Comparative Effectiveness Review
Number 61

Effective Health Care Program

Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies

Executive Summary

Introduction

Nephrolithiasis is a condition in which hard masses (kidney stones) form within the urinary tract. These stones form from crystals that separate out of the urine. Formation may occur when the urinary concentration of crystal-forming substances (e.g., calcium, oxalate, uric acid) is high and/or that of substances that inhibit stone formation (e.g., citrate) is low.

The lifetime incidence of kidney stones is approximately 13 percent for men and 7 percent for women.[1,2] Reports conflict regarding whether incidence is rising overall but consistently report rising incidence in women and a falling male-to-female ratio.[3-5] Although stones may be asymptomatic,[6] potential consequences include abdominal and flank pain, nausea and vomiting, urinary tract obstruction, infection, and procedure-related morbidity. Following an initial stone event, the 5-year recurrence rate in the absence of specific treatment is 35 to 50 percent.[7] Direct medical expenditures associated with kidney stones may exceed $4.5 billion annually in the United States.[1,8]

Approximately 80 percent of adults with kidney stones have stones consisting predominately of calcium oxalate and/or calcium phosphate, with most remaining patients having either struvite or uric acid stones.[9] Many patients with kidney stones have low urine volume and/or one or more biochemical abnormalities, including

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hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia, and either low or high urine pH.[10,11]

In many patients, kidney stones are caused by an interaction between genetic inheritance and environmental exposure.[12] Genetic factors are thought to account for about half the risk of developing kidney stones.[12] Dietary factors associated with increased stone risk include low fluid intake, low calcium intake, and high fructose intake, while evidence is mixed for increased animal protein, increased sodium, increased sucrose, and low magnesium.[13-17]

Risk of kidney stones also may be increased by medical conditions such as primary hyperparathyroidism,[18] obesity,[19] diabetes,[20] gout,[21] and intestinal malabsorption,[22] and by anatomic abnormalities such as medullary sponge kidney and horseshoe kidney.

Previous systematic reviews of randomized controlled trials (RCTs) of dietary and pharmacological therapies have reported that increased fluid intake,[23] thiazide diuretics,[24-26] and citrate pharmacotherapy[26,27] reduce stone recurrence, but that evidence was insufficient regarding the efficacy of other pharmacological treatments.[24,26,28,29] Results of these reviews were limited in that they did not: (1) include more recent RCTs; (2) compare different pharmacological treatments with each other; (3) compare combinations of pharmacological treatments with monotherapy; (4) explicitly account for the effect of fluid and dietary co-interventions on pharmacological treatment efficacy; and/or (5) address the potential impact of patient demographics and comorbidities on treatment outcomes.

Clinical guidelines recommend that patients who experience kidney stones undergo a laboratory evaluation, including analysis of stone composition and possibly of urine and blood biochemistries.[30] Unclear, however, is whether pretreatment laboratory test results predict effectiveness of treatment on stone recurrence and other clinical health outcomes, or whether treatment tailored to pretreatment laboratory results is associated with better clinical health outcomes than empiric therapy. Nor have followup biochemical test results been proven as valid surrogates for predicting the effectiveness of treatment in preventing stone recurrence.

Clinical uncertainty exists regarding the effectiveness, comparative effectiveness, and adverse effects of dietary and pharmacological preventive treatments; the value of urine and blood biochemical measures for initiating and/or modifying treatment; and the potential impact of patient and stone characteristics on important treatment outcomes.

This systematic review and meta-analysis attempts to comprehensively address these questions. We developed an analytic framework that incorporated six Key Questions and specified the patient populations, interventions, comparisons, outcomes, and harms of interest (Figure 1 in the full report). The Key Questions were:

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

Key Question 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?

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

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

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

Key Question 6. In adults with a history of nephrolithiasis being treated to prevent stone recurrence, do results of followup blood and urine biochemistry measures predict final health outcomes and intermediate stone outcomes?

Methods

Data Sources

We searched MEDLINE® from January 1, 1948, through the third week of November 2011 and the Cochrane Central Register of Controlled Trials (CENTRAL) through the fourth quarter of 2011 to identify RCTs of treatments to prevent recurrent nephrolithiasis. Appendix A of the full report contains the full search strategy. We also reviewed reference lists of included studies, previous systematic reviews, and relevant clinical guidelines. With Google Scholar we performed forward citation searching of key included RCTs. To identify unpublished RCTs, we searched ClinicalTrials.gov, Web of Science, and sought industry scientific information packets for relevant

regulatory documents and reports of conducted trials. We selected studies based on prespecified inclusion and exclusion criteria (Appendix B of the full report). Two reviewers evaluated each study at the title or abstract stage and at the full text article stage to determine eligibility for inclusion in the review.

We restricted the review to studies published in full text in English that enrolled adults age 18 years or older with a history of one or more past kidney stone episodes. 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. In an attempt to distinguish the effect of secondary prevention from lithotripsy, we excluded studies with participants who had undergone lithotripsy fewer than 90 days earlier unless participants were documented to be stone free at baseline. We considered studies conducted in all settings and geographic locations.

For questions related to the efficacy of diet therapy, we included RCTs of at least 12 months duration that evaluated individual or multicomponent diets, and trials that evaluated empiric dietary interventions or diets tailored to patient characteristics such as baseline urine or blood biochemical testing and/or stone type. For questions related to the efficacy of pharmacological therapy, we included RCTs of at least 12 months duration that evaluated pharmacological agents currently approved by the U.S. Food and Drug Administration and available in the United States either by prescription or over the counter and that compared these treatments with placebo, usual care/no treatment, or other available active treatments. RCTs addressing efficacy must have reported stone recurrence and/or other clinical outcomes relevant to kidney stones. Stone recurrence may have been symptomatic, identified by scheduled radiographic imaging, or reported as a composite recurrence outcome detected either symptomatically or radiographically. Other clinical outcomes relevant to kidney stones may have included pain, urinary tract obstruction with acute renal failure, infection, morbidity related to a procedure to treat a recurrent stone, emergency room visits or hospitalizations for treatment of recurrent stones, quality of life, and end-stage renal disease. We also considered as eligible studies that reported change in stone size or residual stone clearance.

For questions related to adverse effects of diet or pharmacological therapy, we included RCTs that met the above criteria and were of at least 3 months duration. In addition, for adverse effects of pharmacological therapy, we included trials to prevent recurrent kidney stones that reported only followup blood and/or urine biochemical measures as efficacy outcomes, and prospective observational studies in cohorts of at least 100 patients being treated to prevent recurrent kidney stones, with a minimum duration of 3 months for both study types. 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 similar compositions to those of eligible trials, dietary adverse effects seemed low, and the likelihood of finding reported adverse effects in lower quality diet studies was low.

Data Extraction and Quality Assessment

One reviewer extracted and a second reviewer verified data for each study, including participant entry criteria, intervention and control regimens, followup duration, participant characteristics, stone recurrence and other clinical health outcomes, followup urine and blood measurements, adverse events, and adherence. Two reviewers also assessed each eligible RCT for risk of bias using criteria recommended by the Cochrane Collaboration: (1) adequacy of allocation concealment;[31] (2) blinding methods; (3) data completeness; and (4) whether reasons for dropouts/attrition were reported.[32] We evaluated the quality of studies reporting adverse events by using a subset of questions from the McHarm Scale.[33] We resolved discrepancies in quality ratings by group discussion.

