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REVIEW

Risk of urinary stone formation associated to proton pump inhibitors: A systematic review and metanalysis

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Summary

Objective: *Proton pump inhibitors are widely used as treatment of acid-related disorders. They are considered safe although their long-term use has been associated with some adverse effects including an increased propensity for urinary calculi formation. The aim of this study was to systematically review available data from studies evaluating the association of PPIs and nephrolithiasis*

Materials and methods: *We searched two electronic databases (PubMed and EMBASE) for cohort studies or case-control studies evaluating the relationship between treatment with proton pump inhibitors and the risk of stone formation published up to 31 October 2022. The overall association of PPIs and urinary calculi was analyzed using a random effects model (RevMan5). The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.*

Results: *A total of 550 studies were retrieved; 7 were selected by title and abstract screening; after removal of duplicates, 4 records were evaluated by full-text examination. An additional study was retrieved by handsearching the references included in screened studies. In the unadjusted analysis, the odds of urinary calculi were greater in subjects taking PPIs compared to controls (unadjusted OR = 2.10, 95% CI 1.74-2.52, p < 0.00001). The pooled odds ratio of two case-control studies confirmed that use of PPIs increased the odds of urinary calculi compared with non-use (OR 2.44, 95% CI 2.29 to 2.61). Pooled analysis of three cohort studies evaluating incident nephrolithiasis showed an overall hazard ratio estimate of 1.34 (95% CI = 1.28-1.40). One study found lower urinary citrate and urinary magnesium levels in subjects exposed to PPIs. The Newcastle-Ottawa Quality Assessment Scale scores ranged between 6 and 8.*

Conclusions: *PPIs showed an association with urinary calculi in patients included in the studies included in this review. If these data will be confirmed in adequately powered randomized trials, clinicians may consider limiting the long-term use of PPIs, to avoid unnecessary prolongation of treatment. Urinary magnesium and citrate should be evaluated in renal stone forming patients taking PPIs to supplement their intake when requested.*

KEY WORDS: *Proton pump inhibitors; Urinary calculi; H2-receptor blockers; Magnesium; Citrate.*

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INTRODUCTION

Proton pump inhibitors (PPIs) reduce the gastric acid production by irreversibly blocking the H^+/K^+ ATPase, also known as the proton pump, located in the parietal cells of the gastric wall. PPIs are widely used for the treatment of *gastroesophageal reflux disease* (GERD), *Zollinger-Ellison* syndrome, erosive esophagitis, duodenal or gastric ulcers

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including those caused by *non-steroidal anti-inflammatory drugs* (NSAIDs), and for the eradication of *Helicobacter pylori* in combination with antibiotics.
They have emerged as first-line treatment of acid-related disorders, traditionally treated with *histamine type 2 receptor antagonists/blockers* (H2RAs), that inhibit gastric acid secretion by blocking the histamine stimulation of gastric parietal cells (1).
PPIs are considered safe, though their long-term use has been associated with some serious adverse effects including community acquired pneumonia (2), risk for osteoporosis-related fractures (3, 4), enteric infection (5), Clostridium difficile-associated diarrhea (6, 7), myocardial infarction (8), chronic kidney disease (9), Alzheimer's dementia (10), and hypomagnesemia (4).
In 2019, the analysis of post-marketing safety data from *FDA Adverse Event Reporting System* (FAERS) suggested an increased propensity for nephrolithiasis in subjects taking proton-pump inhibitors (11). Two studies, presented as congress communications but never published as full-text reports, demonstrated that the use of PPIs and H2 blockers was associated with an increased risk of kidney stones (12, 13). More recently, three articles were published, evaluating in three different large population from the United States (N = 2) and Korea (N = 1) the risk of stone formation in patients taking PPIs (14-16). The aim of this study was to systematically review the data from studies evaluating the association of PPIs and nephrolithiasis and, where possible, to perform a pooled analysis of the prevalence of urinary stone disease in patients taking PPIs. Particular attention was devoted to the assessment of the risk of bias in the studies included in the analysis.

Materials and methods

Protocol and registration
The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (17). It was registered on the PROSPERO platform as CRD42022375951.

