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Medical Management to Prevent Recurrent Nephrolithiasis in Adults: A Systematic Review for an American College of Physicians Clinical Guideline

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Background: Optimum management to prevent recurrent kidney stones is uncertain.

Purpose: To evaluate the benefits and harms of interventions to prevent recurrent kidney stones.

Data Sources: MEDLINE, Cochrane, and other databases through September 2012 and reference lists of systematic reviews and randomized, controlled trials (RCTs).

Study Selection: 28 English-language RCTs that studied treatments to prevent recurrent kidney stones and reported stone outcomes.

Data Extraction: One reviewer extracted data, a second checked accuracy, and 2 independently rated quality and graded strength of evidence.

Data Synthesis: In patients with 1 past calcium stone, low-strength evidence showed that increased fluid intake halved recurrent composite stone risk compared with no treatment (relative risk [RR], 0.45 [95% CI, 0.24 to 0.84]). Low-strength evidence showed that reducing soft-drink consumption decreased recurrent symptomatic stone risk (RR, 0.83 [CI, 0.71 to 0.98]). In patients with multiple past calcium stones, most of whom were receiving increased fluid intake, moderate-strength evidence showed that thiazides (RR, 0.52 [CI, 0.39 to 0.69]), citrates (RR, 0.25 [CI, 0.14 to 0.44]), and allopurinol (RR, 0.59 [CI, 0.42 to 0.84]) each further reduced composite stone recurrence risk compared with placebo or control, although the benefit from allopurinol seemed limited to patients with baseline hyperuricemia or hyperuricosuria. Other baseline biochemistry measures did not allow prediction of treatment efficacy. Low-strength evidence showed that neither citrate nor allopurinol combined with thiazide was superior to thiazide alone. There were few withdrawals among patients with increased fluid intake, many among those with other dietary interventions and more among those who received thiazide and citrate than among control patients. Reporting of adverse events was poor.

Limitations: Most trial participants had idiopathic calcium stones. Nearly all studies reported a composite (including asymptomatic) stone recurrence outcome.

Conclusion: In patients with 1 past calcium stone, increased fluid intake reduced recurrence risk. In patients with multiple past calcium stones, addition of thiazide, citrate, or allopurinol further reduced risk.

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Lifetime incidence of kidney stones is approximately 13% for men and 7% for women (1, 2). Although often asymptomatic—incidental stones are identified in approximately 5% of individuals who have abdominal ultrasonography or computed tomography imaging (3, 4)—stones may cause renal colic, urinary tract obstruction, and procedure-related illness. In patients with asymptomatic stones who are followed with serial radiography, 11% to 32% develop symptoms or undergo a procedure within 3 to 4 years (5–7). After a symptomatic stone event, the 5-year recurrence rate is 35% to 50% without specific treatment (8). Annual direct costs in the United States may exceed $4.5 billion (1, 9).

About 80% of kidney stones are composed of calcium oxalate, calcium phosphate, or both; uric acid and struvite stones are less common (10). Many patients with stones have low urine volume or biochemical abnormalities (for example, hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, or abnormal urine pH) (11, 12). Although low fluid or calcium intake increases stone risk, evidence for many other dietary factors is mixed (13–17). Risk is also increased by certain medical conditions, including primary hyperparathyroidism (18), obesity (19), diabetes (20), gout (21), intestinal malabsorption (22), and anatomical abnormalities.

Given these associations and current understanding of kidney stone physiology, treatments aim to prevent stone recurrence by improving the urinary balance between crystal-forming and crystal-inhibiting substances. Systematic reviews report reduced recurrence with increased fluid intake (23), thiazides (24–26), and citrate pharmacotherapy (26, 27), but evidence is insufficient for efficacy of other pharmacologic treatments (24, 26, 28, 29). However, these reviews did not include more recent randomized, controlled trials (RCTs); compare active treatments, including combination regimens; or evaluate the effect of patient factors on treatment outcomes.

Benefits and harms of treatments to prevent recurrent kidney stones are unclear, as are the effects of patient and

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stone characteristics and biochemistry measures on treatment outcomes. We conducted this systematic review to evaluate the evidence on these questions and to guide the American College of Physicians (ACP) clinical guideline on medical management to prevent recurrent nephrolithiasis in adults.

METHODS

We followed a protocol developed with stakeholder input. **Appendix Figure 1** (available at www.annals.org) shows the analytic framework and key questions used to guide this review. The full technical report, which incorporated peer review and public comments, is available at www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1035.

Data Sources

We searched MEDLINE and the Cochrane Library (both through September 2012), Google Scholar, ClinicalTrials.gov, and Web of Science databases. We reviewed reference lists of eligible RCTs and relevant systematic reviews as well as articles suggested by experts. **Appendix Table 1** (available at www.annals.org) shows our complete search strategy.

Study Selection

We included English-language RCTs that involved dietary or pharmacologic treatment to prevent recurrent kidney stones in adults and reported clinical outcomes (including symptomatic, radiographic, or composite [symptomatic or radiographic] stone recurrence or change in stone size) or harms. **Appendix Table 2** (available at www.annals.org) shows our detailed eligibility criteria. Two independent reviewers examined titles, abstracts, and full articles for eligibility and resolved discrepancies by discussion and consensus.

Data Extraction and Quality Assessment

For each article, 1 reviewer extracted details on study design, participant characteristics, outcomes, and adverse events, and a second reviewer checked accuracy. Using criteria developed by the Cochrane Collaboration (30), 2 reviewers rated individual study quality as good, fair, or poor on the basis of adequacy of allocation concealment (31), blinding, reporting reasons for attrition, and how analyses accounted for incomplete data (**Appendix Table 3**, available at www.annals.org). Following methods developed by the Agency for Healthcare Research and Quality (AHRQ)'s Effective Health Care Program (32), 2 reviewers graded the strength of evidence (SOE) for the efficacy of each treatment comparison in preventing stone recurrence on the basis of risk of bias, consistency, directness, and precision (**Appendix Tables 4** to **6**, available at www.annals.org). We resolved discrepancies in quality ratings and SOE grades by discussion and consensus.

Data Synthesis and Analysis

We pooled results if clinical heterogeneity of patient populations, interventions, and outcomes was minimal. Data were analyzed in Review Manager, version 5.1 (The Nordic Cochrane Center, Copenhagen, Denmark). We used random-effects models to generate pooled estimates of relative risks (RRs) and 95% CIs, and we summarized statistical heterogeneity using the I^2 statistic (33). When there were few RCTs for a given treatment and no overlap of reported outcomes, we synthesized data qualitatively. For analyses of pharmacologic treatments, we evaluated results by drug class and individual agent. Where data allowed, we explored treatment efficacy according to patient characteristics, stone characteristics, baseline and follow-up biochemical measures, and study duration.

Role of the Funding Source

This review was nominated to the AHRQ by the American Urological Association and was funded by the AHRQ. AHRQ staff and a technical expert panel that included members of the ACP Clinical Guidelines Committee and the American Urological Association helped to develop and refine the scope and reviewed the draft AHRQ report. Members of the ACP Clinical Guidelines Committee provided support for manuscript preparation and reviewed drafts of this manuscript. The authors are solely responsible for its content.

RESULTS

We included a total of 28 RCTs (8 dietary and 20 pharmacologic) (**Appendix Figure 2**, available at www.annals.org). Among these, 23 included only participants with calcium stones, 3 were limited to those with struvite stones, and 2 included those with any stone type. Nearly all studies excluded participants known to have conditions associated with kidney stones. Six trials reported symptomatic stone recurrence, 8 reported radiographic recurrence, and 18 reported a composite recurrence outcome. Treatment duration was 1 to 5 years. We rated 2 trials as good quality (34, 35), 2 as poor quality (36, 37), and the remainder as fair quality (**Appendix Table 3**). The most common limitations in study quality, which were present in approximately two thirds of trials, were unclear descriptions of allocation concealment and failure to report outcomes according to intention-to-treat principles.

Effectiveness and Harms of Dietary Therapy for Preventing Stone Recurrence

Increased Fluid Intake

Two RCTs randomly assigned participants with 1 past calcium stone either to increase fluid intake to maintain urine output of greater than 2 or 2.5 L/d or to receive no treatment (**Appendix Table 7**, available at www.annals.org). In 1 poor-quality trial, participants who were assigned to increased fluids had a reduced risk for composite stone recurrence compared with no treatment (RR, 0.45

[95% CI, 0.24 to 0.84]) (36); SOE for this outcome was low due to the trial's poor quality and consequent high risk of bias. A fair-quality trial reported reduced risk for recurrent radiographic stones with increased fluid intake, but results did not statistically significantly differ between treatment groups (RR, 0.15 [CI, 0.02 to 1.07]) (38); SOE for this outcome was insufficient because of the small number of stone events. Both trials reported few withdrawals, and neither reported data on adverse events.

Decreased Soft-Drink Intake

One large fair-quality RCT randomly assigned men with more than 1 past kidney stone of any type and soft-drink consumption greater than 160 mL/d to reduced soft-drink intake or no treatment (39) (**Appendix Table 7**). Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR, 0.83 [CI, 0.71 to 0.98]), SOE for this outcome was low because results were from only 1 trial. In a subgroup analysis not reported as prespecified, the benefit seemed to be limited to participants whose most frequently consumed soft drink at baseline was acidified solely by phosphoric acid ($P = 0.02$ for interaction). Total fluid intake was similar in both groups, suggesting that results were explained by type and not amount of fluid intake. The study reported few withdrawals and almost no adverse event data.

High Dietary Fiber or Low Animal Protein

One fair-quality RCT of participants with more than 1 past calcium stone provided low-strength evidence that, compared with a control diet of greater than 2 L of water intake plus 800 to 1000 mg of calcium per day, neither increased dietary fiber intake (RR, 1.18 [CI, 0.66 to 2.12]) nor decreased animal protein intake (RR, 1.00 [CI, 0.52 to 1.91]) statistically significantly reduced the risk for recurrent stones (40) (**Appendix Table 7**). However, because withdrawals exceeded 50% in all groups, robust conclusions cannot be drawn from this trial. Strength of evidence was low for both of these interventions because results could not preclude the exclusion of clinically meaningful benefits or harms. The study reported no data on adverse events.

