nature medicine

Article

https://doi.org/10.1038/s41591-024-03330-x

Empagliflozin in nondiabetic individuals with calcium and uric acid kidney stones: a randomized phase 2 trial

Received: 8 May 2024

Accepted: 30 September 2024

Published online: 2 January 2025

Check for updates

Manuel A. Anderegg[1,4,5], Simeon Schietzel[1,5], Matteo Bargagli[1], Lia Bally[2], Nicolas Faller[1], Matthias B. Moor[1], Grazia M. Cereghetti[1], Marie Roumet[3], Sven Trelle[3] & Daniel G. Fuster[1]

Efficacy of sodium-glucose cotransporter 2 inhibitors for kidney stone prevention in nondiabetic patients is unknown. In a double-blind, placebo-controlled, single-center, crossover phase 2 trial, 53 adults (≥18 and <75 years) with calcium ($n = 28$) or uric acid (UA; $n = 25$) kidney stones (at least one previous kidney stone event) without diabetes (HbA1c < 6.5%, no diabetes treatment) were randomized to once daily empagliflozin 25 mg followed by placebo or reverse (2 weeks per treatment). Randomization and analysis were performed separately for both stone types. Primary analyses were conducted in the per protocol set. Primary outcomes were urine relative supersaturation ratios (RSRs) for calcium oxalate (CaOx), calcium phosphate (CaP) and UA—validated surrogates for stone recurrence. Prespecified RSR reductions (≥15%) were met in both groups of stone formers. In patients with calcium stones, empagliflozin reduced RSR CaP (relative difference to placebo, −36%; 95% confidence interval, −48% to −21%; $P < 0.001$), but not RSRs CaOx and UA. In patients with UA stones, empagliflozin reduced RSR UA (−30%; 95% confidence interval, −44% to −12%; $P = 0.002$) but not RSRs CaOx and CaP. No serious or prespecified adverse events occurred. Thus, empagliflozin substantially reduced RSRs in nondiabetic adults with calcium and UA kidney stones. ClinicalTrials.gov registration: NCT04911660.

Kidney stones constitute an important global healthcare problem, causing substantial morbidity, diminished quality of life and considerable healthcare costs[1,2]. The prevalence of kidney stones has risen worldwide in recent decades, with a current lifetime risk of up to 19.7% in men and 10.6% in women[3]. Kidney stones relapse frequently, with 10-year recurrence rates between 30% and 80% (ref. 4). Most kidney stones are calcium-containing, in the form of CaOx, CaP or a mixture of both. The second most common stone type is UA. The RSR, that is, the degree by which a solute in the urine exceeds its solubility, is the driving force for kidney stone formation. Relevant RSRs for calcium kidney stones are RSR CaOx and RSR CaP, respectively, and RSR UA for UA kidney stones[5]. Reduced risk of stone recurrence is correlated closely with reductions in urinary RSRs in observational studies and randomized controlled trials (RCTs)[6–9].

Existing strategies for the prevention of kidney stone recurrence are limited[10]. Registry data indicate that sodium-glucose cotransporter 2 (SGLT2) inhibitor treatment in type 2 diabetes (T2D) patients is associated with a reduction in kidney stone events[11–13]. Similarly,

[1]Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. [2]Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Bern University Hospital and University of Bern, Bern, Switzerland. [3]Department of Clinical Research, CTU Bern, University of Bern, Bern, Switzerland. [4]Present address: Department of Nephrology and Medical Intensive Care, Charité—Universitätsmedizin Berlin, Berlin, Germany. [5]These authors contributed equally: Manuel A. Anderegg, Simeon Schietzel. e-mail: daniel.fuster@unibe.ch

https://doi.org/10.1038/s41591-024-03330-x

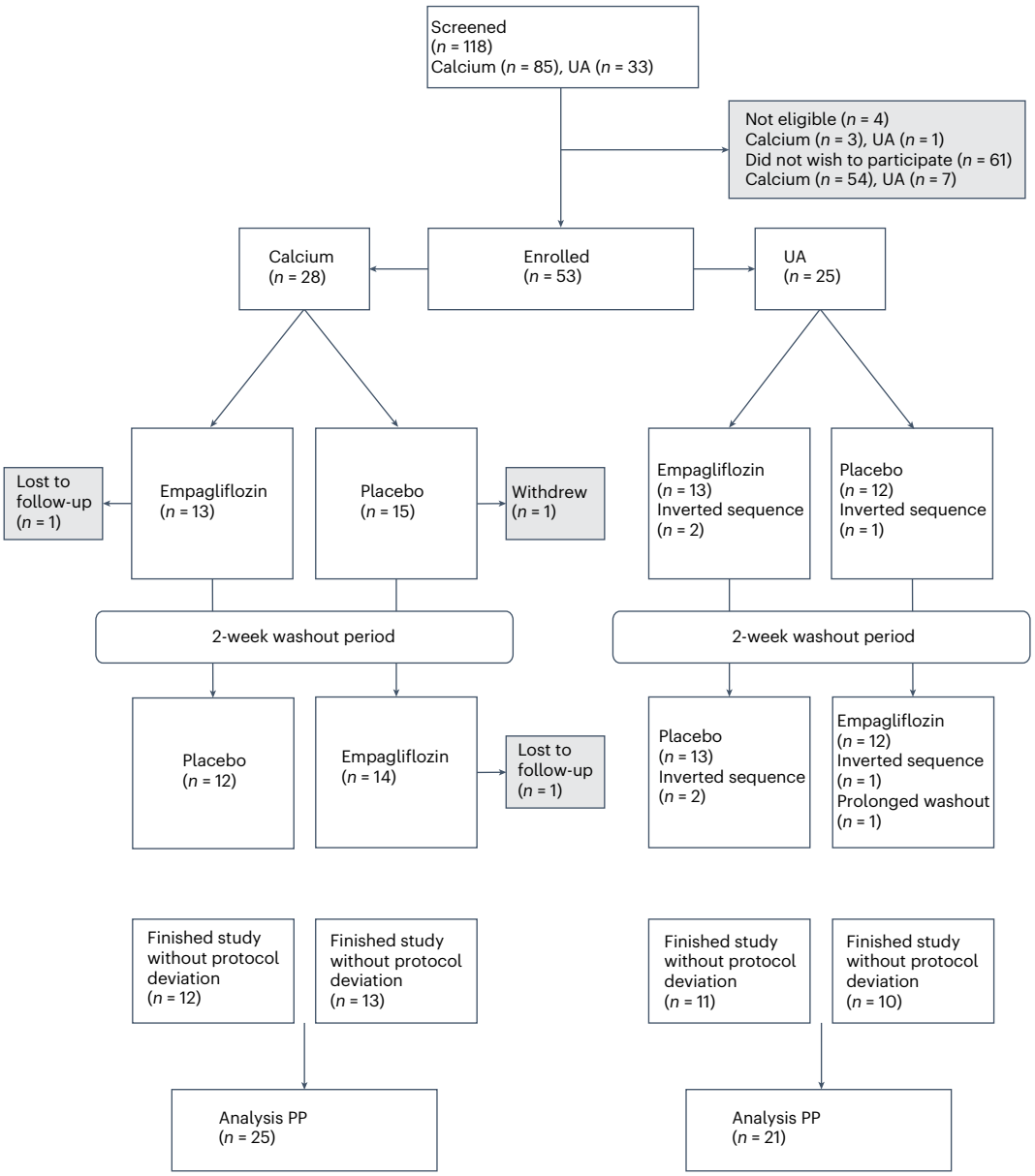


Fig. 1 | Screening, randomization and follow-up in the SWEETSTONE trial. CONSORT flow diagram of patient recruitment. Calcium and UA refer to strata of calcium or UA SF; *n* = number of individuals. Eligible patients were ≥18 and <75 years old, nondiabetic (HbA1c < 6.5%), and had experienced at least one kidney stone event containing ≥80% calcium or ≥80% UA. Patients with secondary causes of kidney stones and patients taking drugs interfering with kidney stone formation were not eligible. Details on randomization, interventions and dropouts are given in both Methods and Results. PP, per protocol.

in a post hoc analysis of phase 1–4 RCTs, empagliflozin treatment was associated with a reduction in kidney stone events compared with placebo[14]. Suggested mechanisms comprise osmotic diuresis with increased urinary flow rate[15,16], anti-inflammatory effects[17] and a variety of urinary changes potentially advantageous for reduced urinary supersaturation[18–20]. Despite their potential beneficial effects on kidney stone formation, SGLT2 inhibitors have not been studied in nondiabetic patients with kidney stones. SWEETSTONE was a randomized, double-blind, placebo-controlled, single-center crossover phase 2 trial to evaluate the therapeutic potential of empagliflozin for the prevention of calcium and UA kidney stones in nondiabetic adults.

Results

Patient disposition

A total of 118 patients underwent screening; 65 failed screening due to noneligibility (*n* = 4) or refusal to participate (*n* = 61) and 53 were enrolled and randomized (28 with calcium kidney stones, 25 with UA kidney stones). First patient enrollment was on 25 August 2021, last patient enrollment was on 9 December 2022. In the group of patients with calcium kidney stones, three discontinued the study early (one for personal reasons, two due to loss to follow-up). In the group of patients with UA kidney stones, three followed an inverted treatment sequence due to erroneously picking the wrong starting bottle, but otherwise completed the study. One patient followed a long washout period between treatment with placebo and empagliflozin (Fig. 1). The last patient's last study visit took place on 30 March 2023, the database was locked 30 May 2023, and the primary analysis was completed 16 August 2023. Characteristics of the study population, including kidney stone composition, are shown in Table 1. Mean (s.d.) age was 50.9 (14.5) years, 40 (75%) identified themselves as men, 13 (25%) as women and all participants were white. The median number of past stone events was 4.0 (interquartile range (IQR) 2.0–7.0), with a median of 3.0

(IQR 2.0–4.0) stone events occurring within 10 years before randomization. Participants with UA kidney stones were older, more likely to be men, had a higher number of past stone events, a higher body mass index and hemoglobin A1c (HbA1c), a higher prevalence of hypertension and a lower estimated glomerular filtration rate (eGFR) compared with participants with calcium stones.

Primary outcomes

Calcium kidney stone participants. Median RSR CaOx with empagliflozin was 9.1 (IQR 7.3–11.9) and 8.9 (IQR 7.7–13.4) with placebo (Fig. 2). Medians for RSR CaP and RSR UA were 1.0 (IQR 0.6–1.7) versus 1.9 (IQR 1.0–2.7) and 2.2 (IQR 1.1–3.0) versus 1.3 (IQR 0.9–2.3), respectively. Individual patient data (differences between empagliflozin and placebo) for primary outcomes (RSRs) are provided in Extended Data Figs. 1–3.

Estimated relative differences (%) were derived from a generalized linear mixed effects model with a Gamma distribution and a log link function with treatment and treatment period included as fixed effects and patient as a random intercept to account for the crossover design. The estimated relative difference in RSR CaP was −36% (95% confidence interval (CI) −48% to −21%) in favor of empagliflozin ($P < 0.001$) (Fig. 2). The corresponding estimates for RSR CaOx and RSR UA were −1% (95% CI −15% to 16%) and 32% (95% CI −14% to 104%), respectively. For both RSR CaOx and RSR UA, the relative difference was not statistically significant between empagliflozin and placebo. Results were similar in the analyses using the full analysis set, which is based on the intention-to-treat (ITT) principle (Extended Data Fig. 4).

UA kidney stone participants. Median RSR UA with empagliflozin was 2.5 (IQR 1.8–3.3) and 3.3 (IQR 2.6–5.4) with placebo (Fig. 2). Medians for RSR CaOx and RSR CaP were 5.8 (IQR 4.4–8.4) versus 6.6 (IQR 4.4–10.0) and 0.4 (IQR 0.3–0.9) versus 0.5 (IQR 0.3–0.8), respectively. Individual patient data (differences between empagliflozin and placebo) for primary outcomes (RSRs) are provided in the Extended Data (Extended Data Figs. 1–3). The estimated relative difference in RSR UA was −30% (95% CI −44% to −12%) in favor of empagliflozin ($P = 0.002$) (Fig. 2). The corresponding estimates for RSR CaOx and RSR CaP were −8% (95% CI −19% to 5%) and 8% (95% CI −16% to 38%), respectively. For both RSR CaOx and RSR CaP, the relative difference was not statistically significant between empagliflozin and placebo. Results were similar in the analyses using the full analysis set, which is based on the ITT principle (Extended Data Fig. 4).

Secondary outcomes. *Calcium kidney stone participants*. Median urine citrate excretion with empagliflozin was 4.9 (IQR 3.3–7.1) mmol per 24 h and 3.2 (IQR 2.1–3.9) mmol per 24 h with placebo (Fig. 3). Median urine pH with empagliflozin was 5.6 (IQR 5.5–6.1) and 5.8 (IQR 5.6–6.4) with placebo, and median urine calcium with empagliflozin was 8.1 (IQR 6.3–9.1) mmol per 24 h and 6.2 (IQR 4.8–8.3) mmol per 24 h with placebo. Median urine and plasma UA were (empagliflozin versus placebo) 4,334.0 (IQR 3,072.4–5,143.2) versus 3,186.6 (IQR 2,573.3–3,776.2) µmol per 24 h and 196.0 (IQR 184.0–226.0) versus 292.0 (IQR 250.5–326.5) µmol l^{-1}, respectively. The estimated relative difference (empagliflozin versus placebo) in urine citrate was 60% (95% CI 39% to 85%), in urine pH −4% (95% CI −7% to 0%), in urine calcium 23% (95% CI 0% to 51%), in urine UA 13% (95% CI 4% to 23%) and in plasma UA −31% (95% CI −38% to 23%) (Fig. 3). Urine oxalate and urine volume were not different between treatment groups. Results were similar in the analyses using the full analysis set, which is based on the ITT principle (Extended Data Fig. 5).

UA kidney stone participants. Median urine citrate excretion with empagliflozin was 4.2 (IQR 3.4–5.6) mmol per 24 h and 3.7 (IQR 2.3–4.5) mmol per 24 h with placebo (Fig. 4). In contrast to participants with calcium kidney stones, median urine pH with empagliflozin was higher compared with placebo (5.6 (IQR 5.2–5.6) versus 5.3 (IQR 5.2–5.5)). Median urine and plasma UA (empagliflozin versus placebo) were 3,855.7 (IQR 3,120.9–4,526.8) versus 4,307.6 (IQR 3,310.0–4,680.3) µmol per 24 h and 290 (IQR 233–323) versus 352 (IQR 313–441) µmol l^{-1}, respectively. The corresponding estimated relative difference (empagliflozin versus placebo) in urine citrate was 40% (95% CI 22% to 62%), in urine pH 3% (95% CI 1% to 5%), in urine UA −7% (95% CI −20% to 8%) and in plasma UA −24% (95% CI −35% to −12%) (Fig. 4). Urine volume, urine calcium and urine oxalate were not different between treatment groups. Results were similar in the analyses using the full analysis set, which is based on the ITT principle (Extended Data Fig. 6).