Types of studies
We considered articles written in English, reporting cohort studies, case-control studies and randomized controlled trials evaluating the relationship between the treatment with PPIs or H2RAs and the risk of kidney stone formation, without time constraints.

Types of patients
Adult participants (> 18 years) of both sexes were involved irrespective of their age or ethnicity.

Types of interventions
Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs).

Outcomes
The main outcome considered for this review was the assessment of the prevalence rate of urinary stones in subjects taking PPIs compared to those not taking this treatment. A secondary outcome was the comparison of renal stone prevalence between subjects taking compared to those non-taking H2Ras.

Search strategy
Two electronic databases (PubMed and EMBASE) were searched for articles published up to 31 October 2022. Search was performed using the following string based on MeSH terms: (proton pump inhibitors OR histamine H2 antagonists OR omeprazole OR esomeprazole OR lansoprazole OR dexlansoprazole OR pantoprazole OR rabeprazole) AND urinary calculi. Relevant data were also hand searched by browsing various sources (e.g., reference lists from reviews and study reports, congress abstracts, clinical trial registers such as www.clinicaltrials.gov, www.clinicaltrialsregister.eu, etc.).

Data collection and analysis

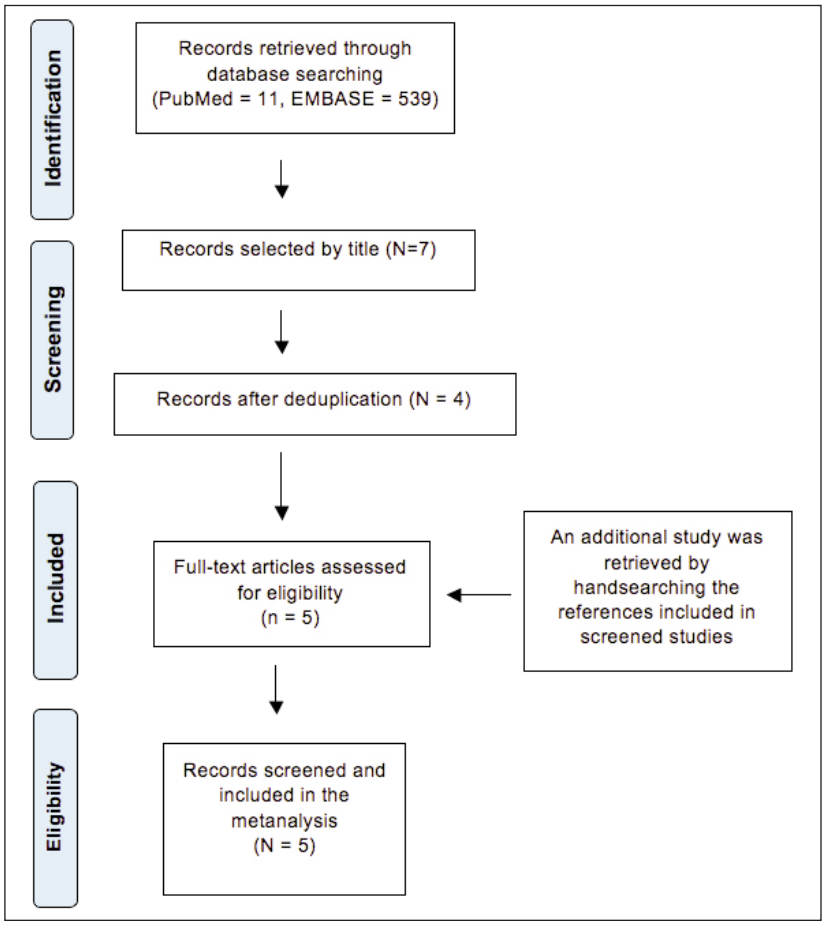
Selection of studies
Title and abstract screening to exclude documents that did not meet the inclusion criteria was performed independently by two authors. Duplicate references were deleted. Full texts were downloaded for full-text screening and to extract relevant information. Controversies were resolved by a third researcher.
A PRISMA flow diagram was drawn to illustrate the results of study selection process (Figure 1).