Multicomponent Diets

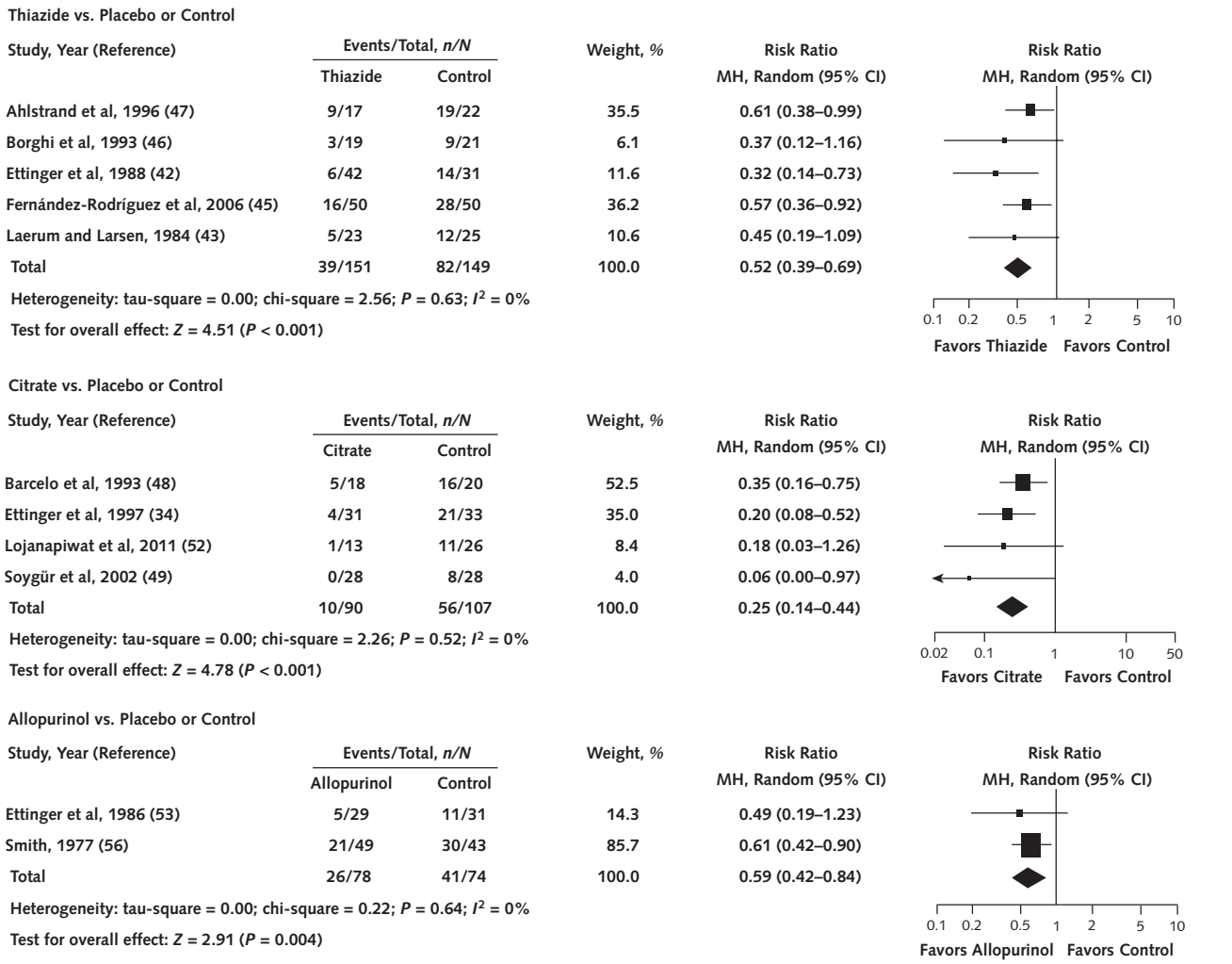
Three RCTs (1 good-, 1 fair-, and 1 poor-quality) randomly assigned participants with 1 (37, 41) or more (35) past calcium stones to different multicomponent diets or a control diet (**Appendix Table 7**). The good-quality RCT, in which participants with hypercalciuria were advised to increase fluid intake and avoid excess oxalate, found that those randomly assigned to a diet that included normal to high calcium (1200 mg/d), low animal protein, and low sodium intake had a reduced risk for composite stone recurrence compared with those assigned to a low-calcium diet (400 mg/d) (RR, 0.52 [CI, 0.29 to 0.95]) (35). The fair-quality RCT reported that compared with participants assigned to increased fluid intake and 500 to 600 mg of dairy or supplemental calcium per day, those also assigned to low animal protein, high fiber, increased bran, and low dietary purine intake had an increased risk for composite stone recurrence (RR, 5.88 [CI, 1.39 to 24.92]) (41). Results for the second trial may have been affected by a low recurrence rate in the control group. However, considered with negative results from 1 trial of low animal protein intake (40), these results raise questions about whether the reduced recurrence in the first multicomponent diet trial should be attributed in any way to reduced intake of animal protein. Any treatment benefit may have instead been attributable to reduced dietary sodium or avoidance of low dietary calcium. The poor-quality RCT found that compared with a limited biochemical evaluation and uniform diet recommendations, an extensive evaluation and diet recommendations tailored to the biochemical findings of the participant reduced the risk for composite stone recurrence (RR, 0.32 [CI, 0.14 to 0.74]) (37). This trial did not report separate results for any biochemical abnormality subgroup or tailored diet type. Despite individual study quality differences, SOE for these 3 treatment comparisons was low because, in each case, evidence was available from only 1 trial. There were fewer overall withdrawals (35, 41) and withdrawals due to adverse events (35) in the intervention groups in the trials that reported these results separately by treatment group. None of the trials reported data on specific adverse events.

Effectiveness and Harms of Pharmacologic Therapy for Preventing Stone Recurrence

Thiazides Versus Placebo or Control

Six fair-quality RCTs randomly assigned participants with recurrent calcium stones to thiazide or either placebo (42–44) or control (45–47) (**Figure** and **Appendix Table 8**, available at www.annals.org). All but 1 trial (45) reported dietary co-interventions in both study groups, most commonly increased fluid and decreased oxalate intake. We found moderate-strength evidence that thiazides decreased risk for composite stone recurrence (RR, 0.52 [CI, 0.39 to 0.69]; 5 trials) (42, 43, 45–47). Although thiazides did not reduce risk for symptomatic recurrence, SOE for this outcome was insufficient due to the small number of recurrent symptomatic stone events and large imprecision of the risk estimate (44). Another trial reported a lower risk for extracorporeal lithotripsy with thiazide than with control (8.0% vs. 26.0%; RR, 0.31 [CI, 0.11 to 0.88]) (45). Results for composite stone recurrence did not seem to differ as a function of study duration (2 vs. ≥3 years) or thiazide type (hydrochlorothiazide, chlorthalidone, or indapamide) or dosing regimen, although no trials studied doses of hydrochlorothiazide or chlorthalidone lower than 50 mg/d and 25 mg/d, respectively, and statistical power to test all of these comparisons was low. Results from 1 trial done in a general practice setting (RR, 0.45 [CI, 0.19 to

Figure. **Forest plots for risk for composite stone recurrence with pharmacologic treatment versus placebo or control.**



MH = Mantel–Haenszel.

1.09]) (43) seemed similar to overall results. Compared with participants in the placebo and control groups, those randomly assigned to receive thiazide were statistically significantly more likely to withdraw for any reason or because of adverse events. Adverse events were inconsistently reported, and no individual event was reported in more than 1 participant in any trial.

Citrate Versus Placebo or Control

Six RCTs (1 good-quality and 5 fair-quality) randomly assigned participants with predominantly recurrent calcium stones to citrate or either placebo (34, 48) or control (49–52). Four of these trials prescribed increased fluid intake to all study participants (48–50, 52), but no other dietary co-intervention was reported in more than 1 trial. We found moderate-strength evidence that citrates reduced risk for composite stone recurrence (RR, 0.25 [CI, 0.14 to 0.44]; 4 trials) (**Figure** and **Appendix Table 8**) (34, 48, 49, 52). Strength of evidence that citrates did not reduce risk for radiographic recurrence was low due to the imprecision of the estimate (50). Although results did not seem to differ as a function of the number of past stone events, citrate type (potassium citrate, potassium–magnesium citrate, or potassium–sodium citrate), or study duration (1 vs. ≥2 years), statistical power to test these comparisons was low (34, 48, 49, 52). Compared with participants in the placebo and control groups, those randomly assigned to receive citrate were statistically significantly more likely to withdraw for any reason or because of adverse events and to report adverse events.

Allopurinol Versus Placebo or Control

Four fair-quality RCTs randomly assigned participants with recurrent calcium stones to allopurinol or either placebo (53, 54) or control (55, 56) (**Figure** and **Appendix Table 8**). Three of these trials prescribed increased fluid

intake to all participants (53, 54, 57), and 1 also instructed all participants to use sodium bicarbonate to keep their urine pH above 6.5 (57). Moderate-strength evidence showed that allopurinol reduced risk for composite stone recurrence (RR, 0.59 [CI, 0.42 to 0.84]; 2 trials) (53, 56). Although allopurinol did not statistically significantly reduce risk for either symptomatic or radiographic stone recurrence (53), SOE for these outcomes was low and insufficient, respectively, due to the small number of recurrent stone events and the magnitude of imprecision of the risk estimates (53, 56). Two trials (53, 56) reported that participants randomly assigned to receive allopurinol less frequently withdrew for any reason or because of adverse events. Adverse events were infrequently reported for both treatment groups.