Table 1 | Baseline characteristics of the study population

Characteristics	Overall, *N*=53	Calcium SF, *N*=28	UA SF, *N*=25
Age at randomization, years	50.9 (14.5)	43.9 (15.0)	58.8 (8.8)
Men	40 (75%)	20 (71%)	20 (80%)
Body mass index, kg m^{-2}	28.4 (5.3)	27.1 (4.7)	29.9 (5.7)
Age at first kidney stone event, years	40.6 (15.0)	35.1 (15.1)	46.8 (12.5)
Total number of stone events	4.0 (2.0, 7.0)	2.5 (1.8, 4.0)	4.0 (3.0, 9.0)
Number of stone events in 10 years before randomization	3.0 (2.0, 4.0)	2.0 (1.0, 4.0)	4.0 (3.0, 7.0)
Lower urinary tract infections	12 (23%)	7 (25%)	5 (20%)
Upper urinary tract infections	14 (26%)	5 (18%)	9 (36%)
Congenital anomalies of the kidneys and of the urinary tract	3 (5.7%)	0 (0%)	3 (12%)
Hypertension	21 (40%)	6 (21%)	15 (60%)
Systolic blood pressure, mmHg	135.4 (18.2)	129.7 (13.6)	141.7 (20.8)
Diastolic blood pressure, mmHg	84.0 (9.5)	83.3 (10.3)	84.8 (8.6)
Heart rate, beats per minute	73.1 (10.7)	74.8 (11.0)	71.2 (10.2)
eGFR, ml min^{-1} per 1.73 m^2 body surface area	90.0 (78.0, 91.0)	91.0 (90.8, 91.0)	81.0 (74.0, 86.0)
HbA1c, %	5.6 (0.4)	5.4 (0.4)	5.7 (0.3)
Stone composition			
Containing calcium oxalate (>0%), *n* (%)	43 (81%)	28 (100%)	15 (60%)
Containing calcium phosphate (>0%), *n* (%)	15 (28%)	15 (54%)	0 (0%)
Predominant (>50%) calcium oxalate content, *n* (%)	26 (49%)	26 (93%)	0 (0%)
Predominant (>50%) calcium phosphate content, *n* (%)	2 (3.8%)	2 (7.1%)	0 (0%)

Characteristics are indicated for all participants and separately for calcium stone former (SF) and UA SF groups. Categorical variables are described by number of participants *N* (%), continuous variables are described by their mean (s.d.) or median (25th, 75th percentile). Numbers (*n*) and percentage (%) for kidney stone composition. Stone analysis results are given for the last stone analyzed before study participation. To be eligible, the last stone analyzed had to contain ≥80% calcium (calcium SF group) or ≥80% UA (UA SF group). 'Men' refers to (male) sex. Gender data were not collected.

https://doi.org/10.1038/s41591-024-03330-x

Type of SF	Primary outcomes	N^a	Placebo (median (IQR))	N^b	Empagliflozin (median (IQR))	Estimated relative difference (% (95% CI))[c]	P value[d]
Calcium	Calcium oxalate supersaturation	25	8.9 (7.7, 13.4)	25	9.1 (7.3, 11.9)	−1 (−15 to 16)	0.921
Calcium	Calcium phosphate supersaturation	25	1.9 (1.0, 2.7)	25	1.0 (0.6, 1.7)	−36 (−48 to −21)	<0.001*
Calcium	UA supersaturation	25	1.3 (0.9, 2.3)	25	2.2 (1.1, 3.0)	32 (−14 to 104)	0.204
UA	Calcium oxalate supersaturation	21	6.6 (4.4, 10.0)	21	5.8 (4.4, 8.4)	−8 (−19 to 5)	0.236
UA	Calcium phosphate supersaturation	21	0.5 (0.3, 0.8)	21	0.4 (0.3, 0.9)	8 (−16 to 38)	0.559
UA	UA supersaturation	21	3.3 (2.6, 5.4)	21	2.5 (1.8, 3.3)	−30 (−44 to −12)	0.002

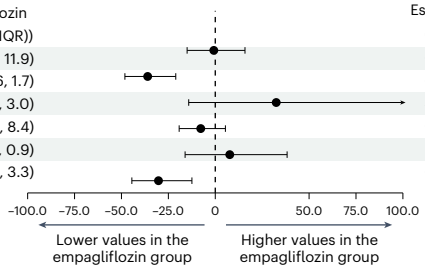


Fig. 2 | Primary analysis in participants with calcium and UA kidney stones. Forest plot of the effect of empagliflozin versus placebo on primary outcomes (PP set). Medians of urine RSRs are shown, with first/third quartile in parentheses. The dots in the forest plot represent the treatment effect on the respective RSRs as estimated relative difference (%), derived from a GLMM with a Gamma distribution and a log link function with treatment and treatment period included as fixed effects and patient as a random intercept to account for the crossover design. Error bars, associated 95% CIs. [a]Number of measurements assessed after placebo treatment. [b]Number of measurements assessed after empagliflozin treatment. [c]Derived from a GLMM. [d]Analysis of primary outcomes was accompanied by P values and hypothesis testing with a two-sided significance level of 0.02. *Exact P value = 3.15×10^{-5}.

Safety

No serious adverse events (SAEs) or prespecified adverse events (AESIs), such as hepatic injury, decreased renal function and metabolic acidosis, including ketoacidosis and diabetic ketoacidosis, occurred during the study.

Exploratory outcomes

In both groups of stone formers (SF), body weight was similar after 2 weeks of treatment with empagliflozin or placebo (Figs. 3 and 4).

Post hoc analyses

For calcium SFs, median renal net acid excretion (NAE) and net gastrointestinal alkali absorption (NGIA) were (empagliflozin versus placebo) 70.7 (IQR 53.2–83.0) versus 62.1 (IQR 34.1–80.4) mEq per 24 h and 49.9 (IQR 34.6–63.6) versus 38.1 (IQR 26.9–57.7) mEq per 24 h, respectively. The estimated relative difference in NAE was 26% (95% CI 15% to 37%) and in NGIA 24% (95% CI 13% to 35%), both in favor of empagliflozin (Fig. 3).

In UA stone formers, median NAE and NGIA were (empagliflozin versus placebo) 64.8 (IQR 52.0–69.4) versus 63.4 (IQR 52.0–78.6) mEq per 24 h and 36.7 (IQR 22.0–49.9) versus 31.9 (IQR 24.4–46.6) mEq per 24 h, respectively. The estimated relative difference in NAE and NGIA (empagliflozin versus placebo) were −9% (95% CI −14 to −3) and 7% (95% CI 6% to 7%)), respectively (Fig. 4).

In participants with calcium and UA kidney stones receiving empagliflozin, 24 h urine citrate excretion, but not RSRs CaP, CaOx und UA, correlated strongly with 24 h glucose excretion (R = 0.62 (95% CI 0.22–0.86) and R = 0.52 (95% CI 0.13–0.78), respectively) (Extended Data Fig. 7).

Discussion

SWEETSTONE is the first prospective trial evaluating an SGLT2 inhibitor in patients with kidney stones. In this double-blind, placebo-controlled crossover trial, empagliflozin significantly lowered urine RSRs—key validated surrogate parameters for kidney stone formation risk—in nondiabetic adults with both calcium or UA kidney stones[7–9,21]. No SAE or AESIs were observed during the trial period, and safety data for SGLT2 inhibitors is generally favorable[22]. RSRs from 24 h urine collections accurately reflect the long-term average supersaturation values in the urine and are highly correlated with kidney stone composition[5,8,9,23]. Short-term changes in RSRs upon initiation of treatment persist over time and associate with kidney stone outcomes[6–9,21,24,25]. In a large, well-characterized cohort of kidney SFs, a 25% reduction of RSR CaP during treatment was associated with an 80% decrease in stone events compared with pretreatment in patients with CaP or mixed CaP/CaOx stones[5]. In men with UA stones, a 40% reduction of RSR UA was associated with a complete cessation of stone recurrence[5]. In a randomized trial involving patients with CaOx stones and idiopathic hypercalciuria, for every 10% decrease in RSR CaOx after 1 week compared with baseline, there was an 8% decrease in future kidney stone recurrence[5].

In SWEETSTONE, empagliflozin treatment was associated with a 36% reduction of RSR CaP in patients with calcium stones, and a 30% reduction of RSR UA in patients with UA stones compared with placebo. In a pooled analysis of phase 1–4 trials in patients with T2D, empagliflozin treatment was associated with a 36% risk reduction of incident kidney stone events[14]. In large cohort studies of patients with T2D, risk reductions of 26–49% for incident kidney stone events were reported with SGLT2 use[11,13]. Considering the correlation of RSR decreases with reductions in recurrent stone events reported previously, we anticipate that the beneficial changes in RSRs observed with empagliflozin in SWEETSTONE will translate into a similar decrease in recurrent stone events in nondiabetic kidney SFs, as has been observed in patients with T2D. Whereas there is substantial evidence to support this notion in patients with pure CaP, mixed calcium and UA stones, the quantitative impact of exclusive RSR CaP reduction on recurrence in patients with pure CaOx is more difficult to estimate, as it is unprecedented. Current dietary and pharmacological interventions employed in patients with kidney stones typically attenuate both RSR CaOx and CaP. Considering the pronounced (60%) increase of urine citrate observed with empagliflozin in patients with calcium stones, it seems very likely that SGLT2 inhibitors will also result in a substantial reduction in recurrent stone events in patients with pure CaOx stones. There is substantial physicochemical evidence supporting this notion: urinary brushite supersaturation (herein referred to as RSR CaP) plays a critical role in the formation of both CaP and CaOx kidney stones. Interstitial CaP plaques (in the form of apatite) at the kidney papilla, known as Randall's plaques, constitute the nidus at which CaOx stone formation occurs[26–29]. In solution, brushite precipitates appear as the earliest solid phase in supersaturated urines and support the energetically beneficial heterogeneous nucleation of CaOx and growth of nonbrushite CaP crystals, such as apatite[30–32]. In contrast, pure CaP kidney stones typically originate as carbonate apatite or brushite plugs obstructing terminal ducts of Bellini, followed by outgrowth towards the urinary space[33]. Key drivers of RSR CaP reduction induced by empagliflozin were the pronounced increase of urine citrate and the decrease in urine pH. In fact, this unique property makes empagliflozin a very attractive treatment option for patients with CaP stones. Current treatments with potassium or sodium alkali increase urine citrate but simultaneously also increase urine pH and hence may increase rather than decrease RSR CaP.

We did not find empagliflozin to significantly increase urinary volume. The osmotic diuretic effect with SGLT2 inhibitors depends on the filtered load of glucose. In nondiabetic individuals enrolled in SWEETSTONE, the filtered load is considerably lower compared with patients with T2D. In support of these findings in nondiabetic patients with kidney stones, empagliflozin was also not associated with an

https://doi.org/10.1038/s41591-024-03330-x

Outcome	N[a]	Placebo (median (IQR))	N[b]	Empagliflozin (median (IQR))	Estimated relative difference [% (95% CI)][c]
Secondary outcomes, blood					
Sodium (mmol l^{-1})	24	140.0 (139.0, 141.0)	25	140.0 (138.0, 141.0)	0 (−1 to 1)
Potassium (mmol l^{-1})	24	3.9 (3.7, 4.0)	25	3.8 (3.7, 4.0)	0 (−2 to 2)
Chloride (mmol l^{-1})	24	105.0 (104.0, 106.0)	25	105.0 (104.0, 106.0)	0 (−1 to 1)
Calcium total (mmol l^{-1})	24	2.4 (2.3, 2.4)	25	2.4 (2.3, 2.4)	0 (−1 to 1)
Calcium ionized (mmol l^{-1})	25	1.2 (1.2, 1.2)	25	1.2 (1.2, 1.2)	−1 (−1 to 0)
Phosphate (mmol l^{-1})	24	1.0 (0.9, 1.2)	25	1.0 (1.0, 1.2)	3 (−2 to 9)
Magnesium (mmol l^{-1})	24	0.8 (0.8, 0.8)	25	0.9 (0.9, 0.9)	7 (5 to 9)
Osmolality (mosm kg^{-1})	24	285.0 (282.8, 289.0)	24	286.5 (284.0, 289.2)	0 (0 to 1)
Glucose (mmol l^{-1})	23	5.0 (4.8, 5.4)	24	5.0 (4.8, 5.4)	−2 (−5 to 0)
Albumin (g l^{-1})	24	39.5 (38.0, 42.2)	25	39.0 (37.0, 42.0)	−1 (−5 to 3)
Creatinine (µmol l^{-1})	24	74.0 (67.2, 84.5)	25	74.0 (65.0, 81.0)	0 (−4 to 3)
Urea (mmol l^{-1})	24	4.4 (3.4, 5.7)	25	4.9 (4.7, 5.9)	14 (7 to 22)
UA (µmol l^{-1})	24	292.0 (250.5, 326.5)	25	196.0 (184.0, 226.0)	−31 (−38 to −23)
Venous pCO_2 (mmHg)	25	44.0 (40.0, 46.0)	25	43.0 (41.0, 47.0)	4 (−3 to 11)
pH	25	7.4 (7.4, 7.4)	25	7.4 (7.4, 7.4)	0 (−1 to 0)
Venous bicarbonate (mmol l^{-1})	25	25.6 (23.9, 26.2)	25	25.1 (23.4, 26.7)	−2 (−6 to 3)
25-OH Vitamin D (nmol l^{-1})	25	59.0 (34.0, 66.0)	25	50.0 (32.0, 67.0)	4 (-3 to 11)
1,25-OH Vitamin D (pmol l^{-1})	25	136.0 (113.0, 154.0)	25	121.0 (94.0, 144.0)	−12 (−20 to −5)
PTH (pg ml^{-1})	25	36.3 (26.5, 49.6)	25	35.2 (29.7, 50.6)	1 (−8 to 12)
FGF23 (pg ml^{-1})	25	41.9 (32.2, 50.2)	24	43.5 (37.0, 51.9)	5 (−8 to 21)
Triglycerides (mmol l^{-1})	23	1.1 (0.9, 1.6)	24	1.1 (0.9, 1.4)	−6 (−16 to 5)
HbA1c (%)	25	5.4 (5.2, 5.8)	25	5.4 (5.2, 5.7)	0 (−1 to 1)
Alkaline phosphatase (U l^{-1})	24	68.5 (63.5, 80.2)	25	75.0 (64.0, 79.0)	3 (−8 to 14)
Total cholesterol (mmol l^{-1})	24	4.8 (4.2, 5.3)	25	5.2 (4.3, 5.6)	4 (1 to 7)
HDL cholesterol (mmol l^{-1})	24	1.3 (1.2, 1.4)	25	1.3 (1.1, 1.5)	1 (−4 to 6)
LDL cholesterol (mmol l^{-1})	24	2.9 (2.1, 3.5)	25	2.9 (2.4, 3.7)	6 (1 to 11)
TSH (mU l^{-1})	25	1.7 (1.4, 2.5)	25	1.5 (1.1, 2.2)	−9 (−18 to 1)
Secondary outcomes, urine					
Sodium (mmol per 24 h)	25	164.4 (132.3, 205.5)	25	184.6 (120.9, 253.0)	14 (−5 to 36)
Potassium (mmol per 24 h)	25	56.8 (42.8, 65.2)	25	60.4 (50.6, 68.4)	12 (0 to 25)
Chloride (mmol per 24 h)	25	151.0 (122.0, 184.0)	25	159.4 (108.0, 234.3)	9 (−6 to 26)
Calcium (mmol per 24 h)	25	6.2 (4.8, 8.3)	25	8.1 (6.3, 9.1)	23 (0 to 51)
Magnesium (mmol per 24 h)	25	4.1 (3.6, 5.0)	25	4.3 (3.3, 5.0)	0 (−9 to 10)
Phosphate (mmol per 24 h)	25	30.5 (21.1, 38.4)	25	35.2 (29.5, 42.9)	18 (9 to 28)
Osmolality (mosm kg^{-1})	22	509.5 (376.5, 640.0)	23	670.0 (522.5, 859.0)	30 (3 to 63)
Osmole excretion (mosm per 24 h)	22	882.9 (697.3, 978.9)	23	1,209.0 (940.5, 1,595.8)	41 (23 to 61)
Glucose (mmol per 24 h)	25	0.5 (0.3, 0.6)	25	289.2 (190.8, 389.2)	68,356 (56,202 to 83,132)
Creatinine (µmol per 24 h)	25	15,129.9 (12,019.4, 16,537.2)	25	15,685.2 (11,418.2, 17,679.1)	−2 (−9 to 5)
Urea (mmol per 24 h)	25	361.8 (284.2, 462.9)	25	384.0 (339.3, 584.5)	17 (5 to 30)
Uric acid (µmol per 24 h)	25	3,186.6 (2,573.3, 3,776.2)	25	4,334.0 (3,072.4, 5,143.2)	13 (4 to 23)
Citrate (mmol per 24 h)	25	3.2 (2.1, 3.9)	25	4.9 (3.3, 7.1)	60 (39 to 85)
Oxalate (µmol per 24 h)	25	513.7 (382.8, 599.1)	25	470.3 (356.4, 626.7)	3 (−12 to 21)
Sulfate (mmol per 24 h)	25	19.4 (14.1, 26.8)	25	24.7 (15.6, 29.8)	15 (5 to 26)
Ammonium (mmol per 24 h)	24	39.7 (20.6, 45.5)	24	42.2 (24.0, 50.0)	10 (1 to 19)
Bicarbonate (mmol per 24 h)	25	1.3 (0.5, 2.6)	25	0.9 (0.4, 1.7)	−46 (−67 to −12)
pCO_2 (mmHg)	25	38.0 (33.9, 57.0)	25	38.6 (27.1, 50.0)	−15 (−32 to 8)
Venous pH	25	5.8 (5.6, 6.4)	25	5.6 (5.5, 6.1)	−4 (−7 to 0)
Total volume per 24 h[d] (l)	25	1.8 (1.2, 2.5)	25	2.3 (1.4, 2.9)	11 (−2 to 26)
Titratable acid[e] (mEq per 24 h)	25	24.3 (16.6, 36.8)	25	33.2 (24.9, 35.8)	16 (4 to 30)
NGIA[e] (mEq per 24 h)	25	38.1 (26.9, 57.7)	25	49.9 (34.6, 63.6)	24 (13 to 35)
NAE[e] (mEq per 24 h)	24	62.1 (34.1, 80.4)	24	70.7 (53.2, 83.0)	26 (15 to 37)
Secondary outcomes, vital signs					
Systolic blood pressure (mmHg)	25	124.7 (118.7, 136.7)	25	122.0 (113.7, 128.7)	−2 (−9 to 5)
Diastolic blood pressure (mmHg)	25	81.0 (72.3, 87.7)	25	78.3 (72.3, 84.3)	−1 (−7 to 5)
Heart rate (beats per min)	25	70.3 (61.7, 79.3)	25	70.0 (62.3, 78.0)	−1 (−10 to 8)
Explorative outcome					
Weight (kg)	25	81.0 (75.0, 99.0)	25	78.0 (74.0, 99.5)	−1 (−1 to 0)