Data extraction
Data extraction was conducted by four authors using a standardized form. The following information was obtained from each study: author(s), publication year, study design, population, intervention, prevalence of stone disease. In case of missing or insufficient information, we considered the impact of missing data on the meta-analysis results.

Risk of bias analysis
Two authors independently performed the assessment of quality of the included studies using the *Newcastle-Ottawa Scale* (NOS), a risk of bias assessment tool for observational studies that is recommended by the Cochrane Collaboration (18). The NOS evaluates three quality parameters (selection, comparability, and outcome) divided across eight specific items. It can be scored a maximum of one 'star' for each item within the 'Selection' and 'Exposure/Outcome' categories and a maximum of two 'stars' for 'Comparability'. The maximum NOS score is 9. A study with score ranging between 7 and 9 is rated as being high quality, between 4 and 6 as medium quality, and between 0 and 3 as low quality. The overall evaluation of the quality of pooled evidence was performed according to GRADE criteria.
Publication bias assessment by Funnel plot analysis was performed in the presence of at least 4 studies. If a potential reporting bias was suspected, the Begg/Mazumdar and Egger's regression tests were used to assess the significance of funnel plot asymmetry and potential publication bias.

Statistical analysis
Statistical analysis was performed using the RevMan5

Figure 1.
Flow diagram.



software. Dichotomous data (presence/absence of stone disease) and number of subjects were extracted to calculate *odds ratios* (OR), *hazard ratios* (HR), *confidence intervals* (CI), and Z statistics. Pooled analyses were performed using the generic inverse-variance random-effects model. Random effect model was used due to high heterogeneity of included studies.

Assessment of heterogeneity
Heterogeneity was assessed by I^2 statistics, reported with 95% CIs, and interpreted as of lesser importance (≤ 40%), moderate (30%-60%), substantial (50%-90%) or considerable (≥ 75%), according to Cochrane criteria.

Results

We retrieved 550 records, 539 from EMBASE and 11 from Medline.
After title and abstract screening of retrieved records and deduplication, we selected 7 articles. After full text reading, we considered 4 articles for meta-analysis. An additional study was retrieved by handsearching the references included in screened studies.