Data Synthesis and Analysis

We qualitatively synthesized and summarized extracted study data in evidence tables relevant to each Key Question. We performed a quantitative meta-analysis of all main interventions and primary outcomes when the patient populations, interventions, and outcomes were clinically comparable. We analyzed data using Review Manager (RevMan) version 5.1 software.[34] We used random effects models to generate pooled estimates of relative risks and 95 percent confidence intervals. We summarized statistical heterogeneity by using the I^2 statistic (50 percent indicates moderate heterogeneity and 75 percent or greater indicates high heterogeneity).[35] For analyses of pharmacological treatments, results were presented for each pharmacological class as a whole and separately for individual agents. We explored the feasibility of performing subgroup analyses for treatment efficacy and adverse events outcomes according to the following prespecified factors: (1) patient demographic and comorbid characteristics (age, gender, race, and selected comorbid conditions); (2) baseline diet characteristics; (3) baseline

stone characteristics (stone composition, frequency of past stone episodes, severity of past stone episodes, past shock-wave lithotripsy, or presence of residual stones/fragments); (4) baseline blood or urine biochemical measures; (5) study duration; (6) patient treatment adherence; (7) followup blood and urine biochemical measures; (8) and study quality.

We evaluated the overall strength of RCT evidence regarding the efficacy of diet and pharmacological treatments for preventing key stone recurrence outcomes (Key Questions 2 and 4) using methods developed by the Agency for Healthcare Research and Quality (AHRQ) and the EHC Program.[36] We did not formally rate strength of evidence for adverse effects (Key Questions 3 and 5) because results for specific and any adverse effects outcomes were so infrequently and heterogeneously reported. We did not formally rate strength of evidence for whether baseline or followup labs predict treatment outcomes (Key Questions 1 and 6) because data were scarce, indirect, and did not seem to fit within the AHRQ framework for strength of evidence rating.

Role of the Funding Source

The topic addressed in this review was nominated to AHRQ by a professional society interested in developing a clinical guideline on treatment to prevent recurrent kidney stones. AHRQ funded the work. The scope and Key Questions were developed with input from stakeholders and a technical expert panel. AHRQ approved the final scope and Key Questions for this review.

Results

Key Question 1: In adults with a history of nephrolithiasis, do results of baseline stone composition and blood and urine chemistries predict the effectiveness of diet and/or pharmacological treatment on final health outcomes and intermediate stone outcomes, and reduce treatment adverse effects?

Key Findings

Stone Composition

- All diet trials, and trials of thiazide, citrate, allopurinol, and magnesium pharmacotherapy that specified stone type were limited to patients with calcium stones, and all acetohydroxamic acid trials were limited to patients with struvite (ammonium-magnesium-phosphate) stones. Therefore, it was not possible to evaluate the effect of these interventions on risk of stone recurrence in patients with other stone types, including the effect of allopurinol in individuals with uric acid stones.

Blood and Urine Biochemistries

- Almost no RCTs reported stone recurrence outcomes between treatments for subgroups stratified by baseline biochemistry levels. In comparisons between studies, results were mixed regarding whether specific baseline biochemical measures predicted the effectiveness of diet or pharmacological treatment relative to control in reducing risk of stone recurrence.
- In two RCTs limited to patients with calcium stones and **hyperuricosuria**[37] or **hyperuricemia**,[38] those randomized to allopurinol versus control had a significantly lower risk of composite recurrent stones (33.3 vs. 55.4%; RR, 0.59 [CI, 0.42 to 0.84]), whereas symptomatic stone recurrence rate did not appear lower with allopurinol in trials of participants unselected for high uric acid levels.[39,40]
- We identified limited evidence that baseline **urine calcium levels** made no significant differences in the efficacy of increased fluid intake, diet, thiazides, citrate, or allopurinol versus control on recurrent stone outcomes (based on comparisons of results between patient groups with,[41] without,[37,42,43] or unselected for baseline hypercalciuria,[38,41,44-50] and in analyses adjusted for baseline urine calcium levels[51]).
- We identified limited evidence that baseline **urine oxalate levels** made no significant differences in the efficacy of increased fluid intake, diet, thiazides, or citrate versus control on recurrent stone outcomes (based on comparisons of results between patient groups with,[52] without,[42,47,48,50] or unselected for hyperoxaluria,[46] or adjusted for baseline urine oxalate levels[44,51] or baseline hyperoxaluria[44]).
- Efficacy of citrate treatment on recurrent stone outcomes did not differ between patient groups with[43] or unselected for **hypocitraturia**.[44,45]
- We identified no RCT data addressing whether the effect of dietary or pharmacological treatment on risk of recurrent stones differs according to **other baseline urine measures**, including magnesium, phosphate, potassium, pH, calcium-oxalate supersaturation, calcium-phosphate supersaturation, or uric acid supersaturation.
- In one RCT, participants randomized to an **extensive biochemical evaluation plus tailored diet treatment** had a significantly lower risk of recurrent stones versus

those assigned a **limited evaluation plus empiric diet treatment**.[53] Because the trial did not report separate results by biochemical abnormality or tailored diet subgroup, it was not possible to isolate the effects of any individual baseline biochemistry measure on treatment outcomes.

Results were limited because a substantial minority of RCTs reported no information on baseline biochemistry measures. Further, many trials that reported prevalence or based participant eligibility on the presence or absence of such abnormalities did not specify how biochemical abnormalities were defined. Though definitions of biochemical abnormalities utilized in trials reporting appeared roughly similar, they were not standardized.

Key Question 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?

Key Findings

- We found low strength of evidence that, compared to no treatment, **increased fluid intake** to maintain daily urine output of >2 L/day significantly reduces risk of composite recurrent stones, but insufficient strength of evidence that intake to maintain daily urine output of >2.5 L/day does not reduce risk of radiographic recurrent stones.[42,46]
- We found low strength of evidence that increased (>2 L/day) **oligomineral water** does not significantly reduce risk of composite recurrent stones compared with >2 L/day of tap water.[54]
- We found low strength of evidence that **advice to reduce soft drink intake** significantly reduces risk of symptomatic recurrent stones compared with no treatment in men with high baseline soft drink consumption.[55]
- In individuals on an increased fluid and moderate calcium diet, we found low strength of evidence that **increased fiber intake** did not reduce risk of recurrent stones compared with a control diet.[56]
- In individuals on an increased fluid and moderate calcium diet, we found low strength of evidence that **decreased animal protein intake** did not reduce risk of recurrent stones compared with a control diet.[56] Trials comparing multicomponent diets that included low animal protein with control diets showed mixed results for risk of stone recurrence.[51,53,57]
- We found low strength of evidence that an intervention involving an **extensive biochemical evaluation followed by a tailored diet** reduces risk of composite recurrent stones compared with a limited evaluation and **empiric diet**. However, no data were reported for specific biochemical abnormality or tailored diet subgroups.[53]
- In individuals on increased fluid intake, results regarding the efficacy of other **multicomponent diet** interventions for reducing risk of stone recurrence were mixed, showing both decreased[51] and increased[57] risk of recurrence.
- We found no evidence regarding whether diets including increased calcium, low sodium, low oxalate, or low purine as isolated diet interventions reduce risk of recurrent kidney stones. However, in one trial, a multicomponent diet including normal to high **dietary calcium** had significantly lower risk of composite recurrent stones compared with a low calcium diet.[51]
- Included diet trials enrolled predominately young to middle-aged men. Half of the diet trials included only participants with a single calcium stone episode, and half included or were limited to those with recurrent stones. Nearly all studies relied on a composite definition of recurrent stone outcomes that included either symptomatic or radiographic recurrence. Few studies reported adherence. Except in one trial in which participants were recruited from primary care settings,[57] study subjects appeared to have been recruited from urology, nephrology, or specialty stone clinics.
- These results are detailed in Table A.