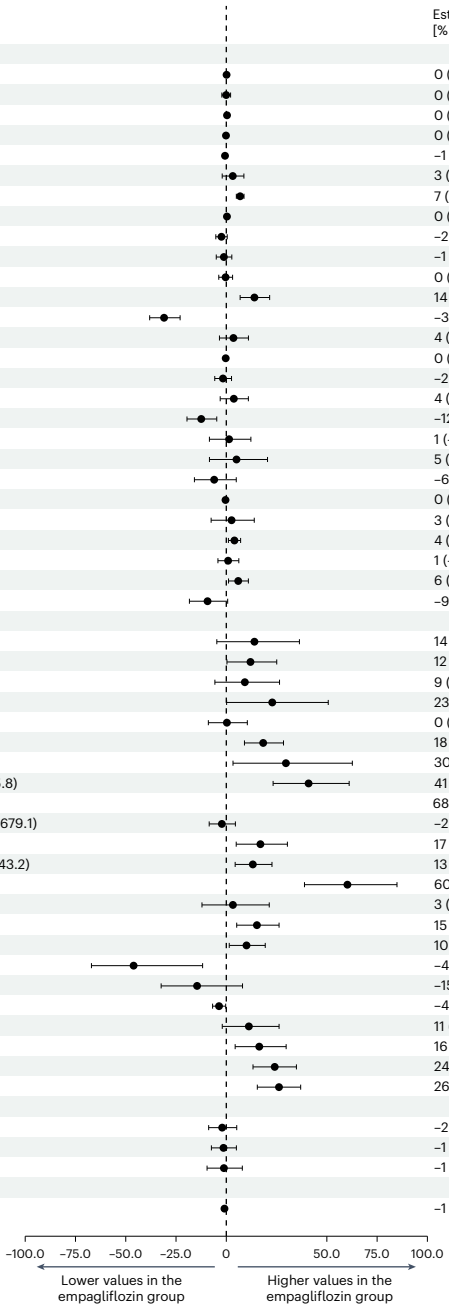


Fig. 3 | Secondary and exploratory outcomes in participants with calcium kidney stones. Forest plot of the effect of empagliflozin versus placebo on secondary and exploratory outcomes (PP set). Shown are medians, with first/third quartile in parentheses. The dots in the forest plot represent the treatment effect on the respective outcomes as estimated relative difference (%), derived from a GLMM with a gamma distribution and a log link function with treatment and treatment period included as fixed effects and patient as a random intercept to account for the crossover design. Error bars, associated 95% CIs. [a]Number of measurements assessed after placebo treatment. [b]Number of measurements assessed after empagliflozin treatment. [c]Derived from a GLMM. [d]Total urine volume per 24 h has been added post hoc (but before unblinding) as a secondary outcome. [e]NAE, NGIA and titratable acid were added post hoc (and after unblinding) as secondary outcomes. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

increase in urine volume in healthy volunteers in a recent study[18]. We thus provide clinical trial evidence that empagliflozin improves the urinary lithogenic profile in patients with kidney stones, independently of changes in urine volume.

The general denominator of empagliflozin therapy was the dramatic increase in urine citrate, which was correlated with the filtered load of glucose, suggesting a close interaction of proximal tubular glucose and citrate metabolism. Citrate is reabsorbed exclusively in the proximal tubule by the apical citrate transporter SLC13A2 (also known as NaDC1)[34,35]. SGLT2 inhibitors attenuate expression and function of several apical solute carriers in the proximal tubule, possibly via alterations in scaffolding proteins[20,36]. We therefore speculate that the empagliflozin-associated increase in urine citrate is mediated by inhibition or downregulation of SLC13A2. Yet, SGLT2 inhibitors are also known to induce important changes to metabolic pathways in proximal tubular cells, including an activation of gluconeogenesis and ammoniagenesis[20,36]. Therefore, an alternative explanation could be that the reabsorption of citrate is attenuated indirectly via a decrease in the activity of cytosolic ATP citrate lyase—the rate-limiting enzyme for citrate metabolism in the proximal tubule[34].

SGLT2 inhibitors decrease the activity of the sodium/hydrogen exchanger 3 (NHE3), the main sodium and bicarbonate reabsorption

https://doi.org/10.1038/s41591-024-03330-x

Outcome	N[a]	Placebo (median (IQR))	N[b]	Empagliflozin (median (IQR))	Estimated relative difference (% (95% CI))[c]
Secondary outcomes, blood					
Sodium (mmol l^{-1})	21	139.0 (138.0, 140.0)	21	140.0 (137.0, 141.0)	0 (−1 to 1)
Potassium (mmol l^{-1})	21	4.0 (3.9, 4.2)	21	4.0 (3.7, 4.2)	−1 (−3 to 1)
Chloride (mmol l^{-1})	21	105.0 (103.0, 106.0)	21	105.0 (102.0, 107.0)	0 (−1 to 2)
Calcium total (mmol l^{-1})	21	2.4 (2.3, 2.5)	21	2.4 (2.3, 2.4)	1 (0 to 2)
Calcium ionized (mmol l^{-1})	21	1.2 (1.2, 1.2)	21	1.2 (1.2, 1.2)	−1 (−2 to 0)
Phosphate (mmol l^{-1})	21	0.9 (0.8, 1.0)	21	1.0 (0.9, 1.1)	3 (−1 to 8)
Magnesium (mmol l^{-1})	21	0.8 (0.8, 0.8)	21	0.9 (0.8, 0.9)	6 (4 to 7)
Osmolality (mosm kg^{-1})	21	287.0 (285.0, 289.0)	21	288.0 (286.0, 291.0)	1 (0 to 2)
Glucose (mmol l^{-1})	21	5.4 (4.8, 5.6)	18	5.3 (5.0, 5.5)	−3 (−8 to 3)
Albumin (g l^{-1})	21	38.0 (36.0, 40.0)	21	38.0 (38.0, 40.0)	2 (−1 to 6)
Creatinine (µmol l^{-1})	21	87.0 (80.0, 95.0)	21	92.0 (88.0, 105.0)	6 (3 to 9)
Urea (mmol l^{-1})	21	6.0 (5.2, 6.6)	21	6.0 (5.3, 7.2)	4 (−1 to 9)
UA (µmol l^{-1})	21	352.0 (313.0, 441.0)	21	290.0 (233.0, 323.0)	−24 (−35 to −12)
Venous pCO_2 (mmHg)	21	42.0 (38.0, 46.0)	21	42.0 (39.0, 47.0)	3 (−5 to 11)
pH	21	7.4 (7.4, 7.4)	21	7.4 (7.4, 7.4)	0 (0 to 0)
Venous bicarbonate (mmol l^{-1})	21	24.5 (23.2, 25.7)	21	24.2 (22.8, 25.8)	0 (−5 to 4)
25-OH Vitamin D (nmol l^{-1})	21	60.0 (53.0, 74.0)	21	60.0 (47.0, 81.0)	−1 (−7 to 4)
1,25-OH Vitamin D (pmol l^{-1})	21	109.0 (77.0, 134.0)	21	98.0 (77.0, 114.0)	−7 (−15 to 1)
PTH (pg ml^{-1})	21	38.8 (36.0, 41.6)	21	40.5 (38.2, 50.0)	8 (−9 to 28)
FGF23 (pg ml^{-1})	21	50.1 (41.0, 62.0)	21	56.8 (45.6, 63.8)	13 (−5 to 34)
Triglycerides (mmol l^{-1})	21	1.7 (1.0, 1.9)	18	1.3 (1.0, 2.0)	−10 (−20 to 2)
HbA1c (%)	21	5.7 (5.4, 5.8)	21	5.8 (5.6, 5.8)	1 (−1 to 2)
Alkaline phosphatase (U l^{-1})	21	73.0 (56.0, 86.0)	21	76.0 (63.0, 88.0)	5 (−11 to 24)
Total cholesterol (mmol l^{-1})	21	5.6 (5.0, 6.2)	21	5.3 (4.8, 5.9)	−6 (−10 to −1)
HDL cholesterol (mmol l^{-1})	21	1.4 (1.1, 1.6)	21	1.3 (1.1, 1.6)	−3 (−6 to 0)
LDL cholesterol (mmol l^{-1})	21	3.3 (3.1, 4.0)	20	3.2 (2.7, 3.7)	−7 (−14 to 0)
TSH (mU l^{-1})	21	1.8 (1.3, 2.4)	21	1.7 (1.2, 2.2)	−9 (−17 to −1)
Secondary outcomes, urine					
Sodium (mmol per 24 h)	21	176.0 (150.7, 204.5)	21	195.2 (143.9, 204.4)	1 (−7 to 10)
Potassium (mmol per 24 h)	21	69.1 (49.1, 77.0)	21	62.6 (51.5, 73.6)	−2 (−9 to 5)
Chloride (mmol per 24 h)	21	163.6 (131.1, 187.5)	21	177.1 (136.4, 197.0)	1 (−7 to 10)
Calcium (mmol per 24 h)	21	4.6 (3.4, 6.4)	21	4.7 (3.3, 6.2)	0 (−9 to 10)
Magnesium (mmol per 24 h)	21	3.7 (3.1, 4.5)	21	3.4 (2.9, 4.1)	−10 (−17 to −2)
Phosphate (mmol per 24 h)	21	34.8 (28.7, 39.5)	21	32.3 (29.6, 37.6)	−6 (−20 to 11)
Osmolality (mosm kg^{-1})	21	622.0 (402.0, 784.0)	21	650.0 (575.0, 783.0)	14 (8 to 22)
Osmole excretion (mosm per 24 h)	21	967.2 (789.8, 1,041.1)	21	1,287.1 (1,085.0, 1,444.9)	31 (24 to 39)
Glucose (mosm per 24 h)	21	0.5 (0.4, 0.6)	21	267.7 (233.2, 311.5)	51,635 (43,644 to 61,085)
Creatinine (µmol per 24 h)	21	14,466.5 (12,456.0, 17,367.8)	21	13,530.0 (11,899.6, 15,896.8)	−6 (−12 to 1)
Urea (mmol per 24 h)	21	456.7 (372.7, 479.9)	21	417.9 (322.0, 469.5)	−7 (−14 to −1)
UA (µmol per 24 h)	21	4,307.6 (3,310.0, 4,680.3)	21	3,855.7 (3,120.9, 4,526.8)	−7 (−20 to 8)
Citrate (mmol per 24 h)	21	3.7 (2.3, 4.5)	21	4.2 (3.4, 5.6)	40 (22 to 62)
Oxalate (µmol per 24 h)	21	438.7 (375.2, 475.4)	21	411.8 (335.5, 575.7)	0 (−7 to 8)
Sulfate (mmol per 24 h)	21	22.4 (19.2, 29.4)	21	21.6 (17.9, 24.9)	−7 (−23 to 13)
Ammonium (mmol per 24 h	21	30.2 (25.3, 33.8)	21	31.3 (23.4, 35.9)	−5 (−21 to 13)
Bicarbonate (mmol per 24 h)	21	0.3 (0.2, 0.3)	21	0.5 (0.2, 0.8)	74 (29 to 135)
pCO_2 (mmHg)	21	26.7 (22.0, 35.3)	21	29.9 (24.2, 32.7)	2 (−11 to 17)
Venous pH	21	5.3 (5.2, 5.5)	21	5.6 (5.2, 5.6)	3 (1 to 5)
Total volume per 24 h[d] (l)	21	1.7 (1.3, 2.2)	21	1.9 (1.7, 2.1)	9 (0 to 18)
Titratable acid[e] (mEq per 24 h)	21	33.8 (27.9, 40.0)	21	31.1 (27.2, 37.1)	−10 (−22 to 5)
NGIA[e] (mEq per 24 h)	21	31.9 (24.4, 46.6)	21	36.7 (22.0, 49.9)	7 (6 to 7)
NAE[e] (mEq per 24 h)	21	63.4 (52.0, 78.6)	21	64.8 (52.0, 69.4)	−9 (−14 to −3)
Secondary outcomes, vital signs					
Systolic blood pressure (mmHg)	21	130.3 (124.0, 144.3)	21	130.3 (120.7, 144.0)	−1 (−9 to 7)
Diastolic blood pressure (mmHg)	21	83.0 (80.7, 87.3)	21	84.0 (76.0, 87.7)	−2 (−8 to 4)
Heart rate (beats per min)	21	68.7 (62.7, 75.3)	21	70.3 (63.3, 74.0)	2 (−6 to 11)
Explorative outcome					
Weight (kg)	21	86.0 (76.0, 93.5)	21	86.0 (76.6, 94.0)	−1 (−1 to 0)

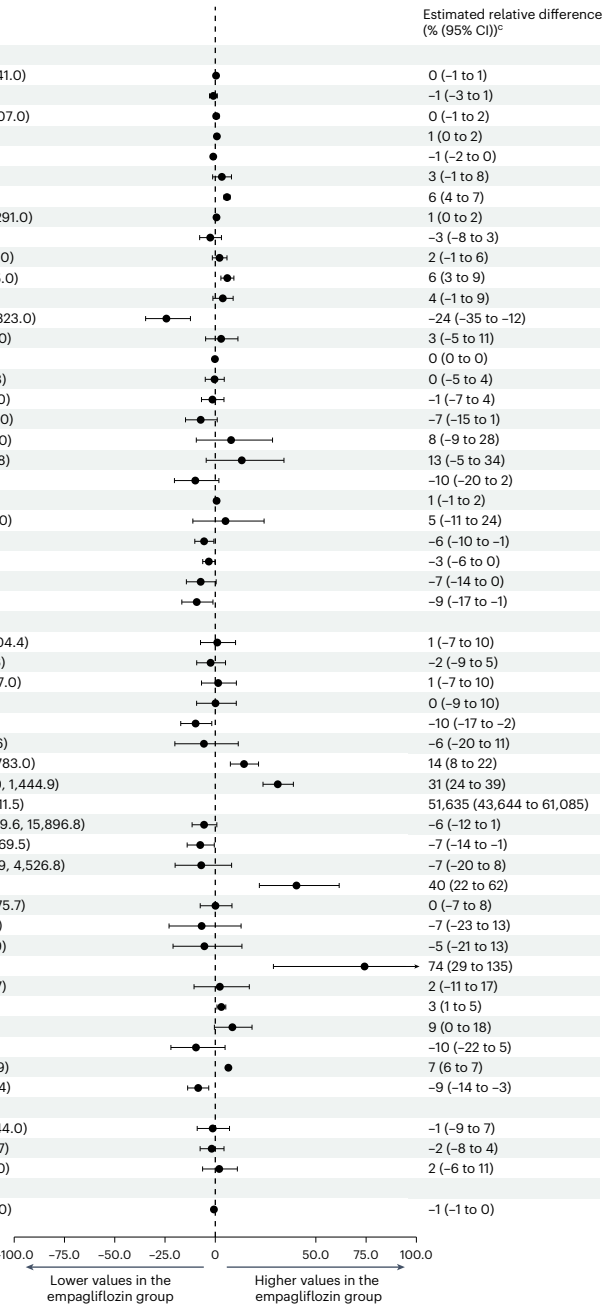


Fig. 4 | Secondary and exploratory outcomes in participants with UA kidney stones. Forest plot of the effect of empagliflozin versus placebo on secondary and exploratory outcomes (PP set). Shown are medians, with first/third quartile in parentheses. The dots in the forest plot represent the treatment effect on the respective outcomes as estimated relative difference (%), derived from a GLMM with a gamma distribution and a log link function with treatment and treatment period included as fixed effects and patient as a random intercept to account for the crossover design. Error bars, associated 95% CIs. [a]Number of measurements assessed after placebo treatment. [b]Number of measurements assessed after empagliflozin treatment. [c]Derived from a GLMM. [d]Total urine volume per 24 h has been added post hoc (but before unblinding) as a secondary outcome. [e]NAE, NGIA and titratable acid were added post hoc (and after unblinding) as secondary outcomes.

pathway in the proximal tubule[20]. Inhibition of NHE3 is expected to decrease paracellular calcium reabsorption in the proximal tubule and augment urine calcium, which is what we observed in patients with calcium stones receiving empagliflozin. This effect was not observed in patients with UA stones receiving empagliflozin, suggesting that patients with high baseline urine calcium are more prone to develop SGLT2 inhibition-associated increases in urine calcium. Importantly, however, the protective rise in urine citrate greatly exceeded the increase of urine calcium observed in patients with calcium stones receiving empagliflozin.

