Effective Health Care Program

Comparative Effectiveness Review
Number 61

Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies

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Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies

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Prepared by:
Minnesota Evidence-based Practice Center
Minneapolis, MN

Investigators:
Howard A. Fink, M.D., M.P.H.
Timothy J. Wilt, M.D., M.P.H.
Keith E. Eidman, D.O.
Pranav S. Garimella, M.D., M.P.H.
Roderick MacDonald, M.S.
Indulis R. Rutks, B.S.
Michelle Brasure, Ph.D., M.S.P.H., M.L.I.S.
Robert L. Kane, M.D.
Manoj Monga, M.D.

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Errata to Comparative Effectiveness Review No. 61, "Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies."

March 27, 2013

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.

The authors 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.

The authors also clarified how they 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.

May 16, 2013

The authors corrected the reported number of subjects in studies for Table 1 (Strength of evidence for prevention of stone recurrence: diet intervention trials) and Table 2 (Strength of evidence for prevention of stone recurrence: pharmacological intervention trials) to consistently and accurately reflect the number of randomized trial subjects. This correction did not affect any of the analyses or conclusions of this report.

This report is based on research conducted by the Minnesota Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0009). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products or actions may not be stated or implied.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews CERs of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative effectiveness reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Key Informants

Gary C. Curhan, M.D., Sc.D.
Harvard University
Boston, MA

Keith E. Folkert, M.D., M.H.A.
Blue Cross and Blue Shield of Minnesota
Eagan, MN

Jim Lipka
Columbia Heights, MN

Margaret S. Pearle, M.D., Ph.D.
University of Texas Southwestern Medical School
Dallas, TX

Kristina L. Penniston, Ph.D.
University of Wisconsin School of Medicine and Public Health
Madison, WI

Jyme H. Schafer, M.D., M.P.H.
Centers for Medicare & Medicaid Services
Baltimore, MD

Jeffery A. Wesson, M.D., Ph.D.
Medical College of Wisconsin
Milwaukee, WI

Technical Expert Panel

John R. Asplin, M.D.
Litholink Corporation
Chicago, IL

Dean Assimos, M.D.
Wake Forest College
Winston Salem, NC

Gary Curhan, M.D., Sc.D.
Harvard University
Boston, MA

Apostolos P. Dallas, M.D.
Carilion Clinic
Roanoke, VA

Margaret Pearle, M.D.
Southwestern Texas
Dallas, TX

Kristina Penniston, Ph.D.
University of Wisconsin
Madison, WI

Peer Reviewers

John Lieske, M.D.
Mayo Clinic
Rochester, MN

Tanveer P. Mir, M.D., M.A.C.P.
Long Island Jewish Medical Center
Long Island, NY

Glenn M. Preminger, M.D.
Duke University Medical Center
Durham, NC

Roswitha Siener, Ph.D.
University of Bonn
Bonn, Germany

Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies

Structured Abstract

Objective. To determine the efficacy and harms of diet and pharmacological interventions for preventing recurrent kidney stones, and whether stone composition and pre- and post-treatment biochemistries predict treatment efficacy.

Data Sources. MEDLINE®, Cochrane Database of Systematic Reviews, Google Scholar, ClinicalTrials.gov, and Web of Science electronic databases; hand searches of references from relevant systematic reviews and eligible trials; and references from expert consultants.

Review Methods. We screened abstracts and full text articles of identified references for eligibility and reviewed randomized controlled trials (RCTs) for evidence on treatment prevention of recurrent kidney stones, and reviewed RCTs and prospective observational studies for evidence on treatment harms. We extracted data, rated quality, and graded strength of evidence. Our primary efficacy outcomes were symptomatic stone recurrence, composite recurrence (either symptomatic or radiographic), or radiographic recurrence. Evidence on treatment benefits and harms was quantitatively synthesized when possible.