Description of studies

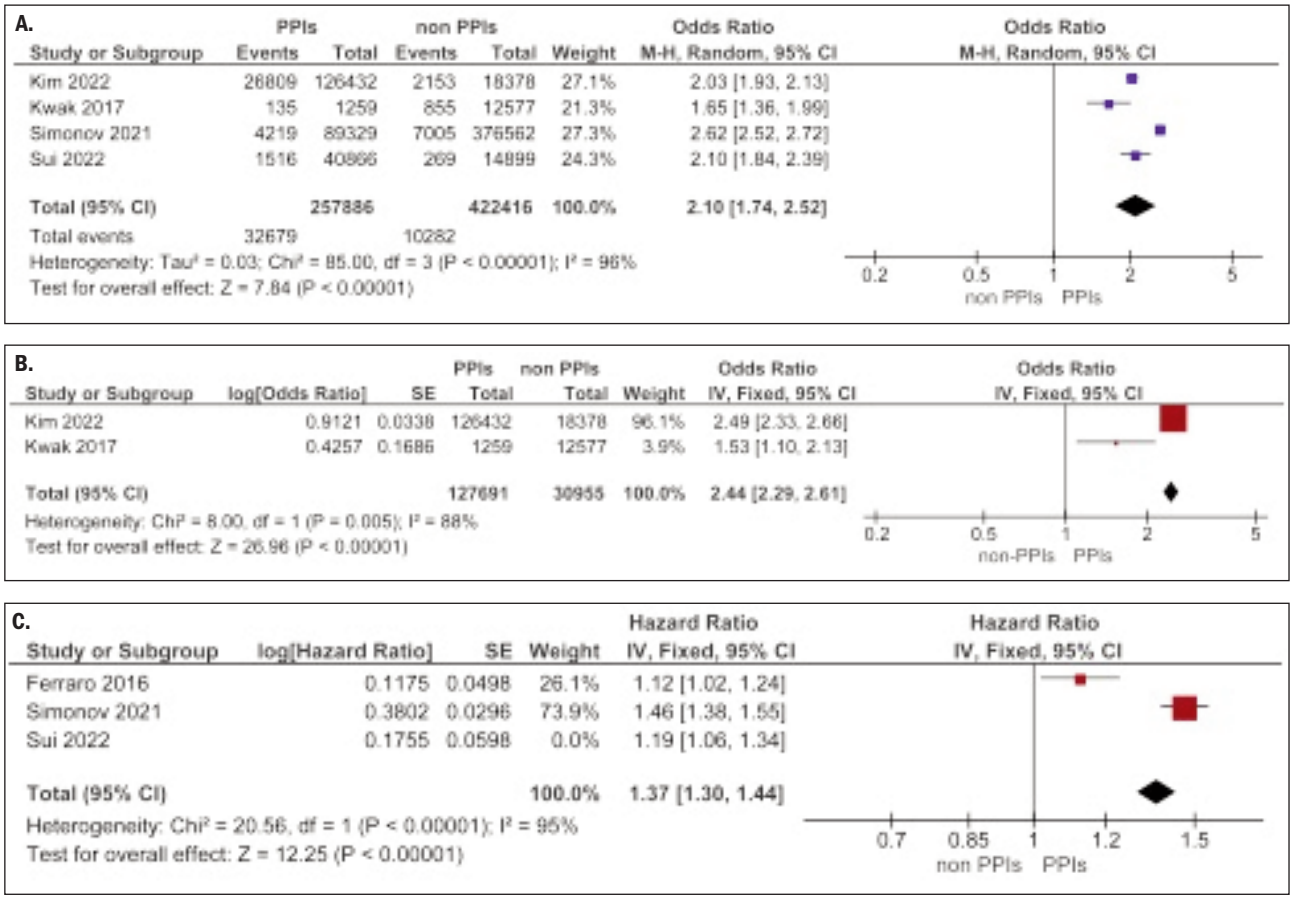
A description of the selected studies, including retrieved data, is shown in the ***Supplementary Materials***.

Ferraro et al. (12) evaluated cohorts of health professionals participating to the *Health Professionals Follow-up Study* (HPFS), and *Nurses' Health Study* (NHS) I and II (n = 187.330). Incident stone episodes were prospectively evaluated during a follow up > 10 years. Urinary excretion risk factors for stone formation was evaluated in a subgroup of 6.520 participants.
Kwak et al. (13) evaluated a cross-sectional sample of the US population in the context of the *National Health and Nutrition Examination Survey* (NHANES), providing a variety of health and nutrition measurements in men and non-pregnant women age > 20 (n = 13836).
Kim et al. (14) conducted a nested case-control study using the *National Health Insurance Service-National Health Screening Cohort in Korea*, that included unselected men and women from the general population, older than 40 years. Renal stone formers and controls were randomly matched for age, sex, income, and region of residence. A total of 28.962 urolithiasis participants and 115.848 control participants were enrolled.
Simonov et al. (15) retrospectively evaluated incident stones in participants to the *Women Veterans Cohort Study* (WVCS), including men and women veterans who were discharged from military service as of October 2001 and who elected to utilize the Veteran Administration medical care (n = 465.891). Subjects with diagnosis of nephrolithiasis or a history of PPI usage prior pre-observation were excluded from the study. A subset of subjects taking PPIs or not (86.264 in each group) were considered for a propensity-matched model. The median observation time was 4 years. A limitation of this study was the younger age of the population, which limited the generalizability of the study findings to other populations.
Sur et al. (16) evaluated the records of the database of clinical data *Vanderbilt Research and Synthetic Derivative*. Medical center electronic health records from 1993 to 2020 were obtained for over three million patients.
The researchers identified a cohort of 55.765 adults with GERD, who were PPI naïve and had no history of nephrolithiasis. Incident nephrolithiasis was retrospectively evaluated using the first PPI use as the date of first GERD diagnosis. The median follow up was 3 years. Urinary 24-hour risk factors for stone formation were evaluated in a subset of 593 patients with GERD.