SGLT2 inhibitors are uricosuric and lower plasma UA, which has raised concerns regarding increased risks for UA stone formation. The exact mechanism of the uricosuric effect is debated[37,38], but seems to be coupled to glucosuria in both rodent and human studies, with increased UA excretion from day 1 of treatment[39]. We now provide clinical trial evidence that, despite decreasing plasma UA, empagliflozin significantly decreases RSR UA in patients with UA kidney stones.

Interestingly, empagliflozin induced differential urine pH changes in patients with calcium and UA kidney stones. Urine pH was clamped to 5.6 with empagliflozin in both groups of patients, resulting in an

increase in urine pH in patients with UA stones and a decrease in urine pH in patients with calcium stones. Given the importance of pH for RSR CaP and RSR UA, these differential urine pH changes probably had a substantial impact on the beneficial changes in RSR CaP and RSR UA observed in patients with calcium and UA kidney stones, respectively. We can only speculate on the mechanism underlying the differential effect on urine pH. Although NGIA increased in both groups of patients treated with empagliflozin, NAE was lower in patients with UA kidney stones and higher in patients with calcium kidney stones treated with empagliflozin. Thus, empagliflozin seems to exhibit differential effects on endogenous acid generation and increased intestinal alkali absorption in the two groups of patients.

Indeed in mice, higher urine ammonium and lower urine pH have been observed with empagliflozin treatment, possibly reflecting a metabolic adaptation to urinary loss of glucose and calories, which stimulates endogenous acid production due to formation of ketone bodies and increased food intake[20]. Patients with UA kidney stones are known to exhibit an impairment in proximal tubular ammoniagenesis[40], which probably explains the lack of increase in urinary ammonium and NAE observed in this group of patients.

Strengths of our trial include the double-blind, placebo-controlled, crossover design and the inclusion of the two most common, yet pathophysiologically distinct, stone phenotypes.

Our trial also has limitations that need to be considered. The number of patients was low and the treatment duration short. However, treatment duration was sufficient for a reliable analysis of the primary outcomes, namely urine RSRs[9]. Further, the trial lacked ethnic diversity and had an underrepresentation of women. However, kidney stone prevalence is by far the highest in white men[41], consequently the trial was representative for the population most affected by kidney stone disease. Finally, our trial strongly suggests that beneficial changes in the urinary lithogenic profile are responsible for attenuated stone formation observed in patients treated with SGLT2 inhibitors. Yet, we cannot exclude the possibility that additional factors, such as suppressed inflammation, tubulointerstitial fibrosis and kidney injury, downregulation of osteopontin expression and decreased reactive oxygen species generation, contribute to the antilithogenic effect in patients receiving long-term treatment with SGLT2 inhibitors[17,42,43].

In conclusion, empagliflozin significantly improved the urinary lithogenic risk profile in nondiabetic patients with calcium and UA kidney stones. Our data suggest SGLT2 inhibition as a safe strategy to prevent kidney stone recurrence in patients with kidney stones.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03330-x.

References

1. Saigal, C. S., Joyce, G. & Timilsina, A. R. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int.* **68**, 1808–1814 (2005).
2. New, F. & Somani, B. K. A complete world literature review of quality of life (QOL) in patients with kidney stone disease (KSD). *Curr. Urol. Rep.* **17**, 88 (2016).
3. Chewcharat, A. & Curhan, G. Trends in the prevalence of kidney stones in the United States from 2007 to 2016. *Urolithiasis* **49**, 27–39 (2021).
4. Vaughan, L. E. et al. Predictors of symptomatic kidney stone recurrence after the first and subsequent episodes. *Mayo Clin. Proc.* **94**, 202–210 (2019).
5. Parks, J. H., Coward, M. & Coe, F. L. Correspondence between stone composition and urine supersaturation in nephrolithiasis. *Kidney Int.* **51**, 894–900 (1997).
6. Siener, R., Glatz, S., Nicolay, C. & Hesse, A. Prospective study on the efficacy of a selective treatment and risk factors for relapse in recurrent calcium oxalate stone patients. *Eur. Urol.* **44**, 467–474 (2003).
7. Borghi, L. et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N. Engl. J. Med.* **346**, 77–84 (2002).
8. Borghi, L. et al. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J. Urol.* **155**, 839–843 (1996).
9. Ferraro, P. M. et al. Short-term changes in urinary relative supersaturation predict recurrence of kidney stones: a tool to guide preventive measures in urolithiasis. *J. Urol.* **200**, 1082–1087 (2018).
10. Dhayat, N. A. et al. Hydrochlorothiazide and prevention of kidney-stone recurrence. *N. Engl. J. Med.* **388**, 781–791 (2023).
11. Kristensen, K. B., Henriksen, D. P., Hallas, J., Pottegard, A. & Lund, L. C. Sodium-glucose cotransporter 2 inhibitors and risk of nephrolithiasis. *Diabetologia* **64**, 1563–1571 (2021).
12. Anan, G. et al. Impact of sodium-glucose cotransporter-2 inhibitors on urolithiasis. *Kidney Int. Rep.* **8**, 925–928 (2023).
13. Paik, J. M. et al. Sodium-glucose cotransporter 2 inhibitors and nephrolithiasis risk in patients with type 2 diabetes. *JAMA Intern. Med.* **184**, 265–274 (2024).
14. Balasubramanian, P. et al. Empagliflozin and decreased risk of nephrolithiasis: a potential new role for SGLT2 inhibition? *J. Clin. Endocrinol. Metab.* **107**, e3003–e3007 (2022).
15. Tang, J., Ye, L., Yan, Q., Zhang, X. & Wang, L. Effects of sodium-glucose cotransporter 2 inhibitors on water and sodium metabolism. *Front Pharm.* **13**, 800490 (2022).
16. Ansary, T. M., Nakano, D. & Nishiyama, A. Diuretic effects of sodium glucose cotransporter 2 inhibitors and their influence on the renin-angiotensin system. *Int. J. Mol. Sci.* **20**, 629 (2019).
17. Anan, G. et al. Inhibition of sodium-glucose cotransporter 2 suppresses renal stone formation. *Pharmacol. Res.* **186**, 106524 (2022).
18. Harmacek, D. et al. Empagliflozin changes urine supersaturation by decreasing pH and increasing citrate. *J. Am. Soc. Nephrol.* **33**, 1073–1075 (2022).
19. Bletsa, E. et al. Effect of dapagliflozin on urine metabolome in patients with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **106**, 1269–1283 (2021).
20. Onishi, A. et al. A role for tubular Na^+/H^+ exchanger NHE3 in the natriuretic effect of the SGLT2 inhibitor empagliflozin. *Am. J. Physiol. Ren. Physiol.* **319**, F712–F728 (2020).
21. Prochaska, M., Taylor, E., Ferraro, P. M. & Curhan, G. Relative supersaturation of 24-hour urine and likelihood of kidney stones. *J. Urol.* **199**, 1262–1266 (2018).
22. Narasaki, Y. et al. Safety of SGLT2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists in US veterans with and without chronic kidney disease: a population-based study. *Lancet Reg. Health Am.* **36**, 100814 (2024).
23. Williams, J. C. Jr et al. Urine and stone analysis for the investigation of the renal stone former: a consensus conference. *Urolithiasis* **49**, 1–16 (2020).
24. Pak, C. Y. & Adams-Huet, B. Elucidation of factors determining formation of calcium phosphate stones. *J. Urol.* **172**, 2267–2270 (2004).
25. Coe, F. L., Strauss, A. L., Tembe, V. & Le Dun, S. Uric acid saturation in calcium nephrolithiasis. *Kidney Int.* **17**, 662–668 (1980).
26. Evan, A. P. et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J. Clin. Invest.* **111**, 607–616 (2003).

27. Asplin, J. R., Mandel, N. S. & Coe, F. L. Evidence of calcium phosphate supersaturation in the loop of Henle. *Am. J. Physiol.* **270**, F604–F613 (1996).
28. Randall, A. An hypothesis for the origin of renal calculus. *N. Engl. J. Med.* **214**, 234–242 (1936).
29. Randall, A. The etiology of primary renal calculus. *Int. Abstr. Surg.* **71**, 209–240 (1940).
30. Meyer, J. L., Bergert, J. H. & Smith, L. H. Epitaxial relationships in urolithiasis: the brushite-whewellite system. *Clin. Sci. Mol. Med.* **52**, 143–148 (1977).
31. Meyer, J. L., Bergert, J. H. & Smith, L. H. Epitaxial relationships in urolithiasis: the calcium oxalate monohydrate-hydroxyapatite system. *Clin. Sci. Mol. Med.* **49**, 369–374 (1975).
32. Pak, C. Y., Eanes, E. D. & Ruskin, B. Spontaneous precipitation of brushite in urine: evidence that brushite is the nidus of renal stones originating as calcium phosphate. *Proc. Natl Acad. Sci. USA* **68**, 1456–1460 (1971).
33. Evan, A. P. et al. Renal histopathology of stone-forming patients with distal renal tubular acidosis. *Kidney Int.* **71**, 795–801 (2007).
34. Tang, R. et al. Control of biomineralization dynamics by interfacial energies. *Angew. Chem. Int. Ed. Engl.* **44**, 3698–3702 (2005).
35. Moe, O. W. & Preisig, P. A. Dual role of citrate in mammalian urine. *Curr. Opin. Nephrol. Hypertens.* **15**, 419–424 (2006).
36. Billing, A. M. et al. Metabolic communication by SGLT2 inhibition. *Circulation* **149**, 860–884 (2024).
37. Novikov, A. et al. SGLT2 inhibition and renal urate excretion: role of luminal glucose, GLUT9, and URAT1. *Am. J. Physiol. Ren. Physiol.* **316**, F173–F185 (2019).
38. Suijk, D. L. S. et al. SGLT2 inhibition and uric acid excretion in patients with type 2 diabetes and normal kidney function. *Clin. J. Am. Soc. Nephrol.* **17**, 663–671 (2022).
39. Chino, Y. et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm. Drug Dispos.* **35**, 391–404 (2014).
40. Bobulescu, I. A. et al. Net acid excretion and urinary organic anions in idiopathic uric acid nephrolithiasis. *Clin. J. Am. Soc. Nephrol.* **14**, 411–420 (2019).
41. Kummer, A. E. et al. Nephrolithiasis as a risk factor for CKD: the atherosclerosis risk in communities study. *Clin. J. Am. Soc. Nephrol.* **10**, 2023–2029 (2015).
42. Endo, A. et al. Sodium glucose cotransporter 2 inhibitor suppresses renal injury in rats with renal congestion. *Hypertens. Res.* **47**, 33–45 (2024).
43. Mima, A. Mitochondria-targeted drugs for diabetic kidney disease. *Heliyon* **8**, e08878 (2022).

Methods

Trial conduct and oversight

SWEETSTONE was an investigator-initiated, randomized, double-blind, placebo-controlled, crossover phase 2 trial designed to investigate the effects of empagliflozin on urine RSRs CaOx, CaP and UA in nondiabetic patients with kidney stones. Patients with calcium or UA kidney stones were investigated separately as if these were two independent trials (subtrials) but everything else was kept similar. For each group of kidney stone type, half of the patients were first treated with empagliflozin, the other half with placebo changing to the respective other treatment protocol after a washout period. Sequence order was determined by randomization. Treatment periods lasted 2 weeks, the washout period was 2–6 weeks. The design of the trial was published previously[44], the trial protocol is available as Supplementary Information Item 1. The trial has been registered on clinicaltrials.gov (NCT04911660) and the Swiss National Clinical Trials Portal (SNCTP000004272). The trial was approved by the responsible ethics committee in the Canton of Bern, Switzerland on 23 February 2021. (no. 2020_02679) and by Swissmedic on 10 May 2021 (no. 2021DR2077). The study was conducted in accordance with the Declaration of Helsinki (2013), the International Council for Harmonization Good Clinical Practice Guideline (E6) and all local regulations. All patients provided written informed consent before participation. The study was performed at the Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Switzerland. Recruitment started in June 2021, and enrollment was completed in December 2022. Database lock and unblinding occurred in May 2023. The CONSORT 2010 checklist has been completed by the authors and is available as Supplementary Information Item 3. Sex and/or gender were not considered in the study design.

Participants

Eligible patients provided informed consent, were ≥18 and <75 years old, nondiabetic (HbA1c < 6.5%, no known diagnosis of diabetes, no antidiabetic medication) and had experienced at least one kidney stone event in the past with the most recent kidney stone analyzed containing ≥80% calcium or ≥80% UA (which determined enrollment in one of the two subtrials). Exclusion criteria were as follows: patients with secondary causes of kidney stones (severe eating disorders, chronic bowel disease, past intestinal or bariatric surgery, sarcoidosis, primary hyperparathyroidism and complete distal tubular acidosis), patients with untreated obstructive uropathy or genito-urinary infection, patients with chronic kidney disease (CKD-EPI eGFR <60 $ml^{-1}\,min^{-1}\,1.73\,m^{-2}$), kidney transplant recipients, pregnant and lactating women, known allergy to study drug, participation in another interventional clinical trial within 4 weeks before baseline or during this trial, inability to understand and follow the protocol as well as intake of drugs interfering with kidney stone formation (thiazide and loop diuretics; carbonic anhydrase inhibitors (including topiramate); xanthine oxidase inhibitors; alkali (including potassium citrate or sodium bicarbonate); 1,25-OH Vitamin D (calcitriol); calcium supplementation; bisphosphonates; denusomab; teriparatide; glucocorticoids). In patients where temporary suspension of interfering drugs was feasible, a washout period of 4 weeks was carried out before randomization. No payment or compensation was given to study participants. Both male and female participants (sex) were included. Gender data were not collected.

Randomization and blinding

The two patient populations (calcium and UA kidney SFs) were investigated separately. In each group, patients were enrolled and randomized separately as if they were two independent trials (subtrials). Participants were assigned in a 1:1 ratio to a specified treatment sequence starting with, for example, empagliflozin 25 mg once daily followed by placebo once daily or in reverse order (Fig. 1). Randomization lists with randomly varying block sizes of 2 and 4 were generated by an independent statistician at CTU Bern and implemented during manufacturing of the investigational medicinal product by Boehringer Ingelheim, Basel. Allocation was concealed using sequentially coded drug bottles that were otherwise identical. Empagliflozin and placebo were provided in identical-looking bottles containing identical-looking tablets. Enrollment was performed by the study investigators, assignment to intervention was implemented by the study nurses by taking the next numbered pair of drug bottles. Blinding remained in place until the statistician at CTU Bern coded the primary analysis of the primary and secondary outcomes and produced a dummy report of the primary analysis using a randomly generated treatment sequence. For the whole study population, first patient enrollment was 25 August 2021 and last on 9 December 2022. Specifically for calcium SFs, first patient enrollment was on 25 August 2021, last on 9 May 2022. For UA SFs, first patient enrollment was 2 September 2021, last enrollment on 9 December 2022.

Intervention and assessments

The intervention of this trial was a 14-day treatment period with empagliflozin 25 mg once daily, followed by a 14-day treatment period with placebo once daily (or the reversed treatment order determined by randomization; crossover design). Patients were instructed to take one tablet per os, once daily in the morning. Between treatment periods, a washout period of 2–6 weeks had to be respected (Fig. 1). Before the first treatment period and on the last day (day 14) of each respective treatment period, we collected fasting blood and a 24-h urine sample, accepting extensions of treatment periods for a maximum of 4 days in case of scheduling impediments. At randomization and at all study visits, participants received state-of-the-art nonpharmacologic recommendations for stone prevention according to current guidelines[45,46]. Compliance of patients was assessed by pill count (both treatment periods) and urinary glucose monitoring during the empagliflozin treatment period. We considered patients with values above 50 mmol per 24 h to be compliant with the study medication. Results of urinary glucose measurements were kept blinded during the trial. Blinding remained in place until the statistician at CTU Bern coded the primary analysis.

Outcomes

Primary outcome. The three primary outcomes were the urine RSRs for CaOx, CaP and UA. RSRs were calculated by EQUIL2 (ref. 47).

Secondary outcomes

Prespecified secondary outcomes included blood and 24 h urine parameters relevant to kidney stone formation and to a possible effect of the study drug. In full, the following parameters were assessed for blood: sodium; potassium; chloride; calcium (total and ionized); magnesium; phosphate; osmolality; albumin; creatinine; urea; UA; alkaline phosphatase; venous blood gas analysis; 25 hydroxy and 1,25 dihydroxy vitamin D; parathyroid hormone (PTH); fibroblast growth factor 23 (FGF23); glucose; HbA1c; lipid panel and thyroid-stimulating hormone (TSH). The following parameters were assessed for 24 h urine: total volume, sodium, potassium, chloride, calcium, magnesium, phosphate, osmolality, glucose, protein, albumin, creatinine, urea, UA, oxalate, citrate, sulfate, ammonium, bicarbonate, pCO_2, pH and calcium. Titratable acid calculated by EQUIL2 (ref. 47). For vital signs, we assessed systolic and diastolic blood pressure as well as heart rate.