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

Key Findings

Overall

- Adverse effects as possibly reflected by withdrawals for any cause were low in trials evaluating increased fluid intake, but high in long-term trials evaluating low soft drink intake, high fiber, low animal protein, and multicomponent dietary interventions; other adverse events reporting was poor.

Table A. Summary of evidence for prevention of kidney stones: Dietary interventions (KQ 2)

Interventions, Studies (Study Quality)	Stone Recurrence Results	Strength of Evidence*
Increased Fluid Intake vs. No Treatment 2 RCTs (1 fair, 1 poor) in patients with single past calcium stone[42,46]	*Symptomatic:* No results reported. *Composite:* Reduced risk (12 vs. 27%; RR, 0.45 [CI, 0.24 to 0.84], n=1 trial) and increased time to recurrence (39 vs. 25 mo., p=0.016, n=1 trial). *Radiographic:* No reduced risk (8 vs. 56%; RR, 0.15 [CI, 0.02 to 1.07], n=1 trial).	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient
Increased Oligomineral Water Intake vs. Increased Tap Water Intake 1 RCT (fair) in patients with recurrent calcium stones.[54]	*Symptomatic:* No results reported. *Composite:* No results reported. *Radiographic:* No reduced risk (17 vs. 23%; RR, 0.73 [CI, 0.48 to 1.09]).	Symptomatic: Insufficient Composite: Insufficient Radiographic: Low
Reduced Soft Drink Intake vs. Control 1 RCT (fair) in men with high soft drink intake and 1 or more past stones[55]	*Symptomatic:* Reduced risk (34 vs. 41%; RR, 0.83 [CI, 0.71 to 0.98]), particularly in participants whose most frequently consumed soft drink was acidified by phosphoric acid and not citric acid (30% vs. 46%; RR, 0.65 [CI, 0.49 to 0.87], p=0.02 for interaction). *Composite:* No results reported. *Radiographic:* No results reported.	Symptomatic: Low Composite: Insufficient Radiographic: Insufficient
Multicomponent Diet (Borghi 2002) vs. Control Diet† 1 RCT (good) in patients with recurrent calcium stones[51]	*Symptomatic:* No results reported. *Composite:* Reduced risk (20 vs. 38%; RR, 0.52 [CI, 0.29 to 0.95]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient
Multicomponent Diet (Hiatt 1996) vs. Control Diet‡ 1 RCT (fair) in patients with single past calcium stone[57]	*Symptomatic:* No results reported. *Composite:* Increased risk (24 vs. 4%; RR, 5.88 [CI, 1.39 to 24.92]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient
Tailored Diet vs. Empiric Diet 1 RCT (poor) in patients with single past calcium stone[53]	*Symptomatic:* No results reported. *Composite:* Reduced risk (6 vs. 19%; RR, 0.32 [CI, 0.14 to 0.74]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient
Decreased Animal Protein Diet vs. Control Diet 1 RCT (fair) in patients with 1 or more past calcium stones[56]	*Symptomatic:* No results reported. *Composite:* No reduced risk (48 vs. 48%; RR, 1.00 [CI, 0.52 to 1.91]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient
Increased Fiber Diet vs. Control Diet 1 RCT (fair) in patients with 1 or more past calcium stones[56]	*Symptomatic:* No results reported. *Composite:* No reduced risk (63 vs. 48%; RR, 1.18 [CI, 0.66 to 2.12]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient

CI = 95 percent confidence interval; KQ = Key Question; RCT = randomized controlled trial; RR = relative risk.

*Strength of evidence was rated using the following grades: (1) high confidence indicated that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate confidence denoted that further research may change our confidence in the estimate of effect and may change the estimate; (3) low confidence indicated that further research is very likely to have an important impact 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 (4) insufficient, indicating that the evidence was unavailable or did not permit a conclusion. Examples when evidence is available, but SOE may be graded as insufficient include when there is an unacceptably high risk of bias, or there is 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, SOE may be graded as insufficient when data are too imprecise. This may be the case when the 95% CI is so wide that it cannot exclude either a clinically significant benefit or harm (e.g. lower CI bound <0.5 and upper CI bound >2).

†Borghi 2002 multicomponent diet (high calcium, low protein and low sodium intake) versus control diet (low calcium intake).

‡Hiatt 1996 multicomponent diet (low animal protein and high fiber intake) versus control diet.

Increased Fluid Intake

- Withdrawals in the two eligible RCTs averaged 9.5 percent (range 0 to 10) and appeared similar between intervention and control groups.
- The one trial reporting stated that no participants withdrew due to adverse events.[42]
- Neither trial reported results regarding the number of participants with at least one adverse event or with specific adverse events.

Increased Oligomineral Water Intake Versus Increased Tap Water Intake

- The single eligible RCT reported no withdrawals from either treatment group but didn't report results regarding the number of participants with at least one adverse event or with any specific adverse event.[54]

Decreased Soft Drink Intake

- The single eligible RCT reported that 8.7 percent of participants withdrew in the intervention group versus 5.5 percent in the control group.[55] In each group, two participants withdrew due to adverse events and two died. The trial reported no other adverse events data.

Multicomponent Dietary Interventions

- Withdrawals in the three eligible RCTs averaged 16.4 percent and were no greater in the intervention groups than the control group in the two studies that reported withdrawal outcomes separately by treatment group.[51,57]
- In one trial reporting, withdrawals due to adverse events were 5.0 percent in the multicomponent dietary intervention group versus 11.7 percent in the control group.[51]
- In one trial reporting, two participants in the control group died, and no other specific adverse event was reported in more than one participant assigned to either treatment group.[51]

High Fiber Intake

- The single eligible RCT reported that after 4 years, 55.0 percent of participants withdrew in the high fiber group versus 61.7 percent in the control group.[56] This trial reported no other adverse event data.

Low Animal Protein Intake

- The single eligible RCT reported that after 4 years, 58.0 percent of participants withdrew in the low protein group versus 61.7 percent in the control group.[56] This trial reported no other adverse events data.