Acetohydroxamic Acid Versus Placebo

Three fair-quality RCTs randomly assigned participants with recurrent struvite (ammonium–magnesium–phosphate) kidney stones and chronic urinary tract infections to receive acetohydroxamic acid (AHA) or placebo (58–60) (**Appendix Table 8**). Most participants were considered nonsurgical candidates. Participants in both groups received concomitant required (60) or optional (58, 59) antibiotics, but no trials reported a dietary co-intervention. There was no statistically significant difference between the AHA and placebo groups in risk for symptomatic or radiographic stone recurrence. Strength of evidence for both of these outcomes was insufficient due to the small number of recurrent stone events and large imprecision of the risk estimates (58, 59). Although each trial reported a statistically significant reduction in stone growth with AHA versus placebo (58–60), each trial defined stone growth differently. Withdrawals and adverse events were common and statistically significantly more frequent with AHA, although individual adverse events were inconsistently reported.

Combination Pharmacologic Therapy

One fair-quality RCT randomly assigned participants with recurrent calcium stones to receive either thiazide plus citrate or thiazide monotherapy, reported no dietary co-intervention, and found no between-group difference in risk for composite stone recurrence or extracorporeal lithotripsy (45) (**Appendix Table 8**). Strength of evidence for the former outcome was low due to the imprecision of the risk estimate. This study reported that no participants withdrew but did not report data on adverse events.

Another fair-quality RCT randomly assigned participants with recurrent calcium stones and hypercalciuria to receive either thiazide plus allopurinol or thiazide monotherapy, reported that all participants were instructed to increase fluid intake and make additional dietary changes, and found no between-group difference in risk for composite stone recurrence (46) (**Appendix Table 8**). Strength of evidence for this outcome was insufficient due to the small number of recurrent stone events and the large imprecision of the risk estimate. Although participants assigned to combination treatment had no statistically significantly decreased risk for withdrawal for any reason or due to adverse events, no data on adverse events were reported for this group.

Pretreatment Stone Composition and Biochemistry Measures to Predict Treatment Efficacy in Preventing Stone Recurrence

We could not determine whether the effect of studied interventions differed by stone type because all 3 AHA trials were limited to participants with struvite stones, 2 trials that included participants with any stone type did not report results as a function of stone type, and the remaining 23 trials limited participation to those with calcium stones. Further, no trials evaluated the effect of any interventions in patients with uric acid or cystine stones.

Results were mixed about whether baseline biochemistry measures predicted treatment effectiveness for reducing stone recurrence risk. In 2 RCTs in patients with calcium stones plus hyperuricosuria (uric acid level >4.76 mmol/d [800 mg/d] in men and >4.43 mmol/d [750 mg/d] in women) (53) or hyperuricemia (uric acid level >356.88 μmol/L [6 mg/dL]) (56), those randomly assigned to allopurinol had a significantly lower risk for composite recurrent stones than those in the control group (RR, 0.59 [CI, 0.42 to 0.84]). However, rates of symptomatic stone recurrence did not seem lower with allopurinol than with control in trials of participants unselected for high urinary or serum uric acid levels (54, 55).

In contrast, other baseline biochemistry measures did not seem to predict efficacy of dietary or pharmacologic treatments compared with control for recurrent stone outcomes. More specifically, baseline urinary calcium levels made no statistically significant difference in the efficacy of increased fluid intake, diet, thiazides, citrate, or allopurinol versus control. We based this observation on comparisons of results from trials that included patients with (46), without (38, 48, 53), or unselected for baseline hypercalciuria (34, 36, 42, 43, 46, 47, 49, 56), as well as analyses adjusted for baseline urinary calcium levels (35). Similarly, baseline urine oxalate levels made no statistically significant difference in the efficacy of increased fluid intake, diet, thiazides, or citrate compared with control; this observation was based on comparisons of results among patient groups with (44), without (38, 42, 47), or unselected for hyperoxaluria (36) and results that were adjusted for baseline urinary oxalate levels (34, 35) or baseline hyperoxaluria (34). Efficacy of citrate treatment for recurrent stone outcomes did not differ between patient groups with (48) or unselected for hypocitraturia (34, 49). Moreover, no RCT data addressed whether the effect of any treatment on risk for recurrent stones differs according to urinary magnesium,

phosphate, or potassium level; urine pH; or any measure of urine supersaturation at baseline.

Finally, in 1 RCT, participants randomly assigned to an extensive biochemical evaluation plus diet treatment tailored to their individual biochemistry results had a statistically significantly lower risk for recurrent stones than those assigned a limited evaluation plus uniform diet treatment (37). However, because the trial did not report separate results by biochemical abnormality, we could not isolate the effects of any individual baseline biochemistry measure on treatment outcomes.

On-Treatment Biochemistry Measures to Predict Treatment Efficacy in Preventing Stone Recurrence

No RCTs compared risk for stone recurrence between treatments according to follow-up biochemistry measures or changes from pretreatment biochemistry values. Although RCTs that involved increased fluid intake (36) and a multicomponent diet (35) reported that treatment reduced both urine supersaturation levels and risk for recurrent stones, neither study formally tested whether these outcomes were associated. In contrast, no pharmacologic RCT reported follow-up urine supersaturation levels. Data from both dietary and pharmacologic RCTs suggest that follow-up urinary calcium levels may have limitations as a predictor of treatment efficacy in preventing stone recurrence. Urinary calcium levels were unchanged from baseline in all diet trials that reported these results (35, 40, 41), including the 1 trial that reported treatment benefit (35). In the 4 thiazide trials that reported follow-up urinary calcium levels, 3 reported statistically significant decreases among participants assigned to thiazide but not to control (42, 44, 61) and 1 reported statistically significant decreases among those in both groups (46). These results suggest that reduction in urinary calcium level may be a sensitive but nonspecific predictor of thiazide efficacy in preventing stone recurrence. We could not determine whether decreases in urinary uric acid level or increases in urine pH predict effectiveness of allopurinol in reducing stone recurrence (53).

Discussion

Few RCTs examined the effect on stone outcomes of modifying individual dietary components. Increased fluid intake more than halved the risk for composite or radiographic stone recurrence and seemed well-tolerated, although SOE for these findings was limited by study quality and size (36, 38). Reducing intake of soft drinks acidified solely by phosphoric acid in men with high intake at baseline modestly decreased risk for recurrent symptomatic stones (39). However, these subgroup results were based on post hoc analyses, and generalizability to other populations is uncertain. Results were inconsistent about whether other dietary interventions added benefit to increased fluid intake. For example, trials that compared diets that included low animal protein intake (alone or as part of a multicomponent diet) with control diets reported reduced stone recurrence (35), no between-group risk difference (40), and increased risk for stone recurrence (41). Even if these discrepant results could be explained in part by discounting the low-quality negative studies, the benefits observed in the single positive study may not have been attributable to low animal protein. Reduction in recurrent stone risk may have been driven by reduced dietary sodium or avoidance of low dietary calcium, but even here the absence of any other trials that compared different dietary sodium or calcium intakes (alone or as part of a multicomponent intervention) raises uncertainty about the benefit of these dietary interventions.

Among pharmacologic treatments, thiazides, citrate, and allopurinol each decreased risk for recurrent calcium stones more than increased fluid intake alone. Although neither the thiazide nor the citrate results seemed to differ as a function of the number of past stone events, drug type or dose, or study duration, statistical power to evaluate these questions was low. Another caveat is that no trials evaluated the efficacy of lower thiazide doses currently used to treat hypertension, so whether these doses similarly reduce recurrence risk is unknown. Limited evidence from RCTs suggests that AHA does not reduce recurrence of symptomatic or radiographic struvite stones, but these trials only addressed management of patients who were not considered surgical candidates. Data directly comparing active pharmacologic treatments to prevent stone recurrence were extremely limited. No trials directly compared thiazide, citrate, or allopurinol monotherapy, and there was only low-strength evidence that addition of citrate (45) or allopurinol (46) to thiazide resulted in no further reduction in stone recurrence risk.

Evidence from RCTs is limited for whether stone composition predicts treatment efficacy in preventing recurrence. No trials enrolled participants with different stone types and reported recurrence outcomes as a function of type, AHA was evaluated only in patients with struvite stones, and all other trials were limited to patients with calcium stones. In addition, no trials examined the effect of any therapy in reducing risk for recurrent uric acid or cystine stones. Because most patients have calcium stones, increasing fluid intake in all patients with kidney stones with or without adding thiazide or citrate therapy might reduce recurrence risk. However, no trials tested this strategy.

Evidence is limited for whether baseline biochemistry measures predict treatment efficacy in preventing stone recurrence. Hyperuricosuria or hyperuricemia may predict reduced risk for recurrent calcium stones with allopurinol treatment. However, because both thiazides (42, 43, 45) and citrates (49) reduced risk for calcium stone recurrence in trials that included at least some patients with hyperuricosuria, and no trials directly compared allopurinol with these agents in patients with high uric acid levels, we do not know whether allopurinol should be the preferred ini-

tial therapy in this subgroup of patients. Patients in 1 trial who were randomly assigned to an extensive biochemical evaluation and tailored diet were less likely to have a recurrent stone than those assigned to a limited biochemical evaluation and uniform treatment (37). However, because the study did not report how biochemistry results were defined as abnormal and reported results only between the 2 treatment groups overall, we could not determine to what extent, if any, the biochemistry testing accounted for the between-group difference in outcomes. It seems likely, on the basis of results from other diet trials, that not all tailored diet subgroups contributed to the overall benefit, and some may have been harmful. We identified limited evidence that efficacy in reducing risk for recurrent stones does not differ for any dietary or pharmacologic treatment compared with control among patient groups with, without, unselected for, or adjusted for baseline hypercalciuria, hyperoxaluria, or hypocitraturia. These results are limited because some RCTs did not report information on baseline biochemistry measures, other trials did not report how biochemical abnormalities were defined, and definitions varied in trials that reported biochemical abnormalities. Because any association between biochemical abnormalities and risk for recurrent stones is not likely to be defined by a single threshold and may be continuous (62), the failure of trials to report results as a function of a standardized series of biochemical thresholds is limiting. Nevertheless, these results raise questions about the necessity of measuring baseline urinary biochemistry values in all patients with initial or even recurrent calcium kidney stones.

