Empagliflozin and the Risk of Nephrolithiasis

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Aims: Nephrolithiasis is a common disease, estimated to affect 10% of the US population. In addition to pain, often severe, it can lead to urinary tract infections and acute kidney injury, while contributing to health care costs from emergency room visits and follow-up interventions necessary to relieve stone burden. Type 2 diabetes (T2D) is a well-known risk factor for nephrolithiasis. Recently in an observational study of patients with T2D, use of sodium-glucose transport protein 2 (SGLT2) inhibitors as glucose lowering agents was associated with a 49% lower risk of nephrolithiasis when compared with use of glucagon like peptide 1 (GLP-1) receptor agonists. We examined, prospectively, the association between renal stone disease and the use of the SGLT2 inhibitor empagliflozin, using existing data from randomized clinical trials.

Methods: Pooled data from 15,081 patients with T2D treated with empagliflozin (10,177) or placebo (4,904) from 20 phase I-IV randomized, placebo-controlled trials including the large cardiovascular outcome trial, EMPA-REG OUTCOME, were included in this analysis. Incident urinary tract stone events were captured using a pre-defined collection of MedDRA terms: nephrolithiasis, renal colic, ureterolithiasis, calculus bladder, calculus urinary, calculus urethral, and nephrocalcinosis (MedDRA version 22.1). A sensitivity analysis used a narrower definition by excluding the terms renal colic and nephrocalcinosis. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated using the relative risk estimate stratified by study.

Results: The median exposure to study drug was 543 (placebo) and 549 (empagliflozin 10 or 25 mg) days We found that a total of 183 patients experienced an incident urolithiasis during follow-up (79 in placebo, 104 in pooled empagliflozin) yielding annual incidence rates of 1.01 versus 0.63 events per 100 patient years in placebo and empagliflozin, respectively. All but one event occurred in patients with no prior history of urinary tract stones. The IRR was 0.64 (95% CI 0.48, 0.86), in favor of empagliflozin. In the sensitivity analysis, now restricted to nephrolithiasis, ureterolithiasis, calculus bladder, calculus urinary, and calculus urethral, the results were similar (IRR, empagliflozin vs. placebo, 0.62 [95% CI 0.45, 0.85]).

Conclusion: As compared to placebo, use of empagliflozin was associated with an approximate 40% reduction in the risk of urolithiasis in patients with T2D. Alterations in lithogenic profile of the urine (including dilutional effects) of potential stone formers after SGLT2 inhibition may explain this finding. Based on these initial observations, mechanistic studies to elucidate the mediator(s) of this seemingly protective effect and dedicated randomized prospective clinical trials appear warranted in patients with renal stone disease. As with follow-up SGLT2 inhibitor investigations conducted in patients with heart failure and chronic kidney disease, such trials should include individuals who do not have T2D.

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