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

Key Findings

- We found moderate strength of evidence that **thiazides** significantly reduce risk of composite recurrent calcium stones.[41,47-50,58] Further results indicated no significant difference in efficacy between different thiazide agents, between hydrochlorothiazide doses of 25 to 50 mg twice daily, between chlorthalidone doses of 25 to 50 mg daily, between patients recruited from stone specialty clinics versus those recruited from primary care, or between trials of at least 3 years in duration and a single 2-year trial. We found insufficient strength of evidence that thiazides do not reduce risk of symptomatic recurrent stones, but this was based on a single 1-year study.[52]
- We found moderate strength of evidence that **citrate pharmacotherapy** significantly reduces risk of composite recurrent calcium stones.[43-45] Further results indicated no significant difference in efficacy between different citrate agents (i.e., potassium citrate, potassium-magnesium citrate, or potassium-sodium citrate), between trials of 1 year versus those at least 2 years in duration, or between patients with single and multiple past stone episodes. We found low strength of evidence that citrates do not reduce risk of radiographic stone recurrence.[59]
- We found moderate strength of evidence that **allopurinol** significantly reduced risk of composite recurrent calcium stones in patients with hyperuricosuria or hyperuricemia. Further results indicated no significant difference in efficacy between allopurinol doses of 100 and 300 mg daily, or between trials of 2 and 5 years in duration. We found low strength of evidence that allopurinol does not reduce risk of recurrent symptomatic stones and insufficient strength of evidence that allopurinol does not reduce risk of radiographic stones.
- We found insufficient strength of evidence that **acetohydroxamic acid** does not reduce risk of radiographic recurrent stones in patients with chronic urea-splitting urinary tract infections and recurrent struvite stones in trials that either mandated or permitted concomitant treatment with suppressive antibiotics.[60-62]

- We found low strength of evidence that **magnesium** does not reduce risk of composite recurrent stones.[47]
- Compared with thiazide alone, we found insufficient strength of evidence that **allopurinol plus thiazide**[41] did not reduce risk of composite recurrent stones and low strength of evidence that **citrate plus thiazide**[58] did not reduce risk of composite recurrent stones.
- Included trials enrolled predominately young to middle-aged men with recurrent stone episodes and no biochemical abnormality that would predispose them to kidney stones. All treatment groups were assigned increased fluid intake, so trials evaluated whether addition of pharmacological interventions had any further benefit. Nearly all studies relied on a composite definition of recurrent stone outcomes that included either symptomatic or radiographic recurrence. Few studies reported adherence. Study subjects appeared to have been recruited from urology, nephrology, or specialty stone clinics. We found no data regarding the efficacy of any pharmacological treatment in uric acid or cystine stones, and virtually no data on pharmacological treatment efficacy within patient subgroups defined by demographic or comorbid characteristics.
- These results are detailed in Table B.

Key Question 5: In adults with a history of nephrolithiasis, what is the evidence that pharmacological therapies to reduce risk of recurrent stone episodes are associated with adverse effects?

Key Findings

Overall

- Adverse effects assessed by withdrawals and withdrawals due to adverse effects were widely variable between trials, even for studies of the same pharmacological treatments. Other adverse events reporting was poor. We identified virtually no additional withdrawal or adverse events data comparing pharmacological treatment with control or placebo treatment from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, from RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies at least 3 months in duration.

Thiazide Diuretics

- Withdrawals (17 vs. 8 percent) and withdrawals due to adverse events (8 vs. 1 percent) appeared more frequent in participants randomized to thiazide versus placebo or control, though incidence ranged widely between trials.
- Specific adverse events were inconsistently reported, particularly in placebo or control group participants, making it impossible to reliably compare risk of specific adverse events between treatment groups.

Citrates

- Withdrawals (36.1 vs. 19.8 percent) and withdrawals due to adverse events (14.8 vs. 1.8 percent) appeared more frequent in participants randomized to citrate versus placebo or control, though incidence ranged widely between trials.
- 24.5 percent of participants randomized to citrate had any adverse event versus none assigned to placebo or control.[59,63] Gastrointestinal complaints were reported in 26.2 percent (range 16 to 42) of participants randomized to citrate and 16.1 percent (range 0 to 39) of those assigned placebo or control.[43-45,59]

Allopurinol

- Neither withdrawals nor withdrawals due to adverse events were higher in participants randomized to allopurinol versus placebo.[37,38]
- No trials reported incidence of any adverse event. The two trials that reported specific adverse events reported no individual adverse event in more than three participants per treatment group.[37,38]

Acetohydroxamic Acid

- In RCTs that reported results in both treatment and placebo groups, 62.7 percent of participants randomized to acetohydroxamic acid (AHA) withdrew versus 46.4 percent of those assigned to placebo; a single trial reported that 30.0 percent of AHA participants withdrew but reported no withdrawal data for the placebo group.
- Withdrawals due to adverse events appeared higher in participants assigned AHA.
- Adverse events occurred in 64.0 percent of participants randomized to AHA compared with 32.5 percent of those assigned to placebo, though studies inconsistently reported specific adverse events.

Magnesium

- In a single eligible RCT, withdrawals were similar in the magnesium and placebo groups, though risk of withdrawal due to adverse events appeared higher in the high dose magnesium group (diarrhea) than in the placebo group (gastrointestinal upset).[47]

Table B. Summary of evidence for prevention of stone recurrence: Pharmacological interventions (KQ 4)

Interventions, Studies (Study Quality)	Stone Recurrence Results	Strength of Evidence*
Thiazide Diuretic vs. Placebo or Control 7 RCTs (fair) in patients with recurrent calcium stones[41,47-50,52,58]	*Symptomatic:* No reduced risk (24 vs. 23%; RR, 1.04 [CI, 0.39 to 2.80], n=1 trial reporting), but reduced risk of lithotripsy (8 vs. 26%, p=0.03, n=1 trial). *Composite:* Reduced risk (25 vs. 49%; RR, 0.53 [CI, 0.41 to 0.68], n=6 trials). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Moderate Radiographic: Insufficient
Citrate vs. Placebo or Control 6 RCTs (1 good, 5 fair) in patients with recurrent calcium stones[43-45,59,63,64]	*Symptomatic:* No results reported. *Composite:* Reduced risk (11 vs. 52%; RR, 0.25 [CI, 0.14 to 0.44], n=4 trials). *Radiographic:* No reduced risk (69 vs. 73%; RR, 0.95 [CI, 0.62 to 1.44], n=1 trial).	Symptomatic: Insufficient Composite: Moderate Radiographic: Low
Allopurinol vs. Placebo or Control 4 RCTs (fair) in patients with recurrent calcium stones[37-40]	*Symptomatic:* No reduced risk (10 vs. 29%; RR, 0.36 [CI, 0.11 to 1.19], n=1 trial) but increased time to recurrent stone (33 vs. 27 months, p<0.05, n=1 trial). *Composite:* Reduced risk (33 vs. 55%; RR, 0.59 [CI, 0.42 to 0.84], n=2 trials). *Radiographic:* No reduced risk (7 vs. 6%; RR, 1.07 [CI, 0.16 to 7.10], n=1 trial).	Symptomatic: Low Composite: Moderate Radiographic: Insufficient
Acetohydroxamic Acid vs. Placebo or Control 3 RCTs (fair) in patients with chronic urea-splitting urinary tract infections and recurrent struvite stones[60-62]	*Symptomatic:* No results reported. *Composite:* No results reported. *Radiographic:* No reduced risk (13 vs. 20%; RR, 0.81 [CI, 0.18 to 3.66], n=2 trials).	Symptomatic: Insufficient Composite: Insufficient Radiographic: Insufficient
Magnesium vs. Placebo 1 RCT (fair) in patients with recurrent calcium stones[47]	*Symptomatic:* No results reported. *Composite:* No reduced risk (29 vs. 45%; RR, 0.65 [CI, 0.37 to 1.16]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient
Thiazide Diuretic plus Citrate vs. Thiazide 1 RCT (fair) in patients with recurrent calcium stones[58]	*Symptomatic:* No results reported. *Composite:* No reduced risk (RR, 0.94 [CI, 0.52 to 1.68]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Low Radiographic: Insufficient
Thiazide Diuretic plus Allopurinol vs. Thiazide 1 RCT (fair) in patients with recurrent calcium stones[41]	*Symptomatic:* No results reported. *Composite:* No reduced risk (RR, 0.79 [CI, 0.18 to 3.49]). *Radiographic:* No results reported.	Symptomatic: Insufficient Composite: Insufficient Radiographic: Insufficient

CI = 95 percent confidence interval; KQ = Key Question; RCT = randomized controlled trial; RR = relative risk.