Safety

Safety assessment consisted of monitoring of SAEs and AESIs such as hepatic injury, decreased renal function and metabolic acidosis, including ketoacidosis and diabetic ketoacidosis (Supplementary Information Item 1).

Exploratory outcomes

We included body weight as a prespecified exploratory outcome.

Post hoc analyses

The following exploratory outcomes derived from prespecified 24 h urine parameters were included post hoc: NGIA (mEq per 24 h): (urine Na + urine K + urine Ca + urine Mg) − (urine Cl + 1.8 × urine Phos)[48], urine titratable acidity (mEq per 24 h)[49] and renal NAE (mEq per 24 h): (urine ammonium + urine titratable acidity) − urine bicarbonate[50].

Sample size calculation

Taking into account the reduction observed in kidney stone event rate in pooled phase 1–3 empagliflozin trials[14], we extrapolated reductions of 30–60% in urinary RSRs with empagliflozin compared with placebo[51,52]. The magnitude of urine RSR reduction closely paralleled the decrease in stone events in patients with calcium kidney stones randomized to a dietary intervention for recurrence prevention[9]. A reduction of ~15% in urinary RSR CaOx has been found to confer an ~12% risk reduction of a recurrent stone event in a post hoc analysis of a previous RCT in patients with calcium kidney stones[9]. There are no comparable RCT data available in patients with UA kidney stones. We considered a 15% reduction in urinary RSRs associated with a 12% reduction in stone events as the lower limit of a clinically meaningful prophylactic benefit of empagliflozin treatment, and hence chose a cut-off of a 15% reduction in any of the three urine RSRs CaOx, CaP and UA as the target treatment effect for the sample size calculation. The calculation was based on the primary outcomes (urine RSRs) of intraindividual comparisons within the two groups of kidney stone formers (calcium and UA) in line with the crossover design. A paired means test was used as implemented in Stata (v.16.1). To account for the several (three) primary endpoints (RSR CaOx, RSR CaP and RSR UA) in both groups of kidney SFs, we adjusted the significance level and fixed it at 0.02 (two sided) with a power set to 85%. Assuming a common s.d. of 20% and an intraindividual correlation of 0.5 (crossover design), we estimated a sample size of 23 patients per group/subtrial (46 patients in total). As all assumptions and processes were identical between both patient populations (calcium and UA kidney SFs), sample size calculation was performed in the same way for both populations (subtrials). Sample size was reassessed by calculating the observed s.d. values using blinded data after 50% of patients completed the trial. Full details of the sample size calculation are provided in the study protocol (Supplementary Information Item 1).

Statistical analysis

Statistical analysis was performed at CTU Bern by a statistician blinded to the group allocation. The prespecified statistical analysis plan (SAP) is available as Supplementary Information Item 2. As prespecified, the analysis of the primary and secondary study outcomes reported in the main manuscript were performed on the per protocol (PP) set. The PP population consists of all participants who did not have any protocol deviations that could confound the interpretation of analyses (violation of eligibility criteria, noncompliance with treatment or assessment schedule). As secondary analysis, we additionally performed a prespecified ITT analysis for the primary and secondary outcomes using the full analysis set (Extended Data Figs. 4–6). The full analysis set includes all participants who were included in the study, regardless of their adherence to study protocol procedures. For analysis of the primary outcomes (RSR CaOx, RSR CaP, RSR UA), a two-sided significance level of 0.02 was set for hypothesis testing to adjust for the various primary outcomes. All primary and secondary analyses were conducted separately for both patient populations (participants with calcium and UA kidney stones, subtrials).

Outcome values observed after the treatment with empagliflozin 25 mg once daily and placebo are summarized as means (s.d.) or medians (IQR). The effect of empagliflozin treatment on primary outcomes was analyzed using a generalized linear mixed effects model (GLMM) with a Gamma distribution and a log link function to account for the skewed, non-normal distribution of the data. Treatment and treatment period were included as fixed effects, whereas patient was included as a random intercept. Detailed model results for the primary outcomes are available in Extended Data Table 1. Non-normally distributed secondary outcomes were analyzed in the same way as primary outcomes. Normally distributed secondary outcomes were analyzed using the same model but with a Gaussian distribution (the SAP mandated an identity link function (linear mixed model), but we decided to switch to a log link post hoc but before unblinding to have consistent effect measures throughout). For normally distributed secondary outcomes with positive and negative values (that is, NAE and NGIA), we used a Gaussian distribution with an identity link function (linear mixed model).

As effect measure, we calculated the ratio between the two treatments, and presented the relative difference (%) and the associated 95% CI. For the outcomes analyzed with a log link function, we calculated the ratio from the model coefficients. For the NAE and NGIA outcomes, we used the model to derive the patient's predicted values and calculated the ratio between treatment periods for each patient as well as the population average.

Analysis of the primary outcomes is accompanied by *P* values and hypothesis testing with a two-sided significance level of 0.02. Normality was assessed based on histograms.

As additional post hoc analysis, we assessed the correlations between each outcome and the level of urine glucose after treatment with empagliflozin 25 mg. We used the nonparametric Spearman correlation coefficient and derived the 95% CIs by bootstrapping (*n* replicates = 1,000). No a priori or post hoc sex-based analyses have been performed due to insufficient sample size to analyse differences between sexes. Gender data were not collected. Statistical analyses were conducted using R, v.4.2.3 (ref. 53) and sample size calculation was performed with Stata, v.16.1 (ref. 54). Full details of the statistical analysis are provided in the SAP.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The study protocol and SAP are provided as Supplementary Information Items 1 and 2. The full dataset of deidentified individual participant data and the data dictionary that underlie the results reported in this article are available from the corresponding author (D.G.F.) for research purposes. Data sharing will be possible from publication onwards. Proposals with specific aims and an analysis plan should be directed to the corresponding author (daniel.fuster@unibe.ch). Timelines can vary depending on the type of request, but data will be provided within a maximum of 3 months.

Code availability

All analyses were conducted using R Statistical Software (v.4.2.3; R Core Team 2023) on a Windows computer (Windows 10 × 64 (build 19042); x86_64-w64-mingw32/x64 (64-bit)). No custom code was used for the analysis of this trial. All packages used for the analysis are available from the Comprehensive R Archive Network via R (listed in Supplementary Information Item 4). The detailed code used to generate the findings of the present study is available from the corresponding author (daniel.fuster@unibe.ch) upon request from qualified researchers in this field. Researchers are asked to provide information on their affiliation and experience in this field and how they intend to use the code. Timelines can vary depending on the type of request, but the code will be provided within a maximum of 3 months.

References

44. Schietzel, S. et al. Impact of the SGLT2 inhibitor empagliflozin on urinary supersaturations in kidney stone formers (SWEETSTONE trial): protocol for a randomised, double-blind, placebo-controlled cross-over trial. *BMJ Open* **12**, e059073 (2022).

45. Scholz, D., Schwille, P. O. & Sigel, A. Double-blind study with thiazide in recurrent calcium lithiasis. *J. Urol.* **128**, 903–907 (1982).
46. Borghi, L., Meschi, T., Guerra, A. & Novarini, A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J. Cardiovasc. Pharmacol.* **22**, S78–S86 (1993).
47. Werness, P. G., Brown, C. M., Smith, L. H. & Finlayson, B. EQUIL2: a BASIC computer program for the calculation of urinary saturation. *J. Urol.* **134**, 1242–1244 (1985).
48. Oh, M. S. A new method for estimating G-I absorption of alkali. *Kidney Int.* **36**, 915–917 (1989).
49. Kok, D. J., Poindexter, J. & Pak, C. Y. Calculation of titratable acidity from urinary stone risk factors. *Kidney Int.* **44**, 120–126 (1993).
50. Relman, A. S. Endogenous production of fixed acid and the measurement of the net balance of acid in normal subjects. *J. Am. Soc. Nephrol.* **11**, 2155–2164 (2000).
51. Kohler, S., Zeller, C., Iliev, H. & Kaspers, S. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. *Adv. Ther.* **34**, 1707–1726 (2017).
52. Kohler, S. et al. Safety and tolerability of empagliflozin in patients with type 2 diabetes. *Clin. Ther.* **38**, 1299–1313 (2016).
53. R Core Team. *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, 2023).
54. *Stata Statistical Software: Release 16.1* (StataCorp LLC, 2020).

Acknowledgements

We are grateful to the study personnel and all the study participants for their time and contribution to the study. The Insel Gruppe AG, Bern University Hospital took the role as Sponsor and provided financial and logistic assistance for the SWEETSTONE trial. Trial drugs and matching placebos were kindly provided by Boehringer Ingelheim, Basel. Boehringer Ingelheim also provided funding for laboratory analyses performed in the study. The Sponsor and Boehringer Ingelheim had no role in trial design, conduct of the study, analysis or interpretation of data or writing or submission of the manuscript. Funding was provided by Inselspital, Boehringer Ingelheim (BI Study No. 1245-0214).

Author contributions

D.G.F. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. D.G.F. and S.T. designed the study, wrote and amended the study protocol and supervised the study. D.G.F. was the principal investigator of the study and obtained funding. M.A.A., S.S., M.B., N.F., M.B.M. and D.G.F. acquired, analyzed and interpreted data. M.A.A., S.S. and M.B. drafted the manuscript. M.A.A., S.S., M.B., N.F., M.B.M., L.B., G.M.C., M.R., S.T. and D.G.F. provided critical input on interpretation of the findings. M.R. and M.B. performed statistical analysis.

Competing interests

D.G.F. served as a consultant for Otsuka, Alnylam, Boehringer Ingelheim and Kyowa Kirin, and received unrestricted research grants from Otsuka, Boehringer Ingelheim and CSL Vifor. The other authors declare no competing interests.

Additional information

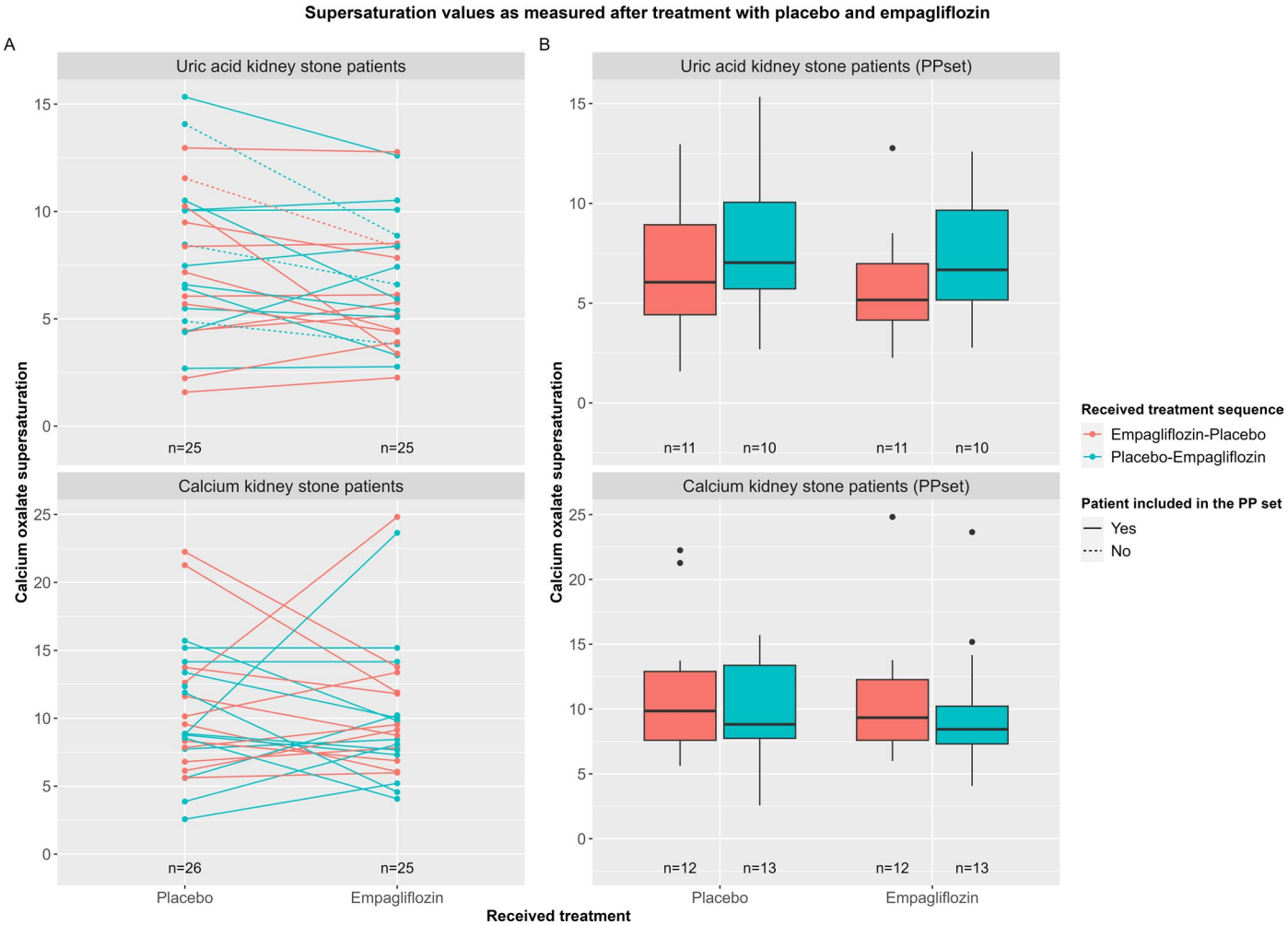
Extended data is available for this paper at https://doi.org/10.1038/s41591-024-03330-x.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-024-03330-x.

Correspondence and requests for materials should be addressed to Daniel G. Fuster.

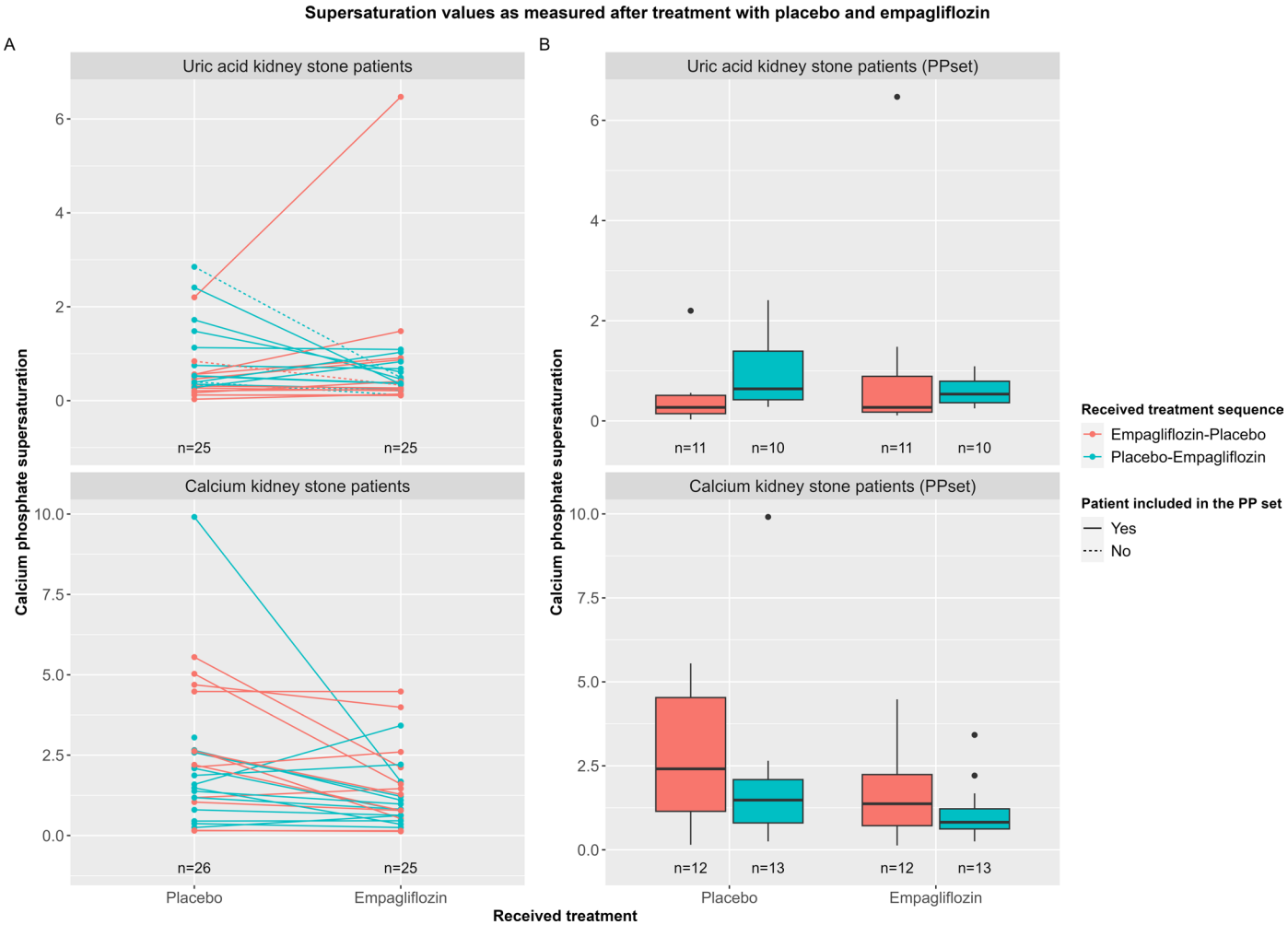
Peer review information *Nature Medicine* thanks Bruce Perkins, Megan Prochaska and Sergey Tarima for their contribution to the peer review of this work. Primary Handling Editor: Liam Messin, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-024-03330-x