Quantitative analysis

Unadjusted data from four studies showed that PPIs use was significantly associated with urinary calculi (OR = 2.10, 95% CI 1.74-2.52, p < 0.00001) (Figure 2A). The study of *Ferrero and coworkers* was excluded from this analysis because it was presented as an abstract lacking crude data to be used for quantitative analysis. No addi-

Figure 2.
A – Rates of urinary calculi in patients taking PPIs and controls (unadjusted data); B – pooled odds ratios of case-control studies investigating urinary calculi in patients taking PPIs compared to controls; C – pooled hazard ratios of incident nephrolithiasis in patients on PPIs treatment compared to controls. Data are adjusted for comorbidities and concurrent medications. Diamonds on the right side of the no-effect line indicate greater odds and hazard ratios in patients treated with PPIs compared to controls placebo. Odds ratio and hazard ratio with 95% confidence intervals and heterogeneity statistics (I^2) are shown.



tional information was obtained from the Authors.
When pooled analyses were performed using data adjusted for comorbidities and concurrent medications, the association between PPIs and urinary calculi remained significant. The pooled odds ratio of two case-control studies confirmed that the use of PPIs increased the odds of urinary calculi compared with non-use (OR 2.44, 95% CI 2.29 to 2.61) (Figure 2B). The pooled hazard ratios of three studies evaluating incident nephrolithiasis showed an overall pooled HR estimate of 1.34 (95% CI = 1.28-1.40) (Figure 2C). Considerable heterogeneity was found in all analyses (I2 = 96%, 92%, and 88% respectively).

Length and dose of treatment

Results concerning the effect of the duration of PPI treatment on the risk of stone formation are controversial. *Kim et al.* (14) found higher odds for urolithiasis when treatment with PPI was extended to 365 days or longer (OR 2.32) compared to shorter periods (30-364 days: OR 1.97, 1-19 days: OR 1.65). This confirms the finding of *Kwak et al.* (13) who reported higher rates of urinary calculi in subjects taking PPIs for more than 5 years. Conversely, *Ferraro et al.* (12) observed that HRs were independent of duration of use. *Simonov et al.* (15) observed that higher doses of PPIs were associated with an increased risk of kidney stones formation.

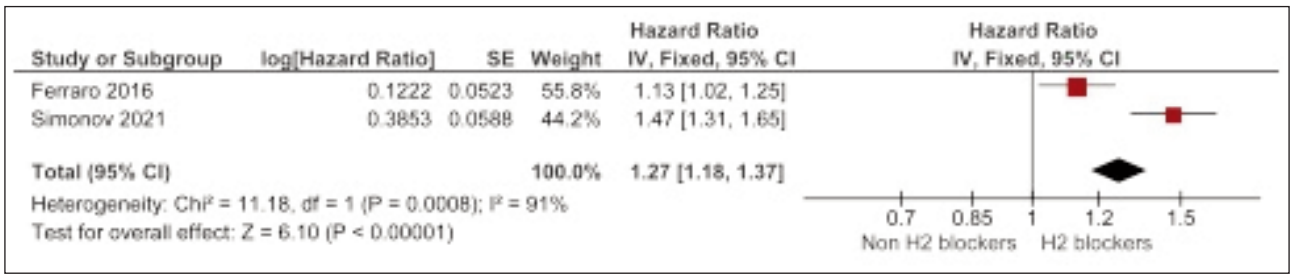
H2 blockers

Ferraro et al. (12) found that the use of H2 blockers is also associated to higher risks of renal stone formation (HR 1.13, 95% CI 1.02, 1.24, p-value = 0.02). *Simonov et al.* (15) confirmed an increased risk for renal stone upon treatment with H2 blockers (adjusted HR, 1.47; CI 1.31-1.64). Pooled hazard ratios of the two studies evaluating incident nephrolithiasis showed an overall pooled HR estimate of 1.27 (95% CI = 1.18-1.37) (Figure 3).
Heterogeneity was 91%. *Kwak et al.* (13) reported greater odds for combined PPI/antacid use (OR: 2.03, 95% CI: 1.28-3.23, p = 0.049) and combined PPI/H2 blocker use (OR: 3.18, 95% CI: 1.12-9.07, p = 0.031).