*Strength of evidence was rated using the following grades: (1) high confidence indicated that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate confidence denoted that further research may change our confidence in the estimate of effect and may change the estimate; (3) low confidence indicated that further research is very likely to have an important impact 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 (4) insufficient, indicating that the evidence was unavailable or did not permit a conclusion. Examples when evidence is available, but SOE may be graded as insufficient include when there is an unacceptably high risk of bias, or there is 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, SOE may be graded as insufficient when data are too imprecise. This may be the case when the 95% CI is so wide that it cannot exclude either a clinically significant benefit or harm (e.g. lower CI bound <0.5 and upper CI bound >2).

- The study did not otherwise report results for occurrence of any specific adverse events.

Thiazide Plus Citrate

In a single eligible RCT, there were no withdrawals in either the thiazide plus citrate or thiazide treatment groups. The study did not report results for adverse events.

Thiazide Plus Allopurinol

In a single eligible RCT, withdrawals and withdrawals due to adverse events, respectively, were not higher in participants randomized to thiazide plus allopurinol (4.0 and 0 percent) versus those assigned to thiazide (24.0 and 8 percent) or control (16.0 and 0 percent).

The study did not report results for adverse events in participants randomized to thiazide plus allopurinol or to control. Hypokalemia and hypotension each were reported in one participant in the thiazide group.

Key Question 6: In adults with a history of nephrolithiasis being treated to prevent stone recurrence, do results of followup blood and urine biochemistry measures predict final health outcomes and intermediate stone outcomes?

Key Findings

- No RCTs reported and prospectively compared subsequent stone recurrence outcomes between treatments stratified by followup biochemistry levels or by changes in these measures from pretreatment baseline.
- Two RCTs involving increased fluid intake[46] and a multicomponent diet,[51] respectively, reported significant reductions in urine calcium-oxalate, uric acid, and calcium-phosphate supersaturation at 1 year or later after baseline and significantly reduced risk of recurrent stones over 5 years of followup. However, neither study formally tested these results for possible associations.
- No eligible pharmacological RCT reported followup urine supersaturation levels. Thus, no RCT data were available regarding whether changes in urine supersaturation measures predict reduced risk of recurrent stones with drug treatment.
- Data from both diet and pharmacological RCTs suggest that followup urine calcium may have limitations as a predictor of treatment efficacy in preventing stone recurrence. Even though urine calcium and recurrent stone risk both significantly decline in patients assigned to thiazides, decline in urine calcium in two thiazide trial control groups,[41,48] moreso in those with baseline hypercalciuria,[48] suggests this finding may have limited specificity and be indicative of regression to the mean, a statistical group phenomenon in which a variable initially measured as extreme (e.g., hypercalciuria) tends to be closer to average on remeasurement.[65]
- Whether reductions in serum or urine uric acid levels predict allopurinol effectiveness in reducing stone recurrence is unclear.[37]

Discussion

What is the Evidence That Treatments Reduce Risk of Kidney Stone Recurrence?

Few trials examined the effect of modifying individual dietary components as isolated interventions. Increased fluid intake was the only dietary modification studied as an isolated intervention in more than one trial. Despite this limited body of evidence, the effect of increased fluids was significant; increasing fluid intake to maintain daily urine output of at least 2 L/day more than halved the risk of composite stone recurrence. Further, this treatment was well tolerated, with high adherence and few withdrawals over 5 years.[42,46] Reduced soft drink intake statistically significantly lowered risk of recurrent symptomatic stones in individuals with a high baseline soft drink consumption. However, the magnitude of this benefit was modest, the intervention was evaluated only in men, and benefit appeared limited to those who previously drank soft drinks acidified solely by phosphoric acid.[55] Though it is possible that treatment benefit was in part attributable to reduced fructose consumption, authors did not report fructose consumption at any time point, nor subgroup analyses based on baseline fructose consumption.

Other trials, which collectively examined the effect of a heterogeneous set of dietary interventions added to increased fluid intake, had mixed and at times conflicting results. For example, one multicomponent diet trial reported a significantly lower risk of stone recurrence in participants randomized to a normal to high calcium, low animal protein, and low sodium diet versus a low-calcium diet.[51] However, results from other trials did not clarify whether high dietary calcium, low animal protein, and low sodium individually are protective and/or whether low dietary calcium increases stone recurrence risk. No other trials assigned participants to different dietary calcium or sodium intakes as isolated interventions or within multicomponent diets. The two other trials that compared a diet including low animal protein with a control diet

reported no reduction in risk of stone recurrence[56] and an increased risk of stone recurrence,[57] respectively. By comparison, two trials that compared a high-fiber diet[56] or a multicomponent diet including high fiber[57] with a control diet suggested that a high-fiber diet may increase recurrent stone risk. In one trial, patients randomized to an extensive biochemical evaluation and tailored diet were statistically significantly less likely to have a recurrent stone than those assigned empiric treatment. However, the study reported results only between the two treatment groups overall, so it was impossible to distinguish whether the benefit was associated with all tailored dietary components and experienced by all biochemical subgroups or whether it was more selective.[53] Important to note is that associations between individual dietary components and risk of stone recurrence were inconsistent in other diet trials, and limited evidence suggests that baseline biochemistries do not predict dietary treatment outcomes. Therefore, it seems likely that not all dietary components of this tailored diet contributed to the observed overall benefit, and some may have been harmful. Consequently, other than increasing fluid intake, the most effective dietary intervention for reducing risk of recurrent stones remains unclear.

When added to increased fluid intake, thiazide diuretics, citrate, and allopurinol pharmacotherapy each significantly decreased risk of recurrent calcium kidney stones more than increased fluid intake alone. Among thiazide agents, hydrochlorothiazide, chlorthalidone, and indapamide each significantly reduced risk of recurrent stones. Risk reduction relative to control did not differ significantly between different thiazides; however, no trial directly compared thiazide agents. The effect of hydrochlorothiazide versus control on risk of recurrent stones did not differ with 50 mg[49,50,58] versus 100 mg per day,[48] or between 50 mg once daily[58] and 25 mg twice daily.[49,50] We found no eligible trials that evaluated whether lower doses of hydrochlorothiazide reduce risk of recurrent stones. Nor did risk of recurrent stones differ between chlorthalidone 25 mg once daily and 50 mg once daily. For citrate pharmacotherapy, potassium citrate, potassium-magnesium citrate, and sodium-potassium citrate all significantly reduced risk of recurrent stones. Efficacy did not appear to differ between these three agents or between the different doses of potassium citrate; however, no trial directly compared the three citrate agents or different doses of potassium citrate with each other.