Although many RCTs reported results of follow-up biochemistry measures, none reported and compared between-treatment outcomes of stone recurrence completely subsequent to and stratified by follow-up biochemistry levels or by changes in these measures from baseline. Results from 2 diet trials suggested that a decrease from baseline in several measures of urine supersaturation may be associated with a reduction in risk for recurrent stones. Future studies testing these follow-up measures as predictors of treatment efficacy are warranted. Data from both dietary and pharmacologic RCTs suggest that follow-up urinary calcium level may be a sensitive but nonspecific predictor of stone recurrence. Reductions in high baseline urinary calcium levels during treatment may be attributable, at least in part, to regression to the mean (63).

The available data limit this review in several ways. First, few trial data existed for some treatment comparisons, owing to few trials and small sample sizes. In these cases, determining whether insufficient evidence for treatment benefit reflects inadequacy of the treatment or limitations in the data may be impossible. This also raises the question of whether, despite our comprehensive search strategy, the results of this review could be affected by publication bias if some unpublished trials were not identified. Second, most trials reported few data on treatment harms, thus limiting our confidence around risk estimates for these outcomes. Third, nearly all trials enrolled adults with idiopathic calcium stones. Therefore, results may not be generalizable to individuals with conditions predisposing them to kidney stones, those with noncalcium kidney stones, or children. Fourth, few trials reported symptomatic stone recurrence as an isolated outcome. Instead, most results were driven by radiographic stone recurrence—at best, a surrogate outcome that clinicians and patients may consider less relevant to their treatment decisions. Fifth, only 1 trial recruited participants from a primary care setting (43). However, because the benefit with thiazide versus control in this study seemed similar to that in trials done in specialty stone centers, the effect of thiazides, at least, may be insensitive to recruitment source. Sixth, this review was limited by inconsistent reporting and categorization of baseline biochemistry measures between trials. Finally, although efficacy of treatment for preventing stone recurrence did not seem to differ as a function of treatment duration among trials lasting at least 1 year, this review had low statistical power to evaluate this question.

In conclusion, we found that increased fluid intake substantially reduced risk for recurrent calcium stones. In men with high soft-drink consumption, decreasing intake reduced recurrent stone risk, although benefit may be limited to those whose most commonly consumed baseline soft drink is acidified solely by phosphoric acid. Results were mixed for the potential benefit of other dietary interventions. In individuals with multiple past calcium stones, most of whom received increased fluid intake as a cointervention, thiazides, citrates, and allopurinol each further reduced risk for stone recurrence. Other than uric acid level, baseline biochemistry measures did not predict efficacy of any treatment. Withdrawals were low in trials evaluating increased fluid intake; high in long-term trials evaluating other dietary interventions; and variable in pharmacologic trials, although higher than for control for both thiazide and citrate treatment. Adverse event reporting was consistently poor. Existing gaps in RCT evidence may require clinicians to use other sources of evidence to inform their clinical management of patients with kidney stones. Future studies should be designed a priori to collect long-term data on symptomatic stone recurrence and other clinical outcomes; report these efficacy outcomes as a function of patient characteristics, including comorbid conditions and baseline biochemistry measures; and predefine and systematically report adverse events. Additional trials directly comparing different active treatments and combination treatments are warranted.

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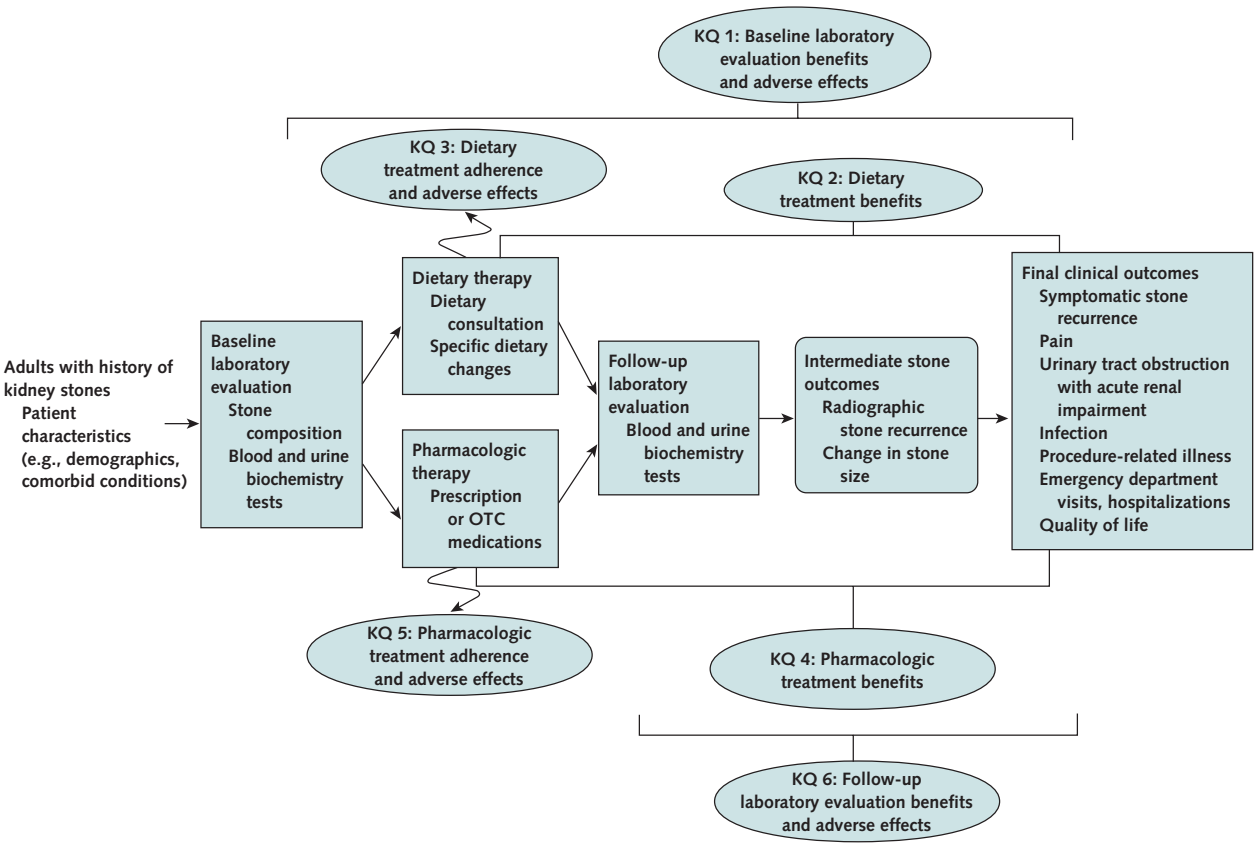
Appendix Figure 1. **Analytic framework and key questions.**



Key Questions:

1. In adults with a history of nephrolithiasis, do results of baseline stone composition and blood and urine biochemistry tests predict the effectiveness of diet and/or pharmacologic treatment on final health outcomes and intermediate stone outcomes and reduce treatment adverse effects?

1a. Do effectiveness and adverse effects of treatment differ according to patient baseline stone composition and blood and urine biochemical measures?

1b. Does treatment tailored to the results of baseline stone composition and blood and urine biochemistry tests improve final health outcomes and intermediate stone outcomes and reduce adverse effects compared with empirical treatment?

2. In adults with a history of nephrolithiasis, what is the effectiveness and comparative effectiveness of different dietary therapies on final health outcomes and intermediate stone outcomes?

2a. Does effectiveness of diet therapy differ according to patient baseline demographic and comorbidity characteristics?

2b. Does effectiveness of diet therapy differ according to patient baseline diet and fluid intake?

2c. Does effectiveness of diet therapy differ according to characteristics of stone history?

3. In adults with a history of nephrolithiasis, what is the evidence that dietary therapies to reduce risk for recurrent stone episodes are associated with adverse effects?

3a. Does the risk for adverse effects differ according to patient baseline demographic and comorbidity characteristics?

3b. Does the risk for adverse effects differ according to patient baseline diet and fluid intake?

3c. Does the risk for adverse effects differ according to characteristics of stone history?

4. In adults with a history of nephrolithiasis, what is the effectiveness and comparative effectiveness of different pharmacologic therapies on final health outcomes and intermediate stone outcomes?

4a. Does effectiveness differ according to patient baseline demographic and comorbidity characteristics?

4b. Does effectiveness differ according to patient baseline diet and fluid intake?

4c. Does effectiveness differ according to characteristics of stone history?

5. In adults with a history of nephrolithiasis, what is the evidence that pharmacologic therapies to reduce risk for recurrent stone episodes are associated with adverse effects?

5a. Does the risk for adverse effects differ according to patient demographic and comorbidity characteristics?

5b. Does the risk for adverse effects differ according to patient baseline diet and fluid intake?

5c. Does the risk for adverse effects differ according to characteristics of stone history?

6. In adults with a history of nephrolithiasis being treated to prevent stone recurrence, do results of follow-up blood and urine biochemistry tests predict final health outcomes and intermediate stone outcomes?

6a. Does prediction of final health outcomes and intermediate stone outcomes differ according to the frequency or duration of follow-up biochemistry measurements?

KQ = key question; OTC = over-the-counter.