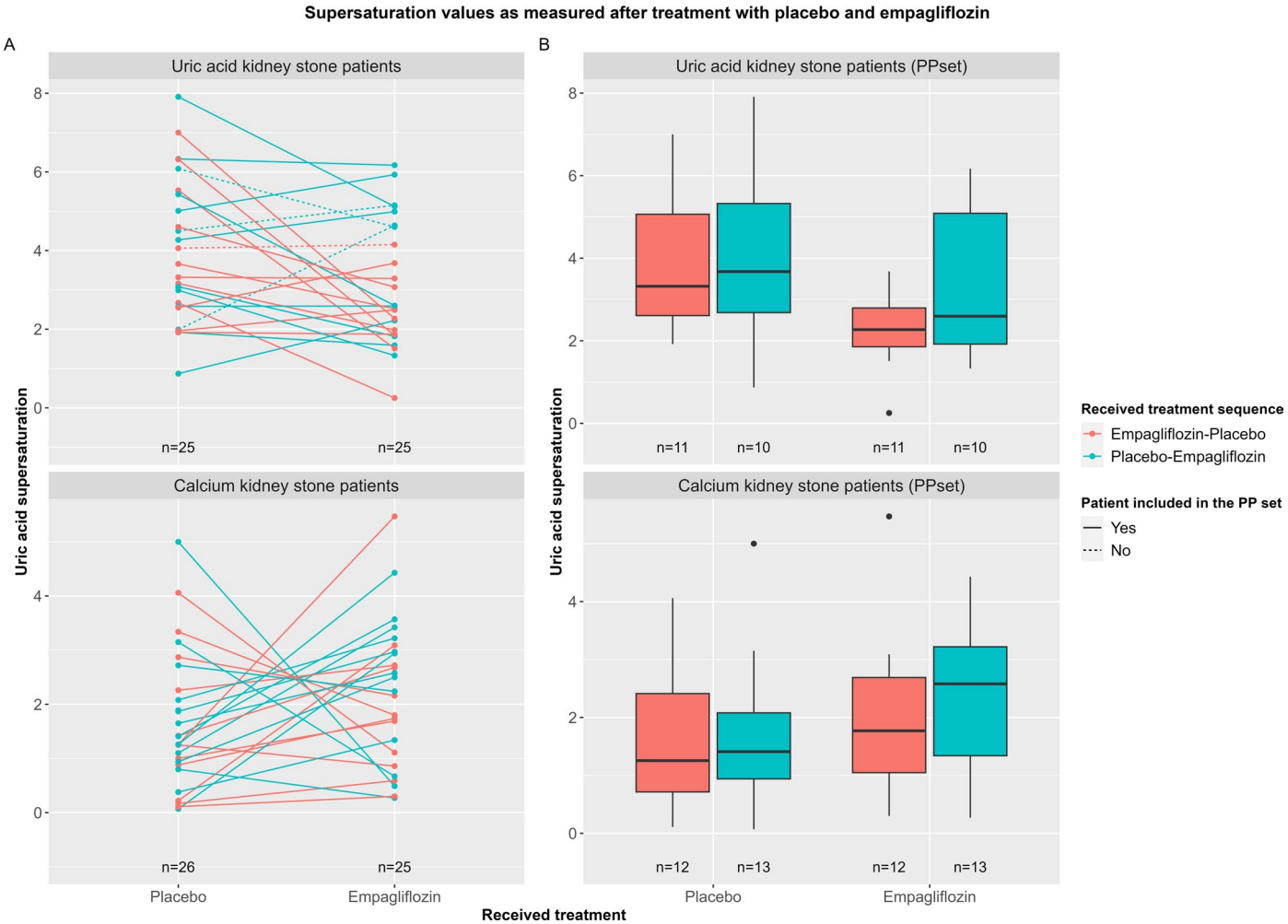
Extended Data Fig. 1 | RSR CaOx values measured after treatment with placebo and empagliflozin (individual patients). Left panel (**A**): Line plots showing, for UA (top panels) and calcium (bottom panels) kidney stone formers, the RSR CaOx values measured at the end of the placebo and empagliflozin treatment phases. N denotes the total number of patients. Patients included in the per protocol (PP) set are represented with solid lines (n = 25 for calcium kidney stones, n = 21 for UA kidney stones), patients not included in the PP set are represented with dotted lines (n = 4 for UA kidney stones). 1 calcium kidney stone former only completed the placebo treatment phase before drop-out (lost to follow-up). Patients starting the study with the placebo treatment are represented in blue, patients starting with empagliflozin in red. Right Panel (**B**): Boxplots showing, for UA (top) and calcium (bottom) kidney stone formers included in the PP set, the RSR CaOx values measured at the end of the placebo and empagliflozin treatment phases. In each boxplot, the bottom and top bounds of the box indicate the 25th and 75th percentiles, so the box indicates the interquartile range. The center line indicates the median (50th percentile). The whiskers extend to the maximum and minimum values within 1.5× the interquartile range. Outliers are presented as dots beyond the whiskers. n, number of patients per condition (PP set).

https://doi.org/10.1038/s41591-024-03330-x



Extended Data Fig. 2 | RSR CaP values measured after treatment with placebo and empagliflozin (individual patients). Left panel (**A**): Line plots showing, for UA (top panels) and calcium (bottom panels) kidney stone formers, RSR CaP values measured at the end of the placebo and empagliflozin treatment phases. N denotes the total number of patients. Patients included in the PP set are represented with solid lines (n = 25 for calcium kidney stones, n = 21 for UA kidney stones), patients not included in the PP set are represented with dotted lines (n = 4 for UA kidney stones). 1 calcium kidney stone former only completed the placebo treatment phase before drop-out (lost to follow-up). Patients starting the study with the placebo treatment are represented in blue, patients starting with empagliflozin in red. Right Panel (**B**): Boxplots showing, for UA (top) and calcium (bottom) kidney stone formers included in the PP set, RSR CaP values measured at the end of the placebo and empagliflozin treatment phases. In each boxplot, the bottom and top bounds of the box indicate the 25th and 75th percentiles, so the box indicates the interquartile range. The center line indicates the median (50th percentile). The whiskers extend to the maximum and minimum values within 1.5× the interquartile range. Outliers are presented as dots beyond the whiskers. n, number of patients per condition (PP set).

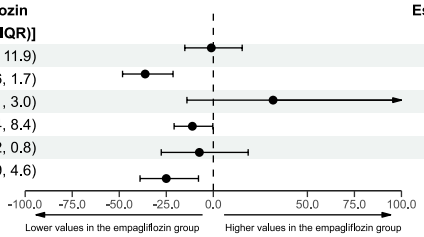
https://doi.org/10.1038/s41591-024-03330-x



Extended Data Fig. 3 | RSR UA values measured after treatment with placebo and empagliflozin (individual patients). Left panel (**A**): Line plots showing, for UA (top panels) and calcium (bottom panels) kidney stone formers, RSR UA values measured at the end of the placebo and empagliflozin treatment phases. N denotes the total number of patients. Patients included in the PP set are represented with solid lines (n = 25 for calcium kidney stones, n = 21 for UA kidney stones), patients not included in the PP set are represented with dotted lines (n = 4 for UA kidney stones). 1 calcium kidney stone former only completed the placebo treatment phase before drop-out (lost to follow-up). Patients starting the study with the placebo treatment are represented in blue, patients starting with empagliflozin in red. Right Panel (**B**): Boxplots showing, for UA (top) and calcium (bottom) kidney stone formers included in the PP set, RSR UA values measured at the end of the placebo and empagliflozin treatment phases. In each boxplot, the bottom and top bounds of the box indicate the 25th and 75th percentiles, so the box indicates the interquartile range. The center line indicates the median (50th percentile). The whiskers extend to the maximum and minimum values within 1.5× the interquartile range. Outliers are presented as dots beyond the whiskers. n, number of patients per condition (PP set).

https://doi.org/10.1038/s41591-024-03330-x

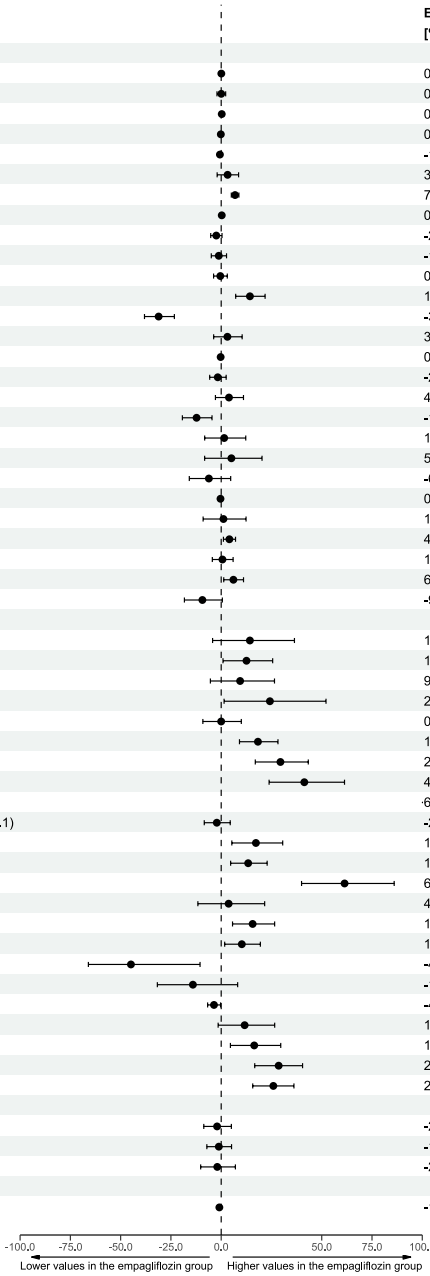
Type of stone former	Primary outcomes	N[a]	Placebo [median (IQR)]	N[b]	Empagliflozin [median (IQR)]	Estimated relative difference [% (95% CI)][c]	p-value[d]
Calcium	Calcium oxalate supersaturation	26	9.2 (7.8, 13.2)	25	9.1 (7.3, 11.9)	-1 (-15 to 15)	0.891
Calcium	Calcium phosphate supersaturation	26	2.0 (1.1, 2.7)	25	1.0 (0.6, 1.7)	-36 (-48 to -21)	<0.001*
Calcium	Uric acid supersaturation	26	1.3 (0.9, 2.2)	25	2.2 (1.1, 3.0)	32 (-14 to 102)	0.205
Uric acid	Calcium oxalate supersaturation	25	7.2 (4.9, 10.1)	25	5.9 (4.4, 8.4)	-11 (-21 to 0)	0.045
Uric acid	Calcium phosphate supersaturation	25	0.5 (0.3, 0.8)	25	0.4 (0.2, 0.8)	-7 (-28 to 19)	0.541
Uric acid	Uric acid supersaturation	25	3.7 (2.6, 5.4)	25	2.6 (1.9, 4.6)	-25 (-39 to -8)	0.006



Extended Data Fig. 4 | Primary analysis in participants with calcium and UA kidney stones (intention-to-treat analysis). Forest plot of the effect of empagliflozin vs placebo on primary outcomes (urine RSRs). Median urine RSRs are shown, with first/third quartile in brackets. The dots in the forest plot represent the treatment effect on the respective RSRs as estimated relative difference (%), derived from a generalized linear mixed effects model with a Gamma distribution and a log link function with treatment and treatment-period included as fixed effects and patient as a random intercept to account for the cross-over design. The error bars represent the associated 95% confidence intervals (CIs). a Number of measurements assessed after placebo treatment. b Number of measurements assessed after empagliflozin. c Derived from a generalized linear mixed effects model. d Analysis of primary outcomes was accompanied by p-values and hypothesis testing with a two-sided significance level of 0.02. * exact p-value = 2.45 x 10-5.