Urinary risk factors

Sur et al. (16) observed significantly lower mean levels of urinary citrate and urinary magnesium in the PPI-exposed group compared to non-exposed subjects. *Ferraro et al.* (12) found lower urinary excretion of calcium in PPI users.

Figure 3.
Pooled hazard ratios of incident nephrolithiasis in patients on treatment with H2-blockers compared to controls. Diamonds on the right side of the no-effect line indicate greater hazard ratios in patients treated with H2-blockers compared to controls placebo. Hazard ratio with 95% confidence intervals and heterogeneity statistics (I^2) are shown.



Risk of Bias, quality of the evidence
According to the quality assessment of NOS, all the studies were characterized by high quality, with scores ranging between 6 and 8 (***Supplementary Materials***).
According to GRADE criteria, the quality of the evidence is low. Downgrading criteria are the observational design of the studies, the presence of moderate risk of bias and the inconsistency due to heterogeneity. The large magnitude of effect (Odds ratio > 2) was considered as criterion for upgrading.
Publication bias assessment by Funnel plot analysis resulted in no statistically significant asymmetry (P = 0.190, Egger's test; P = 0.497, Begg's test). The funnel plot is shown in the Supplementary Materials section. The "*trim-and-fill*" strategy imputed zero missing studies.

Discussion

Urinary stone disease has a complex pathogenesis involving different aspects of the metabolism and depending on the chemical composition of the stones. A non-negligible fraction of cases is caused by the intake of different kinds of drugs that can lead to the formation of stones containing amounts of the same drugs. Other drugs cause alterations of different metabolic steps, resulting in the modification of the urinary excretion of risk factors for stone formation (19).
The potential risk of kidney stone formation in subjects treated with PPIs is still debated, and the factors causing an increased risk have not been fully elucidated. In general, PPI-related increases of gastric pH may lead to deficiencies of minerals (iron, calcium and magnesium) and vitamins (B12 and C) which need a low gastric pH for their absorption and bioavailability (20). However, a specific effect of long-term PPI treatment on mineral metabolism is the reduction of serum magnesium levels resulting from its reduced intestinal absorption. Intestinal absorption of magnesium depends on both active transcellular transporters and passive paracellular absorption mediated by claudins. Active transportation of magnesium through enterocyte cell membranes is mainly mediated by transient receptor potential melastatin 6 and 7 (TRPM6 and TRPM7), whose activity is regulated by intracellular magnesium and pH levels whereby a more acidic milieu increases TRPM6 activity (21). PPIs may alter transporter transcription or channel function by increasing the luminal pH, thus affecting hydrogen proton secretion. The decrease of TRPM6 and TRPM7 activity results in decreased magnesium absorption (22). In vitro studies suggested the concomitant inhibition of passive magnesium absorption by PPIs (23). The extent of the decrease of intestinal magnesium absorption during PPI treatment seems to be minor, but it may cause long-term cumulative deficiency. The effect of PPIs on magnesium metabolism is also enhanced by other medications acting on magnesium metabolism, such as loop diuretics (24). Severe hypomagnesaemia can manifest with musculoskeletal, neurological, or cardiac arrhythmic symptoms, but milder forms may remain undetected (25). Hypomagnesemia induced by PPIs is often associated with multiple electrolyte disturbances, including hypocalcemia, hypophosphatasemia, and hypokalemia. Low serum magnesium levels interfere with calcium-sensing receptors suppressing *parathyroid hormone* (PTH) secretion and increasing organ resistance to PTH by inhibiting receptor binding and intracellular signaling (26). Hypoparathyroidism results in turn in low serum and urinary calcium levels. Hypomagnesemia also causes hypokalemia by inducing kaliuresis (27). Reduced intestinal absorption of magnesium is balanced by changes in renal reabsorption of magnesium resulting in a reduction of urinary magnesium. The reduction of urinary excretion of both calcium and magnesium during PPI treatment may have conflicting effects on the overall risk of kidney stone formation, because the reduced urinary calcium excretion decreases urinary saturation with respect to calcium oxalate and calcium phosphate, but the reduced magnesium excretion increases the risk of stone formation due to the decrease of urinary inhibitory activity of crystallization. Studies focused on the effect of PPIs on the urinary excretion of citrates, which are potent crystallization inhibitors, whose decline in the urine can increase the risk of kidney stone formation (28-30). The urinary levels of citrate are reduced in conditions of acidosis, which induces an increase in the metabolism of citrate in the renal proximal tubule cells with a consequent decreased excretion of citrate in the urine (31). An initial study performed on a small sample of subjects treated for a short time with omeprazole did not demonstrate changes in the daily urinary electrolyte output and urine pH in response to ammonium chloride load (32). However, a case report described metabolic acidosis associated with hypomagnesaemia in a patient receiving omeprazole (33). A recent study in a larger population of