Appendix Table 1. Literature Search Strategies

Ovid MEDLINE

1	urolith*.mp. or exp Urolithiasis/
2	(urinary calcul* or kidney calcul* or ureteral calcul* or renal calcul* or kidney stone*).mp.
3	renal colic.mp. or exp Renal Colic/
4	hypercalciuria.mp. or exp Hypercalciuria/
5	exp Hyperoxaluria, Primary/ or exp Hyperoxaluria/ or hyperoxaluria.mp.
6	hyperuricemia.mp. or exp Hyperuricemia/
7	cystinuria.mp. or exp Cystinuria/
8	(hyperuricosuria or hypercitraturia or nephrolith*).mp.
9	(calcium stone* or calcium phosphate stone* or calcium oxalate stone* or uric acid stone* or urate stone* or cystine stone* or struvite stone*).mp.
10	or/1-9
11	limit 10 to (controlled clinical trial or meta analysis or randomized controlled trial)
12	limit 10 to systematic reviews
13	11 or 12
14	exp meta-analysis/
15	exp randomized controlled trials/ or systematic review.mp.
16	exp controlled clinical trial/
17	or/14-16
18	10 and 17
19	13 or 18
20	limit 19 to English language

Cochrane Central Register of Controlled Trials (CENTRAL)

1	(urolith$ or urolithiasis):ti,ab,kw in Clinical Trials
2	urinary calcul* or kidney calcul* or ureteral calcul* or renal calcul* or kidney stone* in Clinical Trials
3	renal colic in Clinical Trials
4	hypercalciuria in Clinical Trials
5	hyperoxaluria in Clinical Trials
6	hyperuricemia in Clinical Trials
7	cystinuria in Clinical Trials
8	hyperuricosuria or hypercitraturia or nephrolith* in Clinical Trials
9	calcium stone* or calcium phosphate stone* or calcium oxalate stone* or uric acid stone* or urate stone* or cystine stone* or struvite stone* in Clinical Trials
10	urolith* or Urolithiasis in Clinical Trials
11	(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10)

Appendix Table 2. Study Eligibility Criteria

Variable	Inclusion and Exclusion Criteria
Population(s)	For all key questions, we restricted eligibility to full-text studies published in English that enrolled adults aged ≥18 y with a history of ≥1 kidney stone episode. We excluded studies of children and those that addressed acute pain management and treatment to promote expulsion of ureteral stones. Eligible studies could include patients with or without residual stones or stone fragments. To distinguish the effect of secondary prevention from lithotripsy, we excluded studies comprising participants who had undergone lithotripsy within 90 d prior unless they were documented as being stone-free at baseline.
Dietary interventions	For key questions 2 and 3, we restricted the review to studies that evaluated individual dietary interventions (e.g., intake of fluids, calcium, animal protein, sodium, fruit and fiber, purine, oxalate, potassium, soft drinks, or citrus) or multicomponent diets. We also included empirical dietary interventions, as well as those tailored to patient demographic characteristics, comorbid conditions, baseline diet, baseline urine or blood biochemical testing, and/or stone type.
Pharmacologic interventions	For key questions 4 and 5, we restricted the review to studies that evaluated pharmacologic agents currently approved by the FDA and available in the United States for prescription* (e.g., hydrochlorothiazide, chlorthalidone, indapamide, potassium citrate, potassium–magnesium citrate, sodium citrate, allopurinol, magnesium hydroxide, and acetohydroxamic acid). We also included trials of over-the-counter medications and supplements available in the United States and those that combined dietary, pharmacologic, over-the-counter, and/or supplement interventions. For key questions 1 and 6, all of the above interventions were eligible.
Comparators	For all key questions, eligible studies could have compared active treatment with placebo; usual care or no treatment; or other active treatments, including combination treatment and comparisons with the same active treatment at varying dosages. Active pharmacologic comparators were restricted to those currently approved by the FDA or available over the counter in the United States.
Outcomes	For key questions 1, 2, 4, and 6, we considered final clinical health outcomes as the most important measures of treatment benefit, including symptomatic stone recurrence, pain, urinary tract obstruction with acute renal failure, infection, illness related to treatment for a recurrent stone, emergency department visits or hospitalizations for treatment of recurrent stones (e.g., for renal colic or acute renal failure), quality of life (general or urologic), and end-stage renal disease. Intermediate stone outcomes were considered the next most important measures of treatment benefit, including composite stone recurrence (combination of symptomatic recurrence or radiographically detected recurrence), stone recurrence detected only by scheduled radiographic imaging, and change in stone size. For key questions 3 and 5, adverse effects included any reported by eligible trials (e.g., nausea, diarrhea, hypokalemia, weight change, hyperlipidemia, or hyperglycemia). Measures of treatment adherence were those reported by the individual trials (e.g., self-report questionnaire, pill count, or estimate from follow-up urine biochemical measures).
Timing	Eligible studies had to include follow-up ≥12 mo for final clinical health outcomes (e.g., stone recurrence), intermediate stone outcomes, and adherence and ≥3 mo for adverse effects. We believed that follow-up <12 mo would probably not be sufficient for treatments to affect recurrent stone outcomes and that shorter trials would more likely focus on treatments to assist in stone expulsion. However, we considered 3 mo sufficient for most treatment-related adverse effects to manifest.
Setting	We included studies done in all settings, including primary care, urology clinics, nephrology clinics, diet clinics, or other specialty stone clinics. There were no geographic restrictions.
Other eligibility criteria	For the key questions related to effectiveness, we limited eligibility to RCTs meeting the PICOTS criteria and published in full text and in English. We first applied the same requirements to the key questions related to adverse effects; however, these sources offered limited adverse effects data. Thus, for pharmacologic treatments we expanded eligibility to RCTs that involved nephrolithiasis ≥3 mo in duration and reported only blood or urine biochemical outcome measures but not final clinical health outcomes or intermediate stone outcomes. Furthermore, we included prospective observational studies ≥3 mo in duration in cohorts of ≥100 patients being treated for secondary prevention of kidney stones. We did not evaluate these additional types of studies for adverse effects of dietary treatments under the assumptions that we were unlikely to find diet studies with compositions similar to those of eligible trials, dietary adverse effects were low, and the likelihood of finding reported adverse effects in lower-quality diet studies was low. Although limiting trials to those published in English is not ideal, previous research has documented little bias in systematic reviews that limited trials of medical treatments to those published in English (64).

FDA = U.S. Food and Drug Administration; PICOTS = population, intervention, comparator, outcome, timing, and setting; RCT = randomized, controlled trial.

* Limiting eligibility to drugs with current FDA approval for any indication or those available over the counter resulted in exclusion of trials or treatment groups for the following drugs that otherwise met eligibility criteria: bendroflumethiazide ($n = 3$), trichlormethiazide ($n = 2$), magnesium aspartate hydrochloride ($n = 1$), orthophosphate ($n = 1$), potassium acid phosphate ($n = 1$), and sodium cellulose phosphate ($n = 1$). Results for the 5 individual excluded thiazide trials were as follows:

Reference 55: bendroflumethiazide versus no treatment; $n = 45$ (0.22 vs. 0.58 symptomatic stones/patient per year; $P < 0.05$ [pretreatment vs. posttreatment in thiazide group]; no between-group comparison reported)

Reference 65: bendroflumethiazide versus placebo; $n = 62$ (5/33 = 15.2% vs. 5/29 = 17.2% incident composite stone and 0.09 vs. 0.11 stones/patient per year; P = NS)

Reference 66: bendroflumethiazide plus potassium chloride versus placebo; $n = 27$ (0/12 = 0% vs. 4/10 = 40% composite recurrence; $P < 0.1$)

Reference 67: allopurinol plus trichlormethiazide versus allopurinol; $n = 87$ (0.20 vs. 0.24 radiographic stones/patient per year; P = not significant)

Reference 68: trichlormethiazide versus conservative (nondrug) treatment; $n = 210$ (0.13 vs. 0.31 composite stones/patient per year; $P < 0.05$)

Of these trials, only those in references 65 and 66 reported poolable recurrent stone outcomes. The relative risk for composite stone recurrence of thiazides versus placebo when these 2 trials were excluded was 0.52 (95% CI, 0.39 to 0.69). Addition of these 2 trials would not have meaningfully changed the results (relative risk, 0.53 [CI, 0.40 to 0.69]).

Appendix Table 3. Individual Study Quality

Study, Year (Reference)	Allocation Concealment	Blinding	Intention-to-Treat Analysis	Withdrawals Described	Study Rating
Dietary trials					
Dussol et al, 2008 (40)	Adequate	Outcomes assessor only	No	Yes	Fair
Sarica et al, 2006 (38)	Unclear*	None stated	Yes	No withdrawals	Fair
Borghi et al, 2002 (35)	Adequate	Outcomes assessor only	Yes	Yes	Good
Kocvara et al, 1999 (37)	Unclear*	None stated	No	No	Poor
Borghi et al, 1996 (36)	Unclear*	None stated	No	No	Poor
Hiatt et al, 1996 (41)	Unclear*	Outcomes assessor only	Yes	Yes	Fair
Shuster et al, 1992 (39)	Unclear*	Outcomes assessor only	Yes	Yes	Fair
Pharmacologic trials					
Thiazide					
Fernández-Rodríguez et al, 2006 (45)	Unclear*	None stated	Yes	No withdrawals	Fair
Ahlstrand et al, 1996 (47)	Unclear	Open-label	Yes	Yes	Fair
Borghi et al, 1993 (46)	Unclear	Open-label	No	Yes	Fair
Ettinger et al, 1988 (42)	Adequate†	Double-blind (outcomes assessor; no further details)	No	Yes	Fair
Laerum and Larsen, 1984 (43)	Unclear*	Double-blind (no further details)	Yes	Yes	Fair
Scholz et al, 1982 (44)	Unclear*	Double-blind (statistical analyses; no further details)	No	Yes	Fair
Citrate					
Lojanapiwat et al, 2011 (52)	Unclear*	None stated	No	Yes	Fair
Soygür et al, 2002 (49)	Unclear*	Outcomes assessor only	No	Yes	Fair
Premgamone et al, 2001 (51)	Unclear*	Outcomes assessor only	No	Yes	Fair
Ettinger et al, 1997 (34)	Adequate	Double-blind (outcomes assessor; no further details)	Yes	Yes	Good
Hofbauer et al, 1994 (50)	Unclear*	None stated	No	Yes	Fair
Barcelo et al, 1993 (48)	Unclear*	Double-blind (no further details)	No	Yes	Fair
Allopurinol					
Ettinger et al, 1986 (53)	Adequate	Double-blind (outcomes assessor; no further details)	No	Yes	Fair
Miano et al, 1985 (54)‡	Unclear*	Double-blind (no further details)	No†	No withdrawals	Fair
Robertson et al, 1985 (55)	Unclear*	None stated	No†	No withdrawals	Fair
Smith, 1977 (56)	Adequate	Double-blind (no further details)	No	Yes	Fair
Acetohydroxamic acid					
Griffith et al, 1991 (59)	Unclear*	Double-blind (outcome assessor and study personnel; no further details)	Yes	Yes	Fair
Griffith et al, 1988 (58)	Adequate	Double-blind (patient, outcome assessor, and study personnel)	No	Yes	Fair
Williams et al, 1984 (60)	Adequate	Double-blind (outcome assessor and treating physician; no further details)	No	Yes	Fair
Magnesium vs. placebo: Ettinger et al, 1988 (42)	Adequate†	Double-blind (outcomes assessor; no further details)	No	Yes	Fair
Thiazide vs. magnesium: Ettinger et al, 1988 (42)	Adequate†	Double-blind (outcomes assessor; no further details)	No	Yes	Fair
Thiazide plus allopurinol: Borghi et al, 1993 (46)	Unclear	Open-label	No	Yes	Fair
Thiazide plus citrate: Fernández-Rodríguez et al, 2006 (45)	Unclear*	None stated	Yes	No withdrawals	Fair