https://doi.org/10.1038/s41591-024-03330-x

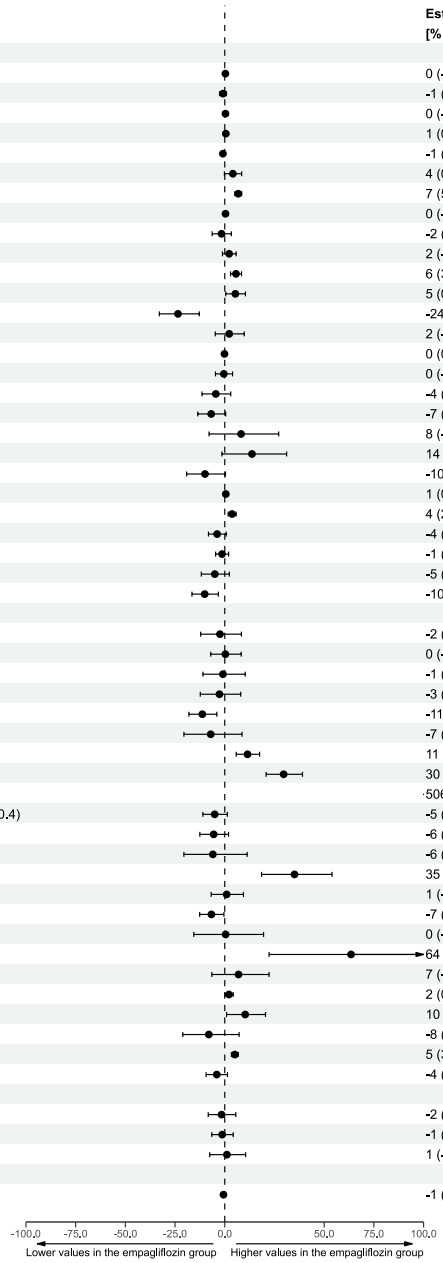
Outcome	N[a]	Placebo [median (IQR)]	N[b]	Empagliflozin [median (IQR)]	Estimated relative difference [% (95% CI)][c]
Secondary outcomes, Blood					
Sodium (mmol/l)	25	140.0 (139.0, 141.0)	25	140.0 (138.0, 141.0)	0 (-1 to 1)
Potassium (mmol/l)	25	3.9 (3.7, 4.0)	25	3.8 (3.7, 4.0)	0 (-2 to 2)
Chloride (mmol/l)	25	105.0 (104.0, 106.0)	25	105.0 (104.0, 106.0)	0 (-1 to 1)
Calcium total (mmol/l)	25	2.4 (2.3, 2.4)	25	2.4 (2.3, 2.4)	0 (-1 to 1)
Calcium ionized (mmol/l)	26	1.2 (1.2, 1.2)	25	1.2 (1.2, 1.2)	-1 (-1 to 0)
Phosphate (mmol/l)	25	1.0 (0.9, 1.2)	25	1.0 (1.0, 1.2)	3 (-2 to 9)
Magnesium (mmol/l)	25	0.8 (0.8, 0.8)	25	0.9 (0.9, 0.9)	7 (5 to 9)
Osmolality (mosm/kg)	25	285.0 (283.0, 289.0)	24	286.5 (284.0, 289.2)	0 (0 to 1)
Glucose (mmol/l)	24	5.1 (4.8, 5.4)	24	5.0 (4.8, 5.4)	-2 (-5 to 0)
Albumin (g/l)	25	40.0 (38.0, 42.0)	25	39.0 (37.0, 42.0)	-1 (-5 to 3)
Creatinine (µmol/l)	25	74.0 (68.0, 86.0)	25	74.0 (65.0, 81.0)	0 (-4 to 3)
Urea (mmol/l)	25	4.4 (3.2, 5.7)	25	4.9 (4.7, 5.9)	14 (7 to 22)
Uric acid (µmol/l)	25	296.0 (253.0, 325.0)	25	196.0 (184.0, 226.0)	-31 (-38 to -23)
Venous pCO2 (mmHg)	26	44.0 (40.0, 46.8)	25	43.0 (41.0, 47.0)	3 (-4 to 10)
pH	26	7.4 (7.4, 7.4)	25	7.4 (7.4, 7.4)	0 (-1 to 0)
Venous bicarbonate (mmol/l)	26	25.6 (23.9, 26.2)	25	25.1 (23.4, 26.7)	-2 (-6 to 2)
25-OH Vitamin D (nmol/l)	26	54.5 (32.5, 66.0)	25	50.0 (32.0, 67.0)	4 (-3 to 11)
1,25-OH Vitamin D (pmol/l)	26	133.5 (108.5, 152.5)	25	121.0 (94.0, 144.0)	-12 (-19 to -5)
Parathyroid hormone (PTH) (pg/mL)	26	35.0 (26.6, 49.1)	25	35.2 (29.7, 50.6)	1 (-8 to 12)
Fibroblast growth factor 23 (FGF23) (pg/mL)	26	42.4 (32.2, 49.6)	24	43.5 (37.0, 51.9)	5 (-8 to 20)
Triglycerides (mmol/l)	24	1.2 (1.0, 1.6)	24	1.1 (0.9, 1.4)	-6 (-16 to 5)
Haemoglobin A1c (%)	26	5.3 (5.2, 5.8)	25	5.4 (5.2, 5.7)	0 (-1 to 1)
Alkaline phosphatase (U/l)	25	69.0 (64.0, 84.0)	25	75.0 (64.0, 79.0)	1 (-9 to 12)
Total Cholesterol (mmol/l)	25	4.8 (4.1, 5.3)	25	5.2 (4.3, 5.6)	4 (1 to 7)
HDL Cholesterol (mmol/l)	25	1.3 (1.2, 1.4)	25	1.3 (1.1, 1.5)	1 (-4 to 6)
LDL Cholesterol (mmol/l)	25	2.8 (1.9, 3.4)	25	2.9 (2.4, 3.7)	6 (1 to 11)
Thyroid stimulating hormone (TSH) (mU/l)	26	1.6 (1.4, 2.5)	25	1.5 (1.1, 2.2)	-9 (-18 to 1)
Secondary outcomes, Urine					
Sodium (mmol/24h)	26	161.7 (132.4, 204.5)	25	184.6 (120.9, 253.0)	14 (-4 to 36)
Potassium (mmol/24h)	26	56.1 (42.0, 65.0)	25	60.4 (50.6, 68.4)	13 (1 to 26)
Chloride (mmol/24h)	26	146.4 (121.2, 183.0)	25	159.4 (108.0, 234.3)	9 (-5 to 27)
Calcium (mmol/24h)	26	5.9 (4.8, 8.0)	25	8.1 (6.3, 9.1)	24 (1 to 52)
Magnesium (mmol/24h)	26	4.2 (3.6, 5.0)	25	4.3 (3.3, 5.0)	0 (-9 to 10)
Phosphate (mmol/24h)	26	30.5 (21.6, 38.1)	25	35.2 (29.5, 42.9)	18 (9 to 28)
Osmolality (mosm/kg)	23	512.0 (406.0, 632.5)	23	670.0 (522.5, 859.0)	29 (17 to 43)
Osmole excretion (mosm/24h)	23	876.1 (687.0, 978.2)	23	1,209.0 (940.5, 1,595.8)	41 (24 to 61)
Glucose (mmol/24h)	26	0.5 (0.3, 0.6)	25	289.2 (190.8, 389.2)	68597 (56524 to 83244)
Creatinine (µmol/24h)	26	14,728.5 (12,134.8, 16,414.4)	25	15,685.2 (11,418.2, 17,679.1)	-2 (-8 to 4)
Urea (mmol/24h)	26	356.5 (261.0, 459.7)	25	384.0 (339.3, 584.5)	17 (5 to 31)
Uric acid (µmol/24h)	26	3,184.9 (2,534.4, 3,729.8)	25	4,334.0 (3,072.4, 5,143.2)	13 (5 to 23)
Citrate (mmol/24h)	26	3.1 (1.8, 3.9)	25	4.9 (3.3, 7.1)	61 (40 to 86)
Oxalate (µmol/24h)	26	507.0 (352.7, 594.1)	25	470.3 (356.4, 626.7)	4 (-12 to 22)
Sulfate (mmol/24h)	26	19.1 (13.0, 26.4)	25	24.7 (15.6, 29.8)	16 (6 to 27)
Ammonium (mmol/24h)	25	39.2 (21.0, 45.4)	24	42.2 (24.0, 50.0)	10 (2 to 19)
Bicarbonate (mmol/24h)	26	1.1 (0.6, 2.4)	25	0.9 (0.4, 1.7)	-45 (-66 to -11)
pCO2 (mmHg)	26	37.8 (34.0, 55.8)	25	38.6 (27.1, 50.0)	-14 (-32 to 8)
Venous pH	26	5.8 (5.6, 6.3)	25	5.6 (5.5, 6.1)	-4 (-7 to 0)
Total volume per 24h[d] (l)	26	1.8 (1.2, 2.5)	25	2.3 (1.4, 2.9)	12 (-2 to 27)
Titratable acid[e] (mEq/24h)	26	24.4 (17.2, 36.8)	25	33.2 (24.9, 35.8)	16 (5 to 30)
Net Gastrointestinal Alkali Absorption (NGIA)[e] (mEq/24h)	26	37.4 (26.0, 57.1)	25	49.9 (34.6, 63.6)	29 (17 to 40)
Net Acid Excretion (NAE)[e] (mEq/24h)	25	57.0 (34.3, 80.0)	24	70.7 (53.2, 83.0)	26 (16 to 36)
Secondary outcomes, Vital signs					
Systolic blood pressure	26	125.0 (118.7, 135.8)	25	122.0 (113.7, 128.7)	-2 (-9 to 5)
Diastolic blood pressure	26	80.5 (72.6, 87.2)	25	78.3 (72.3, 84.3)	-1 (-7 to 5)
Heart rate	26	70.5 (61.9, 80.8)	25	70.0 (62.3, 78.0)	-2 (-10 to 7)
Explorative outcome					
Weight	25	81.0 (75.0, 99.0)	25	78.0 (74.0, 99.5)	-1 (-1 to 0)



Extended Data Fig. 5 | Secondary and exploratory outcomes in participants with calcium kidney stones. (intention-to-treat analysis). Forest plot of the effect of empagliflozin vs placebo on secondary and exploratory outcomes. Shown are medians, with first/third quartile in brackets. The dots in the forest plot represent the treatment effect on the respective outcomes as estimated relative difference (%), derived from a generalized linear mixed effects model with a Gamma distribution and a log link function with treatment and treatment-period included as fixed effects and patient as a random intercept to account for the cross-over design. The error bars represent the associated 95% confidence intervals (CIs). **a** Number of measurements assessed after placebo treatment. **b** Number of measurements assessed after empagliflozin. **c** Derived from a generalized linear mixed effects model. **d** Total urine volume per 24 h has been added post-hoc (but before unblinding) as a secondary outcome. **e** NAE, NGIA, and Titratable acid were added post-hoc (and after unblinding) as secondary outcomes. Blood pressure in mmHg, heart rate in bpm, weight in kg.

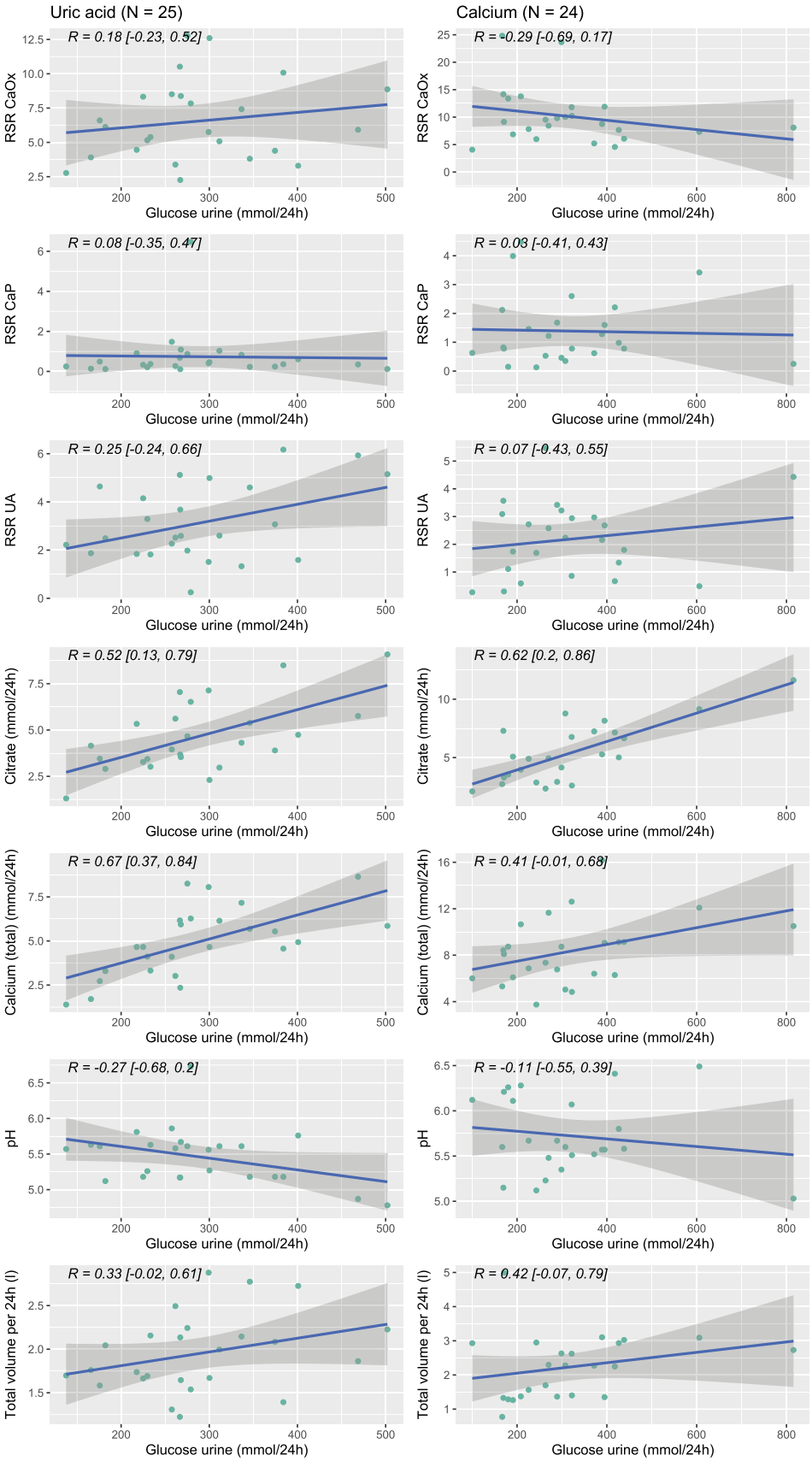
https://doi.org/10.1038/s41591-024-03330-x

Outcome	N[a]	Placebo [median (IQR)]	N[b]	Empagliflozin [median (IQR)]	Estimated relative difference [% (95% CI)][c]
Secondary outcomes, Blood					
Sodium (mmol/l)	25	139.0 (138.0, 140.0)	25	140.0 (138.0, 141.0)	0 (-1 to 1)
Potassium (mmol/l)	25	4.0 (3.9, 4.2)	25	4.0 (3.7, 4.2)	-1 (-3 to 1)
Chloride (mmol/l)	25	105.0 (103.0, 106.0)	25	105.0 (103.0, 107.0)	0 (-1 to 2)
Calcium total (mmol/l)	25	2.4 (2.3, 2.4)	25	2.4 (2.3, 2.4)	1 (0 to 1)
Calcium ionized (mmol/l)	25	1.2 (1.2, 1.2)	25	1.2 (1.2, 1.2)	-1 (-2 to 0)
Phosphate (mmol/l)	25	0.9 (0.8, 1.0)	25	1.0 (0.9, 1.1)	4 (0 to 9)
Magnesium (mmol/l)	25	0.8 (0.8, 0.8)	25	0.9 (0.8, 0.9)	7 (5 to 9)
Osmolality (mosm/kg)	25	287.0 (285.0, 290.0)	25	288.0 (286.0, 291.0)	0 (-1 to 1)
Glucose (mmol/l)	24	5.4 (4.8, 5.6)	22	5.3 (5.2, 5.5)	-2 (-6 to 3)
Albumin (g/l)	25	38.0 (36.0, 40.0)	25	38.0 (38.0, 40.0)	2 (-1 to 6)
Creatinine (µmol/l)	25	86.0 (77.0, 95.0)	25	90.0 (77.0, 105.0)	6 (3 to 8)
Urea (mmol/l)	25	5.9 (5.2, 6.6)	25	6.2 (5.3, 6.8)	5 (0 to 10)
Uric acid (µmol/l)	25	356.0 (337.0, 441.0)	25	290.0 (233.0, 323.0)	-24 (-33 to -13)
Venous pCO2 (mmHg)	25	41.0 (37.0, 46.0)	25	42.0 (38.0, 45.0)	2 (-5 to 10)
pH	25	7.4 (7.4, 7.4)	25	7.4 (7.4, 7.4)	0 (0 to 0)
Venous bicarbonate (mmol/l)	25	24.5 (23.2, 25.7)	25	24.2 (22.6, 25.8)	0 (-5 to 4)
25-OH Vitamin D (nmol/l)	25	60.0 (52.0, 74.0)	25	58.0 (46.0, 81.0)	-4 (-11 to 3)
1,25-OH Vitamin D (pmol/l)	25	109.0 (82.0, 130.0)	25	98.0 (77.0, 114.0)	-7 (-14 to 0)
Parathyroid hormone (PTH) (pg/mL)	25	38.8 (35.3, 44.3)	25	40.3 (36.1, 50.0)	8 (-8 to 27)
Fibroblast growth factor 23 (FGF23) (pg/mL)	25	48.4 (39.0, 60.2)	25	53.2 (43.9, 63.2)	14 (-1 to 31)
Triglycerides (mmol/l)	24	1.7 (1.1, 2.1)	22	1.4 (1.0, 2.1)	-10 (-19 to 0)
Haemoglobin A1c (%)	25	5.7 (5.5, 5.9)	25	5.8 (5.6, 5.9)	1 (0 to 2)
Alkaline phosphatase (U/l)	25	75.0 (59.0, 87.0)	25	76.0 (64.0, 89.0)	4 (2 to 6)
Total Cholesterol (mmol/l)	25	5.4 (4.8, 6.2)	25	5.3 (4.8, 5.8)	-4 (-8 to 1)
HDL Cholesterol (mmol/l)	25	1.2 (1.1, 1.5)	25	1.2 (1.1, 1.5)	-1 (-5 to 2)
LDL Cholesterol (mmol/l)	24	3.3 (2.9, 3.8)	24	3.1 (2.8, 3.6)	-5 (-12 to 2)
Thyroid stimulating hormone (TSH) (mU/l)	25	1.8 (1.5, 2.4)	25	1.7 (1.3, 2.1)	-10 (-17 to -3)
Secondary outcomes, Urine					
Sodium (mmol/24h)	25	177.7 (150.7, 213.2)	25	199.5 (143.9, 211.2)	-2 (-12 to 8)
Potassium (mmol/24h)	25	69.1 (49.8, 77.5)	25	68.3 (51.9, 78.2)	0 (-7 to 8)
Chloride (mmol/24h)	25	166.4 (131.1, 190.1)	25	177.4 (136.4, 203.1)	-1 (-11 to 10)
Calcium (mmol/24h)	25	5.0 (3.4, 6.4)	25	4.7 (3.3, 6.1)	-3 (-12 to 8)
Magnesium (mmol/24h)	25	3.9 (3.1, 4.9)	25	3.4 (2.9, 4.5)	-11 (-18 to -4)
Phosphate (mmol/24h)	25	36.0 (29.1, 39.5)	25	33.0 (30.6, 40.1)	-7 (-21 to 9)
Osmolality (mosm/kg)	25	671.0 (431.0, 784.0)	25	684.0 (580.0, 783.0)	11 (6 to 18)
Osmole excretion (mosm/24h)	25	1,006.1 (789.8, 1,158.3)	25	1,287.1 (1,138.2, 1,488.3)	30 (21 to 39)
Glucose (mmol/24h)	25	0.5 (0.4, 0.7)	25	267.7 (229.7, 336.5)	50688 (43057 to 59670)
Creatinine (µmol/24h)	25	14,876.7 (13,306.6, 18,034.9)	25	14,747.7 (12,612.4, 16,580.4)	-5 (-11 to 1)
Urea (mmol/24h)	25	456.1 (372.7, 479.9)	25	417.9 (349.9, 471.9)	-6 (-13 to 2)
Uric acid (µmol/24h)	25	4,358.7 (3,310.0, 4,830.9)	25	3,866.6 (3,279.0, 4,574.8)	-6 (-21 to 11)
Citrate (mmol/24h)	25	3.8 (2.4, 4.5)	25	4.2 (3.4, 5.6)	35 (19 to 54)
Oxalate (µmol/24h)	25	442.7 (396.0, 560.1)	25	451.5 (370.7, 618.5)	1 (-7 to 9)
Sulfate (mmol/24h)	25	22.4 (19.8, 30.1)	25	21.9 (18.1, 26.9)	-7 (-13 to 0)
Ammonium (mmol/24h)	25	30.2 (25.3, 33.8)	25	32.2 (23.8, 35.9)	0 (-16 to 20)
Bicarbonate (mmol/24h)	25	0.3 (0.2, 0.3)	25	0.5 (0.2, 0.7)	64 (22 to 119)
pCO2 (mmHg)	25	26.7 (22.0, 34.9)	25	30.1 (24.3, 32.7)	7 (-6 to 22)
Venous pH	25	5.3 (5.1, 5.6)	25	5.6 (5.2, 5.6)	2 (0 to 4)
Total volume per 24h[d] (l)	25	1.7 (1.3, 2.2)	25	1.9 (1.7, 2.2)	10 (1 to 20)
Titratable acid[e] (mEq/24h)	25	33.8 (27.9, 40.0)	25	31.6 (28.3, 37.5)	-8 (-21 to 7)
Net Gastrointestinal Alkali Absorption (NGIA)[e] (mEq/24h)	25	36.9 (24.4, 50.3)	25	37.5 (24.1, 52.7)	5 (3 to 7)
Net Acid Excretion (NAE)[e] (mEq/24h)	25	63.1 (52.0, 78.6)	25	64.9 (56.5, 72.1)	-4 (-9 to 1)
Secondary outcomes, Vital signs					
Systolic blood pressure	25	131.0 (124.0, 146.3)	25	130.3 (120.7, 143.7)	-2 (-8 to 6)
Diastolic blood pressure	25	83.3 (80.7, 88.7)	25	84.0 (77.0, 87.7)	-1 (-7 to 4)
Heart rate	25	69.3 (62.7, 79.3)	25	70.7 (63.3, 80.0)	1 (-8 to 11)
Explorative outcome					
Weight	25	88.5 (78.0, 97.5)	25	88.0 (77.5, 96.0)	-1 (-1 to 0)