renal stone patients receiving PPIs showed that patients tended to show decreased citrate levels (28). This finding was explained by the net gastric acid loss due to reduced gastric acid production by proton pump inhibition, resulting in reduced bicarbonate generation and decreased renal excretion of citrate. In this study, the decrease of urinary citrate was not associated to a decrease of urinary magnesium in stone patients taking PPIs. On the contrary, *William et al.* demonstrated reduced urinary magnesium in renal stone patients taking PPIs but a non-statistically significant trend of reduction of urinary citrate (29, 30). *Penniston et al.* also showed lower urinary magnesium in renal stone formers taking omeprazole, but they were not able to show any other change in urinary risk factors (34). Finally, in a large series of patients with GERD, *Sui et al.* demonstrated that patients taking PPIs had significantly lower mean urinary levels of both citrate and magnesium (16). In conclusion, the decrease of inhibitors of urinary crystallization in subjects taking PPIs represents a potential risk for renal stone formation.

Limitations

A major limitation of the studies that were considered in this meta-analysis is represented by the selection of subjects to be assigned to the PPI-exposed group and to the PPI-non exposed group. Exposure to PPIs depends on the presence of acid-related diseases that in themselves may be risk factors for renal stone formation. The indications for treatment with PPIs approved by the FDA are healing and maintenance of healing of *erosive esophagitis* (EE), H. pylori eradication to reduce the risk of recurrence of *duodenal ulcer* (DU), symptomatic *gastroesophageal reflux disease* (GERD), risk reduction of *nonsteroidal anti-inflammatory drug* (NSAID)-associate *gastric ulcer* (GU) and pathological hypersecretory conditions. These acid-related diseases have not been directly associated with kidney stone formation, though the stomach plays an important role in the metabolism of calcium and oxalate (20, 35). On the other hand, acid-related diseases are not associated with other enteric diseases that can promote renal stone formation. A study by *Sonnenberg et al.* (36) demonstrated that *gastro-esophageal reflux disease* (GERD) is inversely associated with all forms of inflammatory bowel diseases that are associated with an increased risk of stone formation due to increased urinary oxalate caused by fat malabsorption. On the contrary, subjects with gastroesophageal reflux-type symptoms showed an higher risk of irritable bowel syndrome that has not been associated with renal stone disease (37). However, acid-related diseases and renal stone diseases share several risk factors. Obesity has been associated with both the presence of symptoms of gastroesophageal reflux disease (38, 39) and the formation of kidney stones (40).

Similarly, a diet rich in proteins and animal fats and low in vegetables and fruit can predispose to both gastroesophageal reflux (41) and kidney stones (42).

Furthermore, concomitant use of antacids may increase the risk of stone formation. Antacids are still used for the treatment of acid-related disorders because they are easily available over the counter and may also be more affordable than prescription medications. These preparations contain magnesium trisilicate, that may cause the formation of silicate calculi, and calcium carbonate that -when administered outside meals- may cause peaks of serum and urinary calcium with an increased risk of calcium crystallization in the urine. Finally, reflux patients tend to avoid citrus fruits that can trigger reflux but are a source of citrates that act as crystallization inhibitors.