No trials compared diet treatment with pharmacological treatment. Instead, nearly all pharmacological trials reported that all groups were assigned a common dietary co-intervention of increased fluid intake with or without additional dietary changes, so that the studies were designed to evaluate the effect of pharmacological treatment when added to this diet therapy. Few trials directly compared active pharmacological treatments. No trials directly compared thiazide versus citrate, thiazide versus allopurinol, or citrate versus allopurinol. Otherwise, there was only low strength of evidence from three small trials that risk of stone recurrence was not significantly lower with chlorthalidone than with magnesium,[47] did not differ significantly between participants randomized to thiazide plus citrate versus those assigned thiazide alone,[58] and did not differ significantly between thiazide plus allopurinol versus thiazide alone.[41]

What is the Evidence That Stone Characteristics and Baseline Biochemistry Results Predict Effectiveness of Treatment To Reduce Risk of Recurrent Stones?

In two RCTs limited to patients with calcium stones and hyperuricosuria[37] or hyperuricemia,[38] those randomized to allopurinol versus control had a significantly lower risk of composite recurrent stones and other stone outcomes.[37] In contrast, symptomatic stone recurrence did not appear reduced with allopurinol versus control in trials of participants unselected for high uric acid levels.[39,40] These results suggest that hyperuricosuria or hyperuricemia may predict which patients with calcium stones will benefit from allopurinol treatment, and may identify patients for whom allopurinol is an appropriate treatment option to reduce recurrent stone risk. However, since both thiazides[47,49,58] and citrates[45] reduced risk of stone recurrence in trials that included at least a minority of patients with hyperuricosuria, and no trials directly compared allopurinol with these agents, we do not know whether allopurinol should be the preferred drug treatment in these patients. Conversely, thiazides or citrates may be preferred initial therapy over allopurinol in patients with calcium stones and no hyperuricosuria or hyperuricemia since thiazides reduce risk of recurrent stones in these patients,[48,50] and citrates reduce risk of recurrent stones in patients with calcium stones unselected for hyperuricosuria.

Though RCT data were incomplete, we otherwise identified limited evidence that there are no differences in the efficacy for reducing risk of recurrent stones of increased fluid intake, diet, thiazide, citrate or AHA treatment between patient groups with, without, unselected for, or adjusted for baseline hypercalciuria, hyperoxaluria, or hypocitraturia. These results are limited because a

substantial minority of RCTs reported no information on baseline biochemistry measures, many other trials did not report how biochemical abnormalities were defined, and definitions of abnormality varied in those trials' reporting. Because any association between biochemical abnormalities and risk of recurrent stones is likely to be continuous and not defined by a single threshold,[66] the failure of trials to report results for patients defined by a standardized series of clinical thresholds for these biochemical measures also is limiting.

Beyond the most commonly reported baseline biochemical measures, we identified no dietary or pharmacological RCT data addressing whether the effect of any treatment on risk of recurrent stones differs according to baseline urine magnesium, phosphate, potassium, pH, calcium-oxalate supersaturation, calcium-phosphate supersaturation, or uric acid supersaturation. Two trials reported that treatment results were not changed after adjustment for baseline urine volume or calcium-oxalate product. In sum, available data did not support the value of any of these individual baseline laboratory measures for directing diet or pharmacological treatments.

In regard to stone type, all diet, thiazide, citrate, allopurinol, and magnesium trials that specified stone type were limited to patients with calcium stones, and all acetohydroxamic acid trials were limited to patients with struvite stones. Thus we could not evaluate the effect of these interventions in patients with other stone types. In addition, we identified no trials that examined the effect of allopurinol, alkalinization, or any other therapy in reducing risk of recurrent uric acid stones, or that examined the effect of any treatment in reducing risk of recurrent cystine stones. Since the vast majority of patients in the community with kidney stones have calcium stones, empirically increasing fluid intake in all patients with kidney stones with or without adding thiazide or citrate therapy might significantly reduce recurrence risk. However, we found no trials that tested this strategy.

What is the Evidence That Biochemistry Results Measured After Beginning Treatment Predict Treatment Effectiveness in Reducing Subsequent Risk of Recurrent Stones?

Many RCTs reported results of followup biochemistry measures, but none reported and compared between-treatment stone recurrence outcomes completely subsequent to and stratified by followup biochemistry levels, or by changes in these measures from pretreatment baseline. However, participants assigned to active treatment in one fluid trial[46] and one multicomponent diet trial[51] had a significant decline from baseline in urine calcium-oxalate supersaturation, uric acid supersaturation, and calcium-phosphate supersaturation measured at 1 year or later, as well as significant reductions in risk of recurrent stones compared with their respective control groups over a 5-year followup. While these fluid and diet studies did not examine stone recurrence risk as a function of followup or change in urine supersaturation levels (and no pharmacological trials even reported followup urine supersaturation levels), these results suggest that future studies to formally test these followup measures as predictors of stone recurrence risk may be warranted. Data from both diet and pharmacological RCTs suggest that followup urine calcium may have limitations as a predictor of stone recurrence. Even where the association between a reduction in urine calcium with reduced recurrent stone risk appears most likely, in patients randomized to thiazide treatment, the significantly reduced urine calcium in the control groups[41,48] and in those with baseline hypercalciuria[48] suggests its limited specificity and the possibility that results are attributable at least in part to regression to the mean.[65]

Applicability

Nearly all trials were limited to individuals with a history of calcium stones. All were conducted in adults, and nearly all predominately comprised young to middle aged men. Many trials excluded participants with biochemical abnormalities, and nearly all reported exclusion of participants with conditions that could predispose them to formation of kidney stones. They otherwise reported almost no data on the prevalence of participant characteristics, including race, body morphometry, and comorbid conditions that might increase risk for kidney stones or affect treatment outcomes. Nearly all trials that reported their study setting indicated that they were conducted in urology, nephrology, or other stone clinics. Only one trial, a comparison of thiazide treatment versus control, explicitly reported that participants were recruited from primary care clinics.[49] About half of trials included participants without regard to baseline biochemistry results. The other half restricted entry based on the presence or absence of lab abnormalities, including studies that only permitted inclusion of participants with or without hypercalciuria, with or without hyperoxaluria, with or without hyperuricosuria or hyperuricemia, and with or without hypocitraturia. Last, very few trials reported symptomatic stone recurrence as an isolated efficacy outcome, and almost none reported any other clinically symptomatic event. Instead, they reported radiographic stone recurrence, stone growth, or a composite outcome

defined by either radiographic stone recurrence, stone passage (symptomatic or asymptomatic), and/or stone growth.

Taking these trial characteristics into account, results from this review may not be generalizable to patients with noncalcium kidney stones (i.e., uric acid or cystine stones), to children, or to older adults. Further, results may not be generalizable to patients with underlying biochemical abnormalities, and may have limited generalizability to those with comorbid conditions not reported (though not explicitly excluded in most cases) in eligible trials (e.g., obesity, pregnancy, hypertension, history of bariatric surgery, chronic kidney disease, solitary kidney, renal transplant, or coronary artery disease). Because both trials of increased fluid intake versus control were conducted in participants with a single past stone episode, treatment effectiveness could differ in patients with multiple past stone episodes. While we don't know whether kidney stone patients followed in specialty centers differ from those followed in primary care, the reduction in stone recurrence risk with thiazide versus control appears similar in both populations. This suggests that the effect of this treatment, at least, may be insensitive to recruitment source. Though many trials restricted entry to participants with or without one or more biochemical abnormalities, since the limited available data suggest that these measures—possibly excepting uric acid—don't predict effectiveness of treatment, it seems reasonable for now to extrapolate most study findings to patients regardless of their baseline biochemical results and to those without measured baseline biochemistries. Regarding treatment outcomes, because radiographic stone recurrence, stone growth, and even asymptomatic stone passage in the absence of adverse clinical consequences may be surrogate outcomes for symptomatic stone recurrence at best and radiographic findings at worst, it is not certain whether interventions that reduce these outcomes will reduce symptomatic stone recurrence. If not, these treatments may be unnecessary and potentially harmful, and their applicability to clinical practice would be limited pending additional research.