* Methods of concealment not described or reported.
† Trial had inadequate sequence generation (medical record number) but adequate concealment (drug groups of identical appearance).
‡ Preliminary results.

Appendix Table 4. Strength of Evidence Grades and Definitions*

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.†

* Based on reference 32.
† Examples where evidence is available but strength of evidence may be graded as insufficient include when there is an unacceptably high risk of bias or a major inconsistency that cannot be explained (e.g., 2 studies with the same risk of bias with opposite results and no clear explanation for the discrepancy). In addition, strength of evidence may be graded as insufficient when data are too imprecise. This may be the case when the 95% CI is so wide that it prevents the exclusion of a clinically significant benefit or harm (e.g., lower CI bound <0.5 and upper CI bound >2).

Appendix Table 5. Strength of Evidence for Prevention of Stone Recurrence: Dietary Intervention Trials

Intervention	Stone Recurrence Type	Trials, *n*	Randomized Patients, *n*	Relative Risk (95% CI)	Risk of Bias*	Directness†	Precision‡	Consistency§	Strength of Evidence
Increased fluid intake vs. control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	220	0.45 (0.24–0.84)	High	Direct	Precise	NA	Low
	Radiographic	1	21	0.15 (0.02–1.07)	Medium	Direct	Imprecise	NA	Insufficient
Reduced soft-drink intake vs. control	Symptomatic	1	1009	0.83 (0.71–0.98)	Medium	Direct	Precise	NA	Low
	Composite	0	–	–	–	–	–	–	Insufficient
	Radiographic	0	–	–	–	–	–	–	Insufficient
Decreased animal protein intake vs. control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	115	1.00 (0.52–1.91)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Increased dietary fiber intake vs. control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	120	1.18 (0.66–2.12)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Low-protein, low-sodium, and normal- to high-calcium diet vs. low-calcium diet	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	120	0.52 (0.29–0.95)	Low	Direct	Precise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Low–animal protein, high-fiber diet vs. control diet	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	99	5.88 (1.39–24.92)	Medium	Direct	Precise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Extensive evaluation and tailored diet vs. limited evaluation and uniform diet	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	242	0.32 (0.14–0.74)	High	Direct	Precise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient

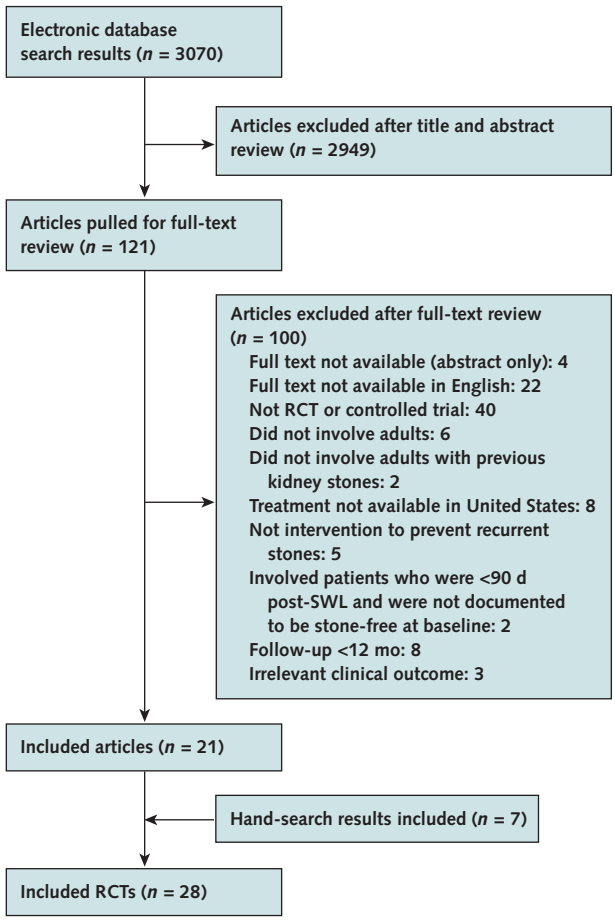
NA = not applicable.
* Rated low, medium, or high on the basis of whether the design and conduct of the studies for a given treatment comparison and outcome indicate good internal validity.
† Indicates whether results reflect a single direct link between the intervention of interest and the outcome and rated either direct or indirect.
‡ Indicates the degree of certainty surrounding an effect estimate of a given outcome and rated either precise or imprecise, with a precise estimate being one that allowed a clinically meaningful conclusion.
§ Indicates whether the included studies found a similar direction of effect and rated consistent; inconsistent; or, in cases where only 1 study was evaluated, unknown or NA.

Appendix Table 6. **Strength of Evidence for Prevention of Stone Recurrence: Pharmacologic Intervention Trials**

Intervention	Stone Recurrence Type	Trials, *n*	Randomized Patients, *n*	Relative Risk (95% CI)	Risk of Bias*	Directness†	Precision‡	Consistency§	Strength of Evidence
Thiazide vs. placebo or control	Symptomatic	1	51	1.04 (0.39–2.80)	Medium	Direct	Imprecise	NA	Insufficient
	Composite	5	314	0.53 (0.41–0.68)	Medium	Direct	Precise	Consistent	Moderate
	Radiographic	0	–	–	–	–	–	–	Insufficient
Citrate vs. placebo or control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	4	250	0.25 (0.14–0.44)	Medium	Direct	Precise	Consistent	Moderate
	Radiographic	1	50	0.95 (0.62–1.44)	Medium	Direct	Imprecise	NA	Low
Allopurinol vs. placebo or control	Symptomatic	1	72	0.36 (0.11–1.19)	Medium	Direct	Imprecise	NA	Low
	Composite	2	204	0.59 (0.42–0.84)	Medium	Direct	Precise	Consistent	Moderate
	Radiographic	1	72	1.07 (0.16–7.10)	Medium	Direct	Imprecise	NA	Insufficient
AHA vs. placebo	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	0	–	–	–	–	–	–	Insufficient
	Radiographic	2	304	0.81 (0.18–3.66)	Medium	Direct	Imprecise	Consistent	Insufficient
Magnesium vs. placebo	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	82	0.65 (0.37–1.16)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Thiazide plus citrate vs. thiazide	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	100	0.94 (0.52–1.68)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Thiazide plus allopurinol vs. thiazide	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	50	0.79 (0.18–3.49)	Medium	Direct	Imprecise	NA	Insufficient
	Radiographic	0	–	–	–	–	–	–	Insufficient

AHA = acetohydroxamic acid; NA = not applicable.
* Rated low, medium, or high on the basis of whether the design and conduct of the studies for a given outcome or comparison indicated good internal validity.
† Indicates whether results reflect a single direct link between the intervention of interest and the outcome and rated either direct or indirect.
‡ Indicates the degree of certainty surrounding an effect estimate of a given outcome and rated either precise or imprecise, with a precise estimate being one that allowed a clinically meaningful conclusion.
§ Indicates whether the included studies found a similar direction of effect and rated consistent; inconsistent; or, in cases where only 1 study was evaluated, unknown or NA.

Appendix Figure 2. **Summary of evidence search and selection.**



RCT = randomized, controlled trial; SWL = shock wave lithotripsy.