In our review, four studies evaluated populations including subjects on treatment with PPIs or not. To rule out an assignment bias, most authors compared patients taking or non-taking PPIs for the presence of comorbidities and dietary patterns and adjusted their analyses for potential confounders. *Ferraro et al.* (12) used Cox proportional hazards regression models adjusted for age, race, *body mass index* (BMI), physical activity, smoking status, comorbidities, use of medications and intake of nutrients, whereas *Kwak et al.* (13) found no difference in dietary or supplemental calcium, vitamin D, liquid, protein, sodium, and potassium intake in subjects taking PPIs or not. The latter adjusted their multivariate analysis for male gender, middle to old age, white ethnicity, obesity, diabetes, and elevated creatinine levels. Similarly, *Kim et al.* (14) adjusted their multivariable logistic regression analysis for age, sex, income, region of residence, total cholesterol, SBP, DBP, fasting blood glucose, CCI score, prescription dates within 1 year of each H2 blocker and NSAID, and number of GERD treatments, and performed subgroup analyses according to age, sex, income, region of residence, obesity, smoking, alcohol consumption, total cholesterol, systolic blood pressure, and fasting blood glucose. *Simonov et al.* (15) used a time-varying Cox proportional hazards model adjusted for baseline covariates including sex, race/ethnicity, age, creatinine, medications (H2RAs, thiazide diuretics, loop diuretics, gout medications), medical history (gastroesophageal reflux disease, peptic ulcer disease, Barrett's disease, gastrointestinal bleed, gastritis, functional dyspepsia, gastrointestinal surgical history, diabetes, gout) and total number of inpatient/outpatient encounters in the previous year. Finally, *Sur et al.* used multivariable Cox models with time-varying covariates after adjusting for age, BMI, gender, history of hypertension, coronary artery disease, hyperlipidemia and type 2 diabetes (16).

Only the study by *Sui et al.* (16) restricted its investigation to subjects with GERD, thus reducing the selection bias of assignment to treatment. Selection bias is known to affect the quality of studies performed on large general populations. However, even in this study a bias related to assignment to treatment with PPIs is still present, because subjects who did not take PPIs may have had a less severe disease than those who were on PPIs.

In general, observational studies are thought to tend to overestimate intervention effects and to have a lower grade of evidence in the hierarchy of research design compared to randomized controlled trials (RCTs). In an editorial, the results of observational studies showing an increased risk of renal stones and other diseases in subjects taking PPIs were critically commented (43). It was highlighted that randomized studies are "*the most powerful design to determine whether PPIs may cause long-term harm*". In fact, the results of a study of over 17.500 aspirin and/or apixaban users randomized to treatment with pantoprazole did not support the results of observational data suggesting that

small increases of risk for some diseases in subjects taking PPIs could be due to confounding factors or biases (44).
This randomized controlled study was not included in our analysis because kidney stone formation was not included among the safety outcomes of the trial. Furthermore, the population studied was not representative of the subjects most frequently affected by calcium renal stones, which occur more frequently between the ages of 30 and 50, whereas the study inclusion criteria were stable coronary and arterial disease in patients older than 65 years or arterial disease involving 2 cardiovascular beds and/or had 2 additional risk factors in younger subjects.
A randomized study to evaluate the risk of stone formation in subjects taking PPis should require the evaluation of a population of subjects aged between 20 and 60 who can be randomized to treatment with PPIs over a period of several years. Ethical issues and financial considerations make such a study unlikely to be accomplished. On the other hand, previous comparisons of randomized controlled studies with cohort or case-control studies assessing a specific intervention demonstrated that well-designed observational studies do not overestimate the effects of the intervention as compared to randomized controlled studies (45).

Conclusions

Our meta-analysis identified a potentially increased risk of kidney stone formation in patients taking PPIs. However, the observational design of included studies points to a strong risk of assignment bias. Consequently, these results must be considered with great caution and do not justify a restriction of the use of PPIs when they are administered in accordance with guidelines recommendations, avoiding unjustified long-term prolongation of the therapy. In fact, PPIs are frequently purchased over the counter, are often used without correct indications, are rarely deprescribed, thus being often used for longer periods than necessary. Administration of magnesium and citrate supplements and/or periodical evaluation of serum and urinary magnesium and urinary citrate levels should be considered for patients on long-term PPI treatment, and especially in stone forming patients on treatment with these drugs.

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