Future Research Recommendations

Table C summarizes the areas needing future research based on the gaps identified in this review.

Table C. Future Research Recommendations

Research Gaps	Future Research Recommendations
General Issues	
• Efficacy results for most trials were driven by nonclinical outcomes (radiographic stones only, radiographic stones included as part of composite stones outcome, and/or stone growth). • Though numerous trials report stone growth as a treatment outcome, consensus is lacking on the clinical importance of this outcome or on a threshold for what constitutes clinically meaningful stone growth. • Other than stone recurrence, there was minimal trial reporting of clinical outcomes. • Followup duration in some trials may have been too short to observe treatment effects. • Inconsistent imaging modalities and testing frequencies were used to ascertain recurrent stones and stone growth. • Inconsistent imaging modalities were used to exclude baseline residual stones, increasing the risk that studies using less sensitive modalities labeled a stone missed by baseline imaging a new stone during treatment followup.	• Prospective observational studies should identify patients with asymptomatic stone growth (using sensitive and standardized detection methods, and including different thresholds to define stone growth), radiographic stone recurrence (again using sensitive and standardized detection methods) and/or asymptomatic stone passage and follow them untreated for several years for symptomatic stone recurrence to help determine whether and under what circumstances these measures are appropriate surrogates for this symptomatic stone recurrence. • RCTs should use symptomatic stones as the primary outcome, or if using composite stone recurrence as the primary outcome, they also should separately report symptomatic and radiographic stones. • RCTs should enroll patients with asymptomatic stone growth above some absolute stone size or growth rate threshold(s), randomize them to intervention vs. observation/watchful waiting, and assess the relative clinical benefits/harms of these treatment strategies, including the number of required interventions and associated complications.

Table C. Future Research Recommendations (continued)

Research Gaps	Future Research Recommendations
General Issues (continued)	
• Modeling studies to estimate the benefits and harms of different kidney stone evaluation, treatment and followup strategies were outside the scope of this report.	• In addition to stone recurrence, RCTs should report other clinical outcomes, including pain, urinary tract obstruction with acute renal failure, infection, procedure related morbidity, emergency room treatment and/or hospitalization related to stone recurrence, quality of life, and/or end-stage renal disease. Studies also should report the laboratory and radiographic testing participants undergo, including their cumulative radiation exposure. • RCTs should be long-term, with possibly standardized minimum followup durations for ascertaining symptomatic, composite, and radiographic stone outcomes, and stone growth respectively. • RCTs should use standard imaging modalities to ascertain presence of baseline residual stones as well as standard modalities and testing frequencies to ascertain incident radiographic stones and stone growth. • Modeling studies should be performed to estimate the effectiveness, cost-effectiveness and harms of different kidney stone evaluation, treatment and followup strategies vs. a control strategy to prevent stone recurrence. Models should account for treatment efficacy and harms, treatment adherence, and costs and adverse effects of baseline and followup biochemistries and imaging procedures, among other factors.
Key Question 1. Do baseline stone composition and blood and urine chemistries predict effectiveness of treatments used to prevent stone recurrence?	
• Almost no RCTs reported and compared stone recurrence outcomes between treatments stratified by baseline biochemistry levels. In comparisons between studies, there was limited evidence that baseline biochemical measures other than hyperuricosuria or hyperuricemia (allopurinol) predicted the effectiveness of diet or pharmacological treatment vs. control in reducing risk of stone recurrence. • Regarding stone composition, there was no RCT evidence for efficacy of any treatment to prevent recurrent uric acid or cystine stones, and minimal RCT evidence for efficacy of AHA in preventing recurrent struvite stones. • A substantial minority of RCTs reported no information on baseline biochemistry measures. Many trials that reported prevalence or based participant eligibility on the presence or absence of such abnormalities did not report how biochemical abnormalities were defined. Though definitions of biochemical abnormalities utilized in trials reporting appeared roughly similar, they were not standardized.	• RCTs for prevention of recurrent uric acid stones should compare dietary purine restriction, allopurinol or alkalinization therapy vs. control. • RCTs for prevention of recurrent cystine stones should compare dietary (e.g., increased fluid, low sodium) and pharmacological interventions (e.g., penicillamine, captopril, tiopronin, others) vs. control. • RCTs for prevention of recurrent struvite stones (and prevention of pyelonephritis and impaired renal function) should compare AHA with and without concomitant antibiotics vs. control. • RCTs for prevention of recurrent calcium phosphate stones should compare citrate and/or thiazide vs. control. These studies may consist entirely of patients with this stone type or may report stratified results for this stone subgroup.

Table C. Future Research Recommendations (continued)

Research Gaps	Future Research Recommendations
Key Question 1. Do baseline stone composition and blood and urine chemistries predict effectiveness of treatments used to prevent stone recurrence? (continued)	
• Increased risk for stone recurrence conferred by biochemical abnormalities appears continuous and not defined by a specific threshold; this may need to be accounted for in evaluations of treatment efficacy as a function of baseline biochemistries. • In patients with hyperuricosuric or hyperuricemic calcium stones, it is unknown whether allopurinol is more effective in preventing stone recurrence than other treatments. • No RCTs were limited to patients with calcium phosphate stones, and no trials that included such patients reported stratified results for this patient subgroup. • It is uncertain whether citrate treatment is more effective in preventing stone recurrence in patients with hypocitraturia than in those without or unselected for hypocitraturia. • In patients with hypocitraturia, it is uncertain whether citrate is more effective in preventing stone recurrence than other treatments. • It is uncertain whether thiazide treatment is more effective in preventing stone recurrence in patients with hypercalciuria than in those without or unselected for hypercalciuria.	• Additional RCTs should be performed, not just in patients with or without defined biochemical abnormalities (which should be standardized across trials and consistently reported), but results also should be reported stratified by different prespecified levels of specific biochemistry measures.that are standardized across trials. • Additional RCTs should evaluate effectiveness and harms of single and/or multicomponent biochemistry screening strategies followed by a comparison of different diet and/or pharmacological treatment strategies (e.g., targeted treatment or empiric treatment or control) with adequate power for clinical outcomes.
Key Question 2. What is the effectiveness and comparative effectiveness of different dietary therapies to reduce stone recurrence and improve other clinical outcomes?	
• Evidence is limited regarding efficacy of individual dietary components for preventing stone recurrence. – Does low dietary calcium increase recurrent stone risk? Does higher dietary calcium lower risk? – Does low animal protein lower or increase recurrent stone risk? • The efficacy of multicomponent diet trials for preventing stone recurrence is uncertain (variable composition of multicomponent diets between trials; inconsistent results) • It is unknown whether the efficacy of diet therapies differs as a function of participant characteristics. – Does efficacy of increased fluid intake differ between patients with single vs. multiple past stone episodes?	• RCTs should be performed comparing individual diet components vs. control for preventing stone recurrence (e.g., low animal protein, low sodium, normal-high calcium, low purine, high fiber, low oxalate). • In addition to reporting overall results, dietary RCTs should report stone recurrence outcomes for any important clinical subgroups included (e.g., gender, single vs. multiple past stone episodes, obesity, diabetes, gout).
Key Question 3. What are the adverse effects of dietary therapies used to reduce risk of recurrent stone episodes?	
• There is limited adverse event data from intervention studies that utilized either individual dietary components or multicomponent diets. • There is limited adverse event data from multicomponent diet studies, and making general conclusions about adverse events associated with multicomponent diets is limited because multicomponent differed between trials.	• RCTs should collect and completely report predefined adverse events in all randomized participants (e.g., any, serious adverse effects, adverse effects causing withdrawal, predefined specific adverse effects). • Prospective cohort studies should be performed in patients being initiated on diet treatment for stone prevention, again collecting and completely reporting predefined adverse events in all study participants.