Appendix Table 7. **Summary of Evidence: Dietary Interventions to Prevent Stone Recurrence**

Intervention (Reference)	Participants	Stone History	Mean Treatment Duration, *mo*	Study Quality	Stone Recurrence Results	Strength of Evidence*	Withdrawals and Adverse Effects
Increased fluid intake vs. no treatment (36, 38)	241 men and women†	1 past CaOx or CaOx–CaPh stone	45 (range, 30–60)	1 fair and 1 poor	Symptomatic: no results reported Composite: reduced risk (12% vs. 27%; RR, 0.45 [95% CI, 0.24–0.84]; NNT, 7; 1 trial; 199 patients) and increased time to recurrence (39 vs. 25 mo; $P = 0.016$; 1 trial; 199 patients) Radiographic: no reduced risk (8% vs. 56%; RR, 0.15 [CI, 0.02–1.07]; NNT, 2; 1 trial; 21 patients)	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (10% vs. 9%; RR, 1.11 [CI, 0.49–2.50]; 2 trials) Withdrawals due to adverse events: no increased risk (0% vs. 0%; 1 trial; 21 patients) Adverse events: no results reported
Reduced soft-drink intake vs. control (39)	1009 men with high (>160 mL/d) soft-drink intake‡	>1 past stone, any type (mean, NR)	36	Fair	Symptomatic: reduced risk overall (34% vs. 41%; RR, 0.83 [CI, 0.71–0.98]; NNT, 14) and in participants whose most frequently consumed soft drink at baseline was acidified solely by phosphoric acid (30% vs. 46%; RR, 0.65 [CI, 0.49–0.87]; $P = 0.02$ for interaction) Composite: no results reported Radiographic: no results reported	Symptomatic: low Composite: insufficient Radiographic: insufficient	Overall withdrawals: borderline increased risk (8.7% vs. 5.5%; RR, 1.57 [CI, 1.00–2.49]) Withdrawals due to adverse events: no increased risk (0.4% vs. 0.4%) Adverse events: no increased risk for death (0.4% vs. 0.4%); no other results reported
Increased-fiber diet vs. control diet (40)	120 men and women without hyperoxaluria	>1 past CaOx or CaOx–CaPh stone (mean [lifetime], 4.2)	48	Fair	Symptomatic: no results reported Composite: no reduced risk (63% vs. 48%; RR, 1.18 [CI, 0.66–2.12]; NNT, 7) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (55% vs. 62%; RR, 0.89 [CI, 0.66–1.21]) Withdrawals due to adverse events: no results reported Adverse events: no results reported
Low–animal protein diet vs. control diet (40)	115 men and women without hyperoxaluria	>1 past CaOx or CaOx–CaPh stone (mean [lifetime], 2.9)	48	Fair	Symptomatic: no results reported Composite: no reduced risk (48% vs. 48%; RR, 1.00 [CI, 0.52–1.91]) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (58% vs. 62%; RR, 0.94 [CI, 0.70–1.27]) Withdrawals due to adverse events: no results reported Adverse events: no results reported

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Appendix Table 7—**Continued**

Intervention (Reference)	Participants	Stone History	Mean Treatment Duration, *mo*	Study Quality	Stone Recurrence Results	Strength of Evidence*	Withdrawals and Adverse Effects
Low-protein, low-sodium, and normal- to high-calcium diet vs. low-calcium diet§ (35)	120 men with hypercalciuria	>1 past CaOx stone (mean [lifetime], 5.4)	60	Good	Symptomatic: no results reported Composite: reduced risk (20% vs. 38%; RR, 0.52 [CI, 0.29–0.95]; NNT, 6) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (13% vs. 15%; RR, 0.89 [CI, 0.37–2.15]) Withdrawals due to adverse events: no increased risk (5% vs. 12%; RR, 0.43 [CI, 0.12–1.58]), including secondary to hypertension (2% vs. 12%; RR, 0.14 [CI, 0.02–1.13]), stroke (2% vs. 0%), and gout (2% vs. 0%) Adverse events: no results reported
Low–animal protein, high-fiber diet vs. control diet (41)	99 men and women‡	1 past CaOx or CaOx–CaPh stone	24	Fair	Symptomatic: no results reported Composite: increased risk (24% vs. 4%; RR, 5.88 [CI, 1.39–24.92]; NNT, 5) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (18% vs. 29%; RR, 0.60 [CI, 0.29–1.24]) Withdrawals due to adverse events: no results reported Adverse events: no results reported
Extensive evaluation and tailored diet vs. limited evaluation and uniform diet (37)	242 men and women‡	1 past calcium stone	36	Poor	Symptomatic: no results reported Composite: reduced risk (6% vs. 19%; RR, 0.32 [CI, 0.14–0.74]; NNT, 8) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Withdrawals for any reason: 14% overall; results not reported separately by treatment group Withdrawals due to adverse events: no results reported Adverse events: no results reported

CaOx = calcium oxalate; CaPh = calcium phosphate; NNT = number needed to treat; NR = not reported; RR = relative risk.

* Rated using the following grades: high, which indicates that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; moderate, which indicates that further research may change the confidence in the estimate of effect and may change the estimate; low, which indicates that further research is very likely to have an important effect on the confidence in the estimate of effect and is likely to change the estimate, meaning there is low confidence that the evidence reflects the true effect; or insufficient, which indicates that the evidence was unavailable or did not permit a conclusion.

† One increased-fluid trial included only participants without hypercalciuria, hyperuricosuria, or hyperoxaluria (n = 21), and 1 increased-fluid trial did not restrict participation on the basis of baseline biochemistry measures.

‡ Trials did not restrict participation on the basis of baseline biochemistry measures.

§ Participants in both treatment groups were advised to avoid consuming large amounts of oxalate-rich foods.

Appendix Table 8. **Summary of Evidence: Pharmacologic Interventions to Prevent Stone Recurrence**

Intervention (Reference)	Participants	Stone History	Mean Treatment Duration, *mo*	Study Quality	Stone Recurrence Results	Strength of Evidence*	Withdrawals and Adverse Events
Thiazide vs. placebo or control (42–47)	365 men and women†	≥2 past CaOx or CaOx–CaPh stones (mean [lifetime], 4.6 [1 trial])	35 (range, 12–47)‡	Fair	Symptomatic: no reduced risk (24% vs. 23%; RR, 1.04 [95% CI, 0.39–2.80]; NNT, 100; 1 trial; 51 patients) but reduced risk for lithotripsy (8% vs. 26%; RR, 0.31 [CI, 0.11–0.88]; NNT, 5.6; 1 trial; 100 patients) Composite: reduced risk (26% vs. 55%; RR, 0.52 [CI, 0.39–0.69]; NNT, 3.4; 5 trials; 300 patients) Radiographic: no results reported	Symptomatic: insufficient Composite: moderate Radiographic: insufficient	Overall withdrawals: 19% vs. 10%; RR, 1.77 (CI, 1.12–2.82); 6 trials; 365 patients Withdrawals due to adverse events: 9% vs. 1%; RR, 5.15 (CI, 1.51–17.57); 6 trials; 365 patients Adverse events: 4 RCTs (215 patients) reported a composite adverse event outcome (42–44, 47), collectively including orthostasis, gastrointestinal upset, erectile dysfunction, fatigue, and muscle symptoms, although none included the same components. Risk for composite adverse events was increased in 1 of 2 trials (101 patients) that reported results separately by treatment group (43, 44). Otherwise, no adverse event was reported in >1 participant in any trial.
Citrate vs. placebo or control (34, 48–52)	385 men and women§	≥2 past CaOx or CaOx–CaPh stones (4 trials), calcium stones (1 trial), or any type of stone (1 trial) (mean in past 3 y, 1.7 [1 trial]; mean [lifetime], 19.3 [1 trial])	25 (range, 12–37)‡	1 good and 5 fair	Symptomatic: no results reported Composite: reduced risk (11% vs. 52%; RR, 0.25 [CI, 0.14–0.44]; NNT, 2.5; 4 trials; 197 patients) Radiographic: no reduced risk (69% vs. 73%; RR, 0.95 [CI, 0.62–1.44]; NNT, 25; 1 trial; 38 patients)	Symptomatic: insufficient Composite: moderate Radiographic: low	Overall withdrawals: increased risk (36% vs. 20%; RR, 1.76 [CI, 1.12–2.75]; 4 trials; 219 patients) (34, 48, 50, 51) Withdrawals due to adverse events: increased risk (15% vs. 2%; RR, 5.18 [CI, 1.51–17.79]; 4 trials; 219 patients) Adverse events: increased risk for any adverse event (24% vs. 0%; RR, 12.47 [CI, 1.68–92.48]; 2 trials; 98 patients) (50, 51) but not for gastrointestinal adverse events (26% vs. 16%; RR, 2.47 [CI, 0.54–11.24]; 3 trials; 171 patients) (34, 48, 50)

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Appendix Table 8—**Continued**

Intervention (Reference)	Participants	Stone History	Mean Treatment Duration, *mo*	Study Quality	Stone Recurrence Results	Strength of Evidence*	Withdrawals and Adverse Events
Allopurinol vs. placebo or control (53–56)	240 men and women‖	≥2 past CaOx or CaOx–CaPh stones (mean, NR)	43 (range, 24–60)‡	Fair	Symptomatic: no reduced risk (10% vs. 29%; RR, 0.36 [CI, 0.11–1.19]; NNT, 5; 1 trial; 60 patients) but increased time to recurrent stone (33 vs. 27 mo; $P < 0.05$; NNT, 17; 1 trial; 60 patients) Composite: reduced risk (33% vs. 55%; RR, 0.59 [CI, 0.42–0.84]; NNT, 4.5; 2 trials; 152 patients) Radiographic: no reduced risk (7% vs. 6%; RR, 1.07 [CI, 0.16–7.10]; NNT, 100; 1 trial; 60 patients)	Symptomatic: low Composite: moderate Radiographic: insufficient	Overall withdrawals: no increased risk (31% vs. 42%; RR, 0.81 [CI, 0.41–1.62]; 2 trials; 74 patients) Withdrawals due to adverse events: no increased risk (4% vs. 8%; RR, 0.53 [CI, 0.16–1.77]; 2 trials; 204 patients) Adverse events: no increased risk for rash (2% vs. 2%; 2 trials; 152 patients)
AHA vs. placebo (58–60)	343 men and women with chronic urea-splitting UTIs	≥2 past struvite stones (mean lifetime stone operations, 1.9; 1 trial)	20 (range, 18–24)	Fair	Symptomatic: no reduced risk for surgery for obstruction or infection (0% vs. 11%; RR, 0.21 [CI, 0.01–4.11]; NNT, 9.5; 1 trial; 39 patients) Composite: no results reported Radiographic: no reduced risk (13% vs. 20%; RR, 0.81 [CI, 0.18–3.66]; NNT, 14; 2 trials; 35 patients)	Symptomatic: insufficient Composite: insufficient Radiographic: insufficient	Overall withdrawals: no increased risk (63% vs. 46%; RR, 1.31 [CI, 0.56–3.05]; 2 trials; 304 patients) Withdrawals due to adverse events: increased risk (22% vs. 5%; RR, 4.39 [CI, 2.02–9.55]; 2 trials; 304 patients) Adverse events: increased risk for any adverse event (64% vs. 32%; RR, 1.95 [CI, 1.29–2.95]; 3 trials; 343 patients) and anemia (18% vs. 8%; RR, 2.18 [CI, 1.13–4.21]; 2 trials; 274 patients) (58, 59). No significantly increased risk for headache (9% vs. 4%; RR, 2.18 [CI, 0.42–11.32]; 1 trial; 94 patients) (59) or alopecia (9% vs. 2%; RR, 4.36 [CI, 0.51–37.53]; 1 trial; 94 patients) (59). Results for tremor (25%) and deep venous thrombosis (16%) were each reported only for the AHA group in 1 trial (20 patients) (60).
Magnesium vs. placebo (42)	82 men and women¶	≥2 past CaOx or CaOx–CaPh stones (mean [lifetime], 4.1)	36‡	Fair	Symptomatic: no results reported Composite: no reduced risk (29% vs. 45%; RR, 0.65 [CI, 0.37–1.16]; NNT, 6) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (18% vs. 17%; RR, 1.09 [CI, 0.40–2.97]) Withdrawals due to adverse events: 6% vs. 3%; RR, 1.82 (CI, 0.20–16.77), with most in the magnesium group attributable to gastrointestinal adverse events Adverse events: no results reported