Extended Data Fig. 6 | Secondary and exploratory outcomes in participants with UA kidney stones (intention-to-treat analysis). Forest plot of the effect of empagliflozin vs placebo on secondary and exploratory outcomes. Shown are medians, with first/third quartile in brackets. The dots in the forest plot represent the treatment effect on the respective outcomes as estimated relative difference (%), derived from a generalized linear mixed effects model with a Gamma distribution and a log link function with treatment and treatment-period included as fixed effects and patient as a random intercept to account for the cross-over design. The error bars represent the associated 95% confidence intervals (CIs). **a** Number of measurements assessed after placebo treatment. **b** Number of measurements assessed after empagliflozin. **c** Derived from a generalized linear mixed effects model. **d** Total urine volume per 24 h has been added post-hoc (but before unblinding) as a secondary outcome. **e** NAE, NGIA, and Titratable acid were added post-hoc (and after unblinding) as secondary outcomes. Blood pressure in mmHg, heart rate in bpm, weight in kg.

https://doi.org/10.1038/s41591-024-03330-x



Extended Data Fig. 7 | Correlation of urinary glucose with urinary lithogenic parameters. Plots showing non-parametric Spearman correlation between urinary glucose and a selected subset of primary and secondary outcomes in patients treated with empagliflozin. The fitted line (blue line) and associated 95 % confidence interval (grey shadowed area) are shown along with the R, Spearman correlation coefficient and the associated 95% confidence interval (CI) in brackets. N, number of patients assessed.

https://doi.org/10.1038/s41591-024-03330-x

Extended Data Table 1 | Generalized Linear Mixed Model (GLMM) Results for Primary Outcomes of the SWEETSTONE trial

Calcium kidney stone formers			
RSR CaOx	**Estimate**	**95% CI[1]**	**p-value**
FIXED EFFECTS	**exp (coef)**		
Received treatment			
Placebo	—	—	
Empagliflozin	0.99	[0.85, 1.16]	0.921
Treatment period			
First period	—	—	
Second period	1.03	[0.88, 1.20]	0.724
RANDOM EFFECTS	**SD**		
Patient	0.32		
Residual	0.33		
RSR CaP	**Estimate**	**95% CI[1]**	**p-value**
FIXED EFFECTS	**exp (coef)**		
Received treatment			
Placebo	—	—	
Empagliflozin	0.64	[0.52, 0.79]	<0.001
Treatment period			
First period	—	—	
Second period	1.03	[0.83, 1.27]	0.784
RANDOM EFFECTS	**SD**		
Patient	0.80		
Residual	0.50		
RSR UA	**Estimate**	**95% CI[1]**	**p-value**
FIXED EFFECTS	**exp (coef)**		
Received treatment			
Placebo	—	—	
Empagliflozin	1.32	[0.86, 2.04]	0.204
Treatment period			
First period	—	—	
Second period	1.03	[0.67, 1.59]	0.890
RANDOM EFFECTS	**SD**		
Patient	0.00		
Residual	0.68		
[1]CI = Confidence Interval			

UA kidney stone formers			
RSR CaOx	**Estimate**	**95% CI[1]**	**p-value**
FIXED EFFECTS	**exp (coef)**		
Received treatment			
Placebo	—	—	
Empagliflozin	0.92	[0.81, 1.05]	0.236
Treatment period			
First period	—	—	
Second period	0.98	[0.86, 1.12]	0.783
RANDOM EFFECTS	**SD**		
Patient	0.38		
Residual	0.29		
RSR CaP	**Estimate**	**95% CI[1]**	**p-value**
FIXED EFFECTS	**exp (coef)**		
Received treatment			
Placebo	—	—	
Empagliflozin	1.08	[0.84, 1.38]	0.559
Treatment period			
First period	—	—	
Second period	0.66	[0.52, 0.85]	0.001
RANDOM EFFECTS	**SD**		
Patient	0.76		
Residual	0.53		
RSR UA	**Estimate**	**95% CI[1]**	**p-value**
FIXED EFFECTS	**exp (coef)**		
Received treatment			
Placebo	—	—	
Empagliflozin	0.70	[0.56, 0.88]	0.002
Treatment period			
First period	—	—	
Second period	1.23	[0.98, 1.54]	0.081
RANDOM EFFECTS	**SD**		
Patient	0.33		
Residual	0.39		
[1]CI = Confidence Interval			

Generalized Linear Mixed Model (GLMM) results for the primary analysis of Calcium oxalate (CaOx), Calcium phosphate (CaP) and uric acid (UA) relative supersaturation (RSR) values measured after treatment with placebo and empagliflozin in participants with calcium kidney stones (left panel) and uric acid (UA) kidney stones (right panel). The GLMM was fitted with a Gamma distribution and a log link function to account for the skewed, non-normal distribution of the data. Treatment and treatment-period were included as fixed effects, whereas patient was included as a random intercept. Analysis of primary outcomes was accompanied by p-values and hypothesis testing with a two-sided significance level of 0.02. The analysis was performed on the per protocol (PP) set. Sample size of the per protocol set was n=25 for participants with calcium kidney stones and n=21 for participants with UA kidney stones. exp (coef), exponential coefficient estimates. The exact p-value for treatment effect for RSR CaP in calcium kidney stone formers is = 0.0000315086.

nature portfolio

Corresponding author(s): Daniel G. Fuster

Last updated by author(s): Sep 24, 2024

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection besides electronic implementation of case report forms using a dedicated electronic data capturing system (secuTrial®).
Data analysis	All statistical analyses were conducted using R, version 4.2.3 on a Windows computer [Windows 10 x64 (build 19042); x86_64-w64-mingw32/ x64 (64-bit)]. No custom code was used for the analysis of this trial. All packages used for the analysis (listed in Supplementary Information item # 4.) are available from the Comprehensive R Archive Network via R. Sample size calculation was performed in Stata (Release 16.1). Code availability: The detailed code used to generate the findings of the present study is available from the corresponding author (daniel.fuster@unibe.ch) upon request from qualified researchers in this field. Researchers are asked to provide information on their affiliation and experience in this field and how they intend to use the code. Timelines can vary depending on the type of request, but the code will be provided within a maximum of 3 months.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The trial has been registered on clinicaltrials.gov (NCT04911660, https://clinicaltrials.gov/study/NCT04911660) and the Swiss National Clinical Trials Portal (SNCTP000004272, https://www.kofam.ch/en/snctp-portal/searching-for-a-clinical-trial/196655/study/54893).
Data availability: The study protocol and statistical analysis plan are provided as Supplementary Information items # 1 and # 2. The full dataset of de-identified individual participant data and the data dictionary that underlie the results reported in this article are available from the corresponding author (DGF) for research purposes. Data sharing will be possible from publication onwards. Proposals with specific aims and an analysis plan should be directed to the corresponding author (daniel.fuster@unibe.ch). Timelines can vary depending on the type of request, but data will be provided within a maximum of 3 months.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	We included both female and male participants. 75% of participants were male (sex), 25% were female (sex) which is consistent with the published epidemiology of kidney stone disease. No sex-based analyses have been performed a priori. No post-hoc sex-based analysis has been performed as the study unfortunately does not have a big enough sample size to perform valid analysis on differences between sexes. Gender data was not collected for this study.
Reporting on race, ethnicity, or other socially relevant groupings	We did not perform categorization according to socially constructed variables. Ethnicity was reported as provided by participants.
Population characteristics	Characteristics of the study population were: mean age was 50.9 (SD 14.5) years, BMI was 28.4 (SD 5.3) kg/m2, Haemoglobin A1c 5.6 (SD 0.4) %, 21 (40%) had hypertension, mean eGFR was 90.0 (25/75th percentiles: 78.0, 91.0) mL/min per 1.73 m2 BSA. 40 (75%) were male, 13 (25%) were female and all participants were of European descent. Total median number of past stone events was 4.0 (interquartile range:2.0, 7.0), with a median of 3.0 (interquartile range: 2.0, 4.0) stone events occurring within 10 years prior to randomization.
Recruitment	Participants with a past history of calcium containing or uric acid containing kidney stones were screened and recruited at the Department of Nephrology and Hypertension, Inselspital, Bern, Switzerland. After approval by the ethics commitee and competent authority, the study was announced to the Nephrology and Urology staff at Inselspital, Bern, Switzerland. If available medical history indicated that an individual may be eligible for study participation, the individual was informed in detail about the study by the study investigators. Given the nature of the study (crossover design) we do not expect self-selection bias to substantially impact applicability of results. Eligible patients were ≥18 and <75 years old, non-diabetic (HbA1c <6.5%, no known diagnosis of diabetes, no antidiabetic medication), and had experienced ≥1 kidney stone event(s) containing ≥80% of calcium or ≥80% of UA. We excluded patients with secondary causes of kidney stones and patients taking drugs interfering with kidney stone formation. No payment or compensation was given to study participants.
Ethics oversight	The trial was approved by the responsible ethics committee of the Canton of Bern (Kantonale Ethikkommission), Switzerland and also by the competent authority (CA) Swissmedic.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was calculated using the following assumptions and methods: 1. Taking into account the reduction observed in kidney stone event rate in pooled phase I-III empagliflozin trials 14, we extrapolated reductions of 30 – 60 % in urinary supersaturations (RSRs) with empagliflozin compared to placebo. 2. The magnitude of urine RSR reduction closely paralleled the decrease in stone events in patients with calcium kidney stones randomized to a dietary intervention for recurrence prevention. 3. A reduction of ~15% in urinary calcium oxalate supersaturation has been found to confer a ~12% risk reduction of a recurrent stone event

in a post-hoc analysis of a previous RCT in patients with calcium kidney stones (Ferraro et al., doi: 10.1016/j.juro.2018.06.029). There are no comparable RCT data available in patients with uric acid (UA) kidney stones. We considered a 15 % reduction in urinary RSRs associated with a 12 % reduction in stone events as the lower limit of a clinically meaningful prophylactic benefit of empagliflozin treatment, and hence chose a cut-off of a 15 % reduction in any of the three urine RSRs CaOx, CaP and UA as the target treatment effect for the sample size calculation.
4. Sample size calculation was based on the primary outcomes (urine RSRs) of intraindividual comparisons within the different groups with a crossover design, based on a paired means test.
5. To account for the multiple (3) primary endpoints, significance level was adjusted and fixed at 0.02 (two sided) with a power set to 85 %.
6. A common standard deviation of 20 % and an intraindividual correlation of 0.5 (crossover design) was assumed.
7. As all assumptions and processes were identical between both patient populations (calcium and UA kidney stone formers), sample size calculation was performed in the same way for both populations (sub-trials).
8. Sample size calculation was performed with the previously mentioned assumptions using Stata (Release 16.1)
9. Sample size was reassessed by calculating the observed standard deviations using blinded data after 50% of patients completed the trial. This resulted in a sample size of 23 patients per group (46 patients in total).

Data exclusions

The primary analysis (of all primary and secondary outcomes) was performed on the per-protocol set (PP), e.g., all subjects in the full analysis set (FAS) who did not have any protocol deviations that could confound the interpretation of analyses (violation of eligibility criteria, non-compliance with treatment or assessment schedule). The complete data including all subjects, independent of protocol violations, the full analysis set (FAS) was used for an additional pre-specified intention-to-treat (ITT) analysis for the primary and secondary outcomes performed (Extended Data).
53 patients were enrolled and randomized (28 patients with calcium kidney stones, 25 patients with uric acid kidney stones). For patients with calcium kidney stones, 3 patients discontinued the study early (one for personal reasons, 2 due to loss of follow-up). In the group of patients with uric acid kidney stones, 3 patients followed an inverted treatment sequence due to erroneously picking the wrong starting bottle and one patient followed a long washout period between treatment with placebo and empagliflozin.
Consequently, for the PP analysis, 25 patients with calcium stones and 21 patients with uric acid stones were included.

Replication

No replication of the data was performed due to the nature of the study design: randomized crossover trial.

Randomization

Randomization was performed separately for patients with calcium and uric acid kidney stones, respectively, as if they were two independent trials (sub-trials), assigning participants in a 1:1 ratio to a specified treatment sequence (start with empagliflozin 25mg followed by placebo once daily or in the reverse order). Randomization lists (randomly varying block sizes of 2/4) were generated by an independent statistician at CTU Bern and implemented during manufacturing of the investigational medicinal product (IMP). Allocation was concealed using sequentially coded drug bottles that were otherwise identical. Empagliflozin and placebo were provided in identically looking bottles containing identically looking tablets. Assignment to intervention was implemented by the study nurses according to generated randomization lists.

Blinding

Both investigators and patients were blinded to group allocation. Blinding remained in place until the statistician at CTU Bern coded the primary analysis of the primary and secondary outcomes and produced a dummy report of the primary analysis using a randomly generated group variable/treatment sequence. The true group variable was revealed after completion of the dummy report. The dummy report was then replaced by the final report, which underwent quality control by a second statistician.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration

NCT04911660.

Study protocol

The full study protocol is available in the Supplementary Information.

Data collection

The study was performed at the Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Switzerland. Recruitment started in June 2021, first patient enrollment was on 25th of August 2021 and last enrollment was on the 9th of December 2022. The last patient's last study visit took place on March 30 2023, the database was locked May 30 2023.

Outcomes

The three primary outcomes were the urine relative supersaturation ratios (RSRs) for CaOx, CaP and UA to assess effect of empagliflozin 25mg treatment on RSRs vs placebo. RSRs were calculated from measures obtained from 24h urines by the the use of the program EQUIL2. Each of the primary outcomes has been assessed separately due to them reflecting different mechanisms.
Pre-specified secondary outcomes included blood and 24-h urine parameters relevant to kidney stone formation and to a possible effect of the study drug. Additional secondary outcomes were vital signs such as blood pressure, heart rate. Body weight was included as an exploratory endpoint. Net gastrointestinal alkali absorption (NGIA), urine titratable acidity (TA) and renal net acid excretion (NAE) derived from pre-specified 24h urine parameters were included post-hoc.
Safety outcomes included vital signs, serious adverse events, pre-specified adverse events of special interest (such as hepatic injury, decreased renal function, metabolic acidosis, including ketoacidosis and diabetic ketoacidosis (DKA)).

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.