Table C. Future Research Recommendations (continued)

Research Gaps	Future Research Recommendations
Key Question 4. What is the effectiveness and comparative effectiveness of different pharmacological therapies to reduce stone recurrence and improve other clinical outcomes?	
• It is unclear if there is a best empiric pharmacological treatment to prevent stone recurrence. • The optimal thiazide dosing regimen (i.e., dose, frequency) to prevent stone recurrence is uncertain. • It is uncertain whether the effectiveness of potassium-magnesium-citrate formulation available in U.S. (much smaller dose per pill) is comparable to that used in the trial included in this review. • The most effective treatment to prevent stone recurrence in patients with hyperuricosuric calcium stones is uncertain (e.g., allopurinol vs. thiazides). • There are no RCT data on efficacy of allopurinol in preventing stone recurrence in patients with uric acid stones. • The importance of adjuvant suppressive antibiotic therapy in patients with struvite stones being treated with AHA is uncertain. • It is uncertain whether magnesium reduces stone recurrence in patients with calcium stones, overall or in those with hypomagnesuria. • It is unclear if any combination therapy is more effective in preventing stone recurrence than thiazide, citrate or allopurinol monotherapy, in patients unselected for stone type and biochemical abnormality or within specific subgroups. • All eligible monotherapy trials since 1988 have studied only previously studied drugs.	• RCTs should compare thiazide vs. citrate to prevent stone recurrence in patients unselected for stone or biochemical characteristics. • RCTs should compare different thiazide dosing regimens (e.g., HCTZ 12.5 mg/day vs. 12.5 mg twice daily vs. 25 mg/day) for prevention of stone recurrence. • RCTs should compare different thiazide agents (i.e., HCTZ, chlorthalidone, indapamide) for prevention of stone recurrence. • Additional RCTs should compare thiazide and citrate combination treatment vs. monotherapy to prevent stone recurrence. • RCTs should compare AHA vs. control in patients with struvite stones and report recurrent stones (and other clinical outcomes including pyelonephritis and acute kidney injury), with a factorial design involving additional randomization to suppressive antibiotic treatment or no antibiotics. • RCTs should compare magnesium vs. control to prevent stone recurrence in patients with hypomagnesuria. • RCTs are needed of novel treatment strategies to prevent stone recurrence (e.g., febuxostat, pyridoxine, fish oil, oxalobacter formigenes and other probiotics, others). Better understanding is needed regarding kidney stone pathogenesis to help develop potential new preventive treatments, including the possible identification of molecular markers of stone disease.
Key Question 5. What are the adverse effects of pharmacological therapies used to reduce risk of recurrent stone episodes?	
• Adverse events reporting is poor (e.g., incomplete, not reported separately by treatment group, not clearly prespecified) in RCTs of patients being treated to prevent stone recurrence; minimal additional data are available from prospective observational studies of patients with kidney stones.	• RCTs should collect and completely report predefined adverse events including effects on comorbid conditions as well as any adverse events, serious adverse events, adverse events causing withdrawal, and any withdrawals in all randomized participants. • Prospective cohort studies should be performed in patients being started on pharmacological treatment for stone prevention, again collecting and completely reporting predefined adverse events in all study participants.

Table C. Future Research Recommendations (continued)	
Research Gaps	**Future Research Recommendations**
Key Question 6. Do results of followup blood and urine biochemistry tests collected after initiation of treatment predict treatment effectiveness in preventing stone recurrence?	
• No RCTs or prospective observational studies reported stone recurrence outcomes collected completely subsequent to post-baseline measurements of biochemistries. • Participants assigned to active treatment in one fluid trial[46] and one multicomponent diet trial[51] had a significant decline from baseline in urine calcium-oxalate supersaturation, uric acid supersaturation, and calcium-phosphate supersaturation measured at 1 year or later, as well as significant reductions in risk of recurrent stones vs, their respective control groups over a 5-year followup. However, these studies did not examine stone recurrence risk as a function of followup or change in urine supersaturation levels (and no pharmacological trials even reported followup urine supersaturation levels).	• RCTs should report and correlate/stratify the effect of diet and/or pharmacological treatment vs control on risk of recurrent stones (preferably symptomatic stones) in patients subsequent to measurement of post-baseline biochemistries, including urine calcium, calcium-oxalate supersaturation, uric acid supersaturation, calcium-phosphate supersaturation, and others. • Studies could adjust stone recurrence outcomes by results for change in or followup level of biochemistry measure. • Prospective cohort studies should report and correlate the risk of recurrent symptomatic stones in patients subsequent to measurement of post-baseline biochemistries.

AHA = acetohydroxamic acid; HCTZ = hydrochlorothiazide; RCT = randomized controlled trial

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Full Report

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Errata

In response to late comments to the AHRQ comparative effectiveness review, the authors clarified the criteria for assessing individual study quality, and re-evaluated the individual study quality and strength of evidence grading in the report.

We rated the risk of bias as low, medium, or high based on whether the design and conduct of the studies for a given treatment comparison and outcome indicated good internal validity. This resulted in the following changes in individual study quality: (1) the Borghi 2002 study comparing low protein/low sodium/high calcium diet to low calcium diet was assessed as "good" quality, rather than "fair" quality; (2) the Kovcara 1999 study comparing evaluation and tailored diet to limited evaluation and uniform diet was assessed as "poor" quality" rather than "fair" quality; and (3) the Borghi 1996 study comparing increased fluid intake to control was assessed as "poor" rather than "fair" quality.

We also clarified how we assessed the four domains for judgment of the strength of evidence for each grade (high, moderate, low and insufficient). Five strength of evidence grades were reassessed as insufficient rather than low for the following recurrent nephrolithiasis outcomes and comparisons: increased fluid vs. no treatment for radiographic recurrence, thiazides vs. placebo for symptomatic recurrence, allopurinol vs. placebo for radiographic recurrence, AHA vs. placebo radiographic for recurrence, and thiazide + allopurinol vs. thiazide for composite recurrence.

These decisions are reflected in the executive summary, full report and appendixes. The comments and full response to comments are included in the updated Disposition of Comments table.

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