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Appendix Table 8—**Continued**

Intervention (Reference)	Participants	Stone History	Mean Treatment Duration, *mo*	Study Quality	Stone Recurrence Results	Strength of Evidence*	Withdrawals and Adverse Events
Thiazide vs. magnesium (42)	93 men and women¶	≥2 past CaOx or CaOx–CaPh stones (mean [lifetime], 3.8)	36‡	Fair	Symptomatic: no results reported Composite: no reduced risk (14% vs. 29%; RR, 0.49 [CI, 0.21–1.14]; NNT, 7) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (0% vs. 0%) Withdrawals due to adverse events: no increased risk (0% vs. 0%) Adverse events: no results reported
Thiazide plus citrate vs. thiazide (45)	100 patients (sex NR)¶	≥2 past CaOx or CaOx–CaPh stones (mean, NR)	36‡	Fair	Symptomatic: no results reported Composite: no reduced risk (30% vs. 32%; RR, 0.94 [CI, 0.52–1.68]; NNT, 50) Radiographic: no results reported	Symptomatic: insufficient Composite: low Radiographic: insufficient	Overall withdrawals: no increased risk (0% vs. 0%) Withdrawals due to adverse events: no increased risk (0% vs. 0%) Adverse events: no results reported
Thiazide plus allopurinol vs. thiazide (46)	50 men and women with hypercalciuria	≥2 past CaOx or CaOx–CaPh stones (mean, NR)	36‡	Fair	Symptomatic: no results reported Composite: no reduced risk (13% vs. 16%; RR, 0.79 [CI, 0.18–3.49]; NNT, 33) Radiographic: no results reported	Symptomatic: insufficient Composite: insufficient Radiographic: insufficient	Overall withdrawals: no increased risk (4% vs. 24%; RR, 0.17 [CI, 0.02–1.29]) Withdrawals due to adverse events: no increased risk (0% vs. 8%; RR, 0.20 [CI, 0.01–3.97]) Adverse events: no results reported for combination group. Hypokalemia and hypotension were each reported in 1 participant assigned to thiazide monotherapy.

AHA = acetohydroxamic acid; CaOx = calcium oxalate; CaPh = calcium phosphate; NNT = number needed to treat; NR = not reported; RCT = randomized, controlled trial; RR = relative risk.

* Rated using the following grades: high, which indicates that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; moderate, which indicates that further research may change the confidence in the estimate of effect and may change the estimate; low, which indicates that further research is very likely to have an important effect on the confidence in the estimate of effect and is likely to change the estimate, meaning there is low confidence that the evidence reflects the true effect; and insufficient, which indicates that the evidence was unavailable or did not permit a conclusion.

† One trial of thiazide versus placebo or control included only participants with hypercalciuria (n = 50); 1 trial included only participants with hyperoxaluria (n = 51); 1 trial included only participants who did not have hypocitraturia, hyperuricosuria, or hyperoxaluria (n = 41); and 3 thiazide trials did not restrict participation on the basis of baseline biochemistry measures.

‡ Mean study duration and range for these treatment comparisons included results from at least 1 trial that included other treatment interventions and reported only overall mean study duration but did not report results separated by assigned treatment group.

§ One citrate trial included only participants with hypocitraturia and not hypercalciuria or hyperoxaluria (n = 57), whereas 5 citrate trials did not restrict participation on the basis of baseline biochemistry measures.

‖ One allopurinol trial included only participants with hyperuricosuria and no hypercalciuria (n = 72), whereas 3 allopurinol trials did not restrict participation on the basis of baseline biochemistry measures.

¶ No trials restricted participation on the basis of baseline biochemistry measures.

Correction: Medical Management to Prevent Recurrent Nephrolithiasis in Adults

In a recent guideline (1), the heading and some of the data in the fourth columns of Appendix Tables 5 and 6 were incorrect. The corrected tables appear below.

This has been corrected in the online version.

Reference

1. Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. Ann Intern Med. 2013;158:535-43.

Appendix Table 5. **Strength of Evidence for Prevention of Stone Recurrence: Dietary Intervention Trials**

Intervention	Stone Recurrence Type	Trials, *n*	Randomized Patients, *n*	Relative Risk (95% CI)	Risk of Bias*	Directness†	Precision‡	Consistency§	Strength of Evidence
Increased fluid intake vs. control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	220	0.45 (0.24–0.84)	High	Direct	Precise	NA	Low
	Radiographic	1	21	0.15 (0.02–1.07)	Medium	Direct	Imprecise	NA	Insufficient
Reduced soft-drink intake vs. control	Symptomatic	1	1009	0.83 (0.71–0.98)	Medium	Direct	Precise	NA	Low
	Composite	0	–	–	–	–	–	–	Insufficient
	Radiographic	0	–	–	–	–	–	–	Insufficient
Decreased animal protein intake vs. control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	115	1.00 (0.52–1.91)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Increased dietary fiber intake vs. control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	120	1.18 (0.66–2.12)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Low-protein, low-sodium, and normal- to high-calcium diet vs. low-calcium diet	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	120	0.52 (0.29–0.95)	Low	Direct	Precise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Low–animal protein, high-fiber diet vs. control diet	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	99	5.88 (1.39–24.92)	Medium	Direct	Precise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Extensive evaluation and tailored diet vs. limited evaluation and uniform diet	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	242	0.32 (0.14–0.74)	High	Direct	Precise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient

NA = not applicable.
* Rated low, medium, or high on the basis of whether the design and conduct of the studies for a given treatment comparison and outcome indicate good internal validity.
† Indicates whether results reflect a single direct link between the intervention of interest and the outcome and rated either direct or indirect.
‡ Indicates the degree of certainty surrounding an effect estimate of a given outcome and rated either precise or imprecise, with a precise estimate being one that allowed a clinically meaningful conclusion.
§ Indicates whether the included studies found a similar direction of effect and rated consistent; inconsistent; or, in cases where only 1 study was evaluated, unknown or NA.

Appendix Table 6. **Strength of Evidence for Prevention of Stone Recurrence: Pharmacologic Intervention Trials**

Intervention	Stone Recurrence Type	Trials, *n*	Randomized Patients, *n*	Relative Risk (95% CI)	Risk of Bias*	Directness†	Precision‡	Consistency§	Strength of Evidence
Thiazide vs. placebo or control	Symptomatic	1	51	1.04 (0.39–2.80)	Medium	Direct	Imprecise	NA	Insufficient
	Composite	5	314	0.53 (0.41–0.68)	Medium	Direct	Precise	Consistent	Moderate
	Radiographic	0	–	–	–	–	–	–	Insufficient
Citrate vs. placebo or control	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	4	250	0.25 (0.14–0.44)	Medium	Direct	Precise	Consistent	Moderate
	Radiographic	1	50	0.95 (0.62–1.44)	Medium	Direct	Imprecise	NA	Low
Allopurinol vs. placebo or control	Symptomatic	1	72	0.36 (0.11–1.19)	Medium	Direct	Imprecise	NA	Low
	Composite	2	204	0.59 (0.42–0.84)	Medium	Direct	Precise	Consistent	Moderate
	Radiographic	1	72	1.07 (0.16–7.10)	Medium	Direct	Imprecise	NA	Insufficient
AHA vs. placebo	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	0	–	–	–	–	–	–	Insufficient
	Radiographic	2	304	0.81 (0.18–3.66)	Medium	Direct	Imprecise	Consistent	Insufficient
Magnesium vs. placebo	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	82	0.65 (0.37–1.16)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Thiazide plus citrate vs. thiazide	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	100	0.94 (0.52–1.68)	Medium	Direct	Imprecise	NA	Low
	Radiographic	0	–	–	–	–	–	–	Insufficient
Thiazide plus allopurinol vs. thiazide	Symptomatic	0	–	–	–	–	–	–	Insufficient
	Composite	1	50	0.79 (0.18–3.49)	Medium	Direct	Imprecise	NA	Insufficient
	Radiographic	0	–	–	–	–	–	–	Insufficient

AHA = acetohydroxamic acid; NA = not applicable.
* Rated low, medium, or high on the basis of whether the design and conduct of the studies for a given outcome or comparison indicated good internal validity.
† Indicates whether results reflect a single direct link between the intervention of interest and the outcome and rated either direct or indirect.
‡ Indicates the degree of certainty surrounding an effect estimate of a given outcome and rated either precise or imprecise, with a precise estimate being one that allowed a clinically meaningful conclusion.
§ Indicates whether the included studies found a similar direction of effect and rated consistent; inconsistent; or, in cases where only 1 study was evaluated, unknown or NA.