:**

P.B., S.E.I., A.P.O. and A.E. drafted the manuscript. A.E. performed the statistical analyses. All authors were involved and provided input in the development of the final manuscript, and approved the final version.

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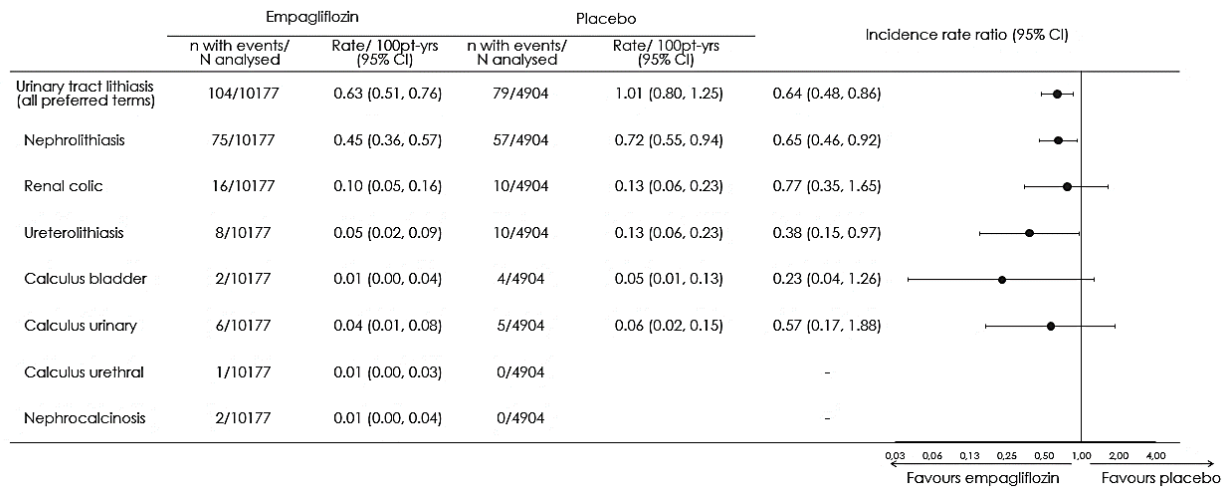
Characteristic	Occurrence of urinary tract lithiasis		No occurrence of urinary tract lithiasis	
	Placebo (n=79)	Pooled empagliflozin (n=104)	Placebo (n=4825)	Pooled empagliflozin (n=10073)
Age, years, mean (SD)	59.5 (10.2)	59.6 (9.1)	60.6 (9.8)	60.3 (9.7)
Age group, years, n (%)				
<65	57 (72.2)	75 (72.1)	3140 (65.1)	6564 (65.2)
65 to <75	18 (22.8)	24 (23.1)	1359 (28.2)	2863 (28.4)
75 to <85	4 (5.1)	5 (4.8)	314 (6.5)	625 (6.2)
≥85	0	0	12 (0.2)	21 (0.2)
Female sex, n (%)	24 (30.4)	25 (24.0)	1761 (36.5)	3623 (36.0)
BMI, kg/m <sup>2</sup> , mean (SD)	31.54 (5.21)	30.97 (5.72)	30.36 (5.53)	30.47 (5.60)
Baseline BMI group, kg/m <sup>2</sup> , n (%)				
<25	8 (10.1)	19 (18.3)	799 (16.6)	1615 (16.0)
25 to <30	24 (30.4)	26 (25.0)	1643 (34.1)	3370 (33.5)
30 to <35	27 (34.2)	33 (31.7)	1398 (29.0)	2985 (29.6)
≥35	20 (25.3)	26 (25.0)	964 (20.0)	2064 (20.5)
Missing	0	0	21 (0.4)	39 (0.4)
Race, n (%)				
White	47 (59.5)	71 (68.3)	2997 (62.1)	6531 (64.8)
Asian	29 (36.7)	28 (26.9)	1318 (27.3)	2573 (25.5)
Black/ African American	3 (3.8)	5 (4.8)	276 (5.7)	507 (5.0)
Other	0	0	51 (1.1)	101 (1.0)
Missing	0	0	183 (3.8)	361 (3.6)
Region, n (%)				
Europe	18 (22.8)	26 (25.0)	1803 (37.4)	3926 (39.0)
Asia	28 (35.4)	27 (26.0)	1392 (28.8)	2701 (26.8)
North America	25 (31.6)	32 (30.8)	1032 (21.4)	2187 (21.7)
Latin America	6 (7.6)	16 (15.4)	468 (9.7)	992 (9.8)
Africa/Middle East	2 (2.5)	3 (2.9)	130 (2.7)	267 (2.7)
Time since T2D diagnosis, n (%)				
≤1 year	5 (6.3)	7 (6.7)	254 (5.3)	609 (6.0)
>1 to 5 years	16 (20.3)	22 (21.2)	1061 (22.0)	2194 (21.8)

>5 years	58 (73.4)	75 (72.1)	3495 (72.4)	7239 (71.9)
Missing	0	0	15 (0.3)	31 (0.3)
eGFR, ml/min/1.73m <sup>2</sup> , mean (SD)	74.6 (19.6)	78.6 (20.6)	81.0 (21.0)	82.4 (20.2)
Baseline eGFR group, ml/min/1.73m <sup>2</sup> , n (%)				
≥90	22 (27.8)	34 (32.7)	1911 (39.6)	4143 (41.1)
60 to <90	37 (46.8)	51 (49.0)	2086 (43.2)	4426 (43.9)
45 to <60	13 (16.5)	11 (10.6)	506 (10.5)	992 (9.8)
30 to <45	7 (8.9)	7 (6.7)	270 (5.6)	438 (4.3)
<30	0	1 (1.0)	52 (1.1)	70 (0.7)
Missing	0	0	0	4 (<0.1)
Albumin/creatinine ratio categories, n (%)				
Normal	49 (62.0)	58 (55.8)	3112 (64.5)	6693 (66.4)
Microalbuminuria	22 (27.8)	37 (35.6)	1234 (25.6)	2485 (24.7)
Macroalbuminuria	7 (8.9)	7 (6.7)	428 (8.9)	778 (7.7)
Missing	1 (1.3)	2 (1.9)	51 (1.1)	117 (1.2)
History of hypertension, n (%)	67 (84.8)	93 (89.4)	3887 (80.6)	7920 (78.6)
History of urinary tract lithiasis, n (%)	0	1 (1.0)	3 (0.1)	5 (<0.1)
Baseline use of any diuretics, n (%)	19 (24.1)	38 (36.5)	1641 (34.0)	3311 (32.9)
Baseline use of loop diuretic, n (%)	3 (3.8)	9 (8.7)	485 (10.1)	900 (8.9)
Baseline use of anti-gout medication, n (%)	8 (10.1)	13 (12.5)	247 (5.1)	444 (4.4)
Baseline use of insulin, n (%)	31 (39.2)	48 (46.2)	1801 (37.3)	3462 (34.4)
Baseline use of sulphonyl urea, n (%)	38 (48.1)	43 (41.3)	1478 (30.6)	2940 (29.2)

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; T2D, type 2 diabetes

**Table.** Baseline patient characteristics in placebo and empagliflozin treatment groups by occurrence of urinary tract lithiasis during follow-up





**Figure:** Incidence rate ratios of empagliflozin vs. placebo of urinary tract lithiasis in 15,081 patients with type 2 diabetes.

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