Results. We found 28 eligible RCTs (8 diet, 20 pharmacological), all but one of fair quality. In patients with a single past calcium stone, increased fluid intake reduced risk of composite stone recurrence (RR, 0.45 [95 percent CI, 0.24 to 0.84]), n=1 trial), and low animal protein and high fiber diets as isolated interventions did not reduce stone recurrence. In men with high soft drink intake, decreased soft drink consumption reduced symptomatic stone recurrence (RR, 0.83 [CI, 0.71 to 0.98], n=1 trial). Multi-component diet interventions were heterogeneous in composition and had mixed results. In one trial, a low animal protein, normal to high calcium, and low sodium diet reduced risk of composite stone recurrence compared with a low calcium diet (RR, 0.52 [CI, 0.29 to 0.95]), whereas in a second trial a low animal protein, high fruit and fiber, and low purine diet increased risk of composite stone recurrence compared with a control diet (RR, 5.88 [CI, 1.39 to 24.92]). In another trial, extensive biochemical evaluation and tailored diet reduced the risk of composite stone recurrence versus a limited evaluation and empiric diet (RR, 0.32 [CI, 0.14 to 0.74]). Strength of evidence for all these interventions was low. In patients with multiple past calcium stones, we found moderate strength of evidence that treatment reduces risk of composite recurrent stones versus control for thiazide diuretics (RR, 0.53 [CI, 0.41 to 0.68], n=6 trials), citrate (RR, 0.25 [CI, 0.14 to 0.44], n=4 trials), and allopurinol (RR, 0.59 [CI, 0.42 to 0.84], n=2 trials), but not for magnesium. We found that acetohydroxamic acid does not reduce risk of recurrent struvite stones (RR, 0.81 [0.18 to 3.66], n=2 trials) (low strength of evidence), and that neither addition of citrate (RR, 0.94 [CI, 0.52 to 1.68], n=1 trial) (low strength of evidence) nor allopurinol (RR, 0.79 [CI, 0.18 to 3.49], n=1 trial) to thiazide (insufficient strength of evidence) reduces risk of recurrent calcium stones compared with thiazides alone. Adverse event reporting was poor. Allopurinol effectiveness may be limited to participants with hyperuricosuria or hyperuricemia. Based on limited data, baseline urine calcium, oxalate, and citrate do not appear to affect stone recurrence outcomes of empiric diet or pharmacological treatments. We identified no RCT data regarding whether followup biochemistries predict

treatment efficacy in preventing stone recurrence. Scant data suggest that reduction in urine supersaturation may correlate with reduced stone recurrence.

Conclusions. Increased fluid intake, reduced soft drink consumption, thiazide diuretics, citrate pharmacotherapy, and allopurinol reduce risk of recurrent calcium stones. Effects of other dietary interventions appear mixed. We identified no RCTs for uric acid or cystine stones. Data regarding whether baseline or followup biochemistries predict treatment efficacy is extremely limited.

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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 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:

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?
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?
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?
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?
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?
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 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 as follows:

Table A. Summary of evidence for prevention of stone recurrence: 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

Abbreviations: 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

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.

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.

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

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

Interventions, Studies (Study Quality)	Stone Recurrence Results	Strength of Evidence*
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

Abbreviations: 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).

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]
- 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. • Modeling studies to estimate the benefits and harms of different kidney stone evaluation, treatment and followup strategies were outside the scope of this report.	• 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. • 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.

Table C. Future research recommendations (continued)

Research Gaps	Future Research Recommendations
	• 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. • 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	• 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. • 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.

Table C. Future research recommendations (continued)

Research Gaps	Future Research Recommendations
more effective in preventing stone recurrence in patients with hypercalciuria than in those without or unselected for hypercalciuria.	
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. o Does low dietary calcium increase recurrent stone risk? Does higher dietary calcium lower risk? o 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. o 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.
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	• 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.

Table C. Future research recommendations (continued)

Research Gaps	Future Research Recommendations
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 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.
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.

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

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Introduction

Definition of Nephrolithiasis

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.

Epidemiology of Nephrolithiasis

Although kidney stones may present at any age, onset is more common in young and middle-aged adults. Lifetime prevalence is 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] Following an initial stone event, the 5-year recurrence rate in the absence of specific treatment is 35 to 50 percent.[7]

Approximately 80 percent of adults with kidney stones have stones consisting predominately of calcium oxalate and/or calcium phosphate. Struvite stones and uric acid stones each account for 5 to 10 percent of stones, and cystine stones are rare.[9] Given that kidney stones are more likely to form when conditions favor separation of crystals out of the urine, it is not surprising that many patients with kidney stones, in addition to having low urine volume, have one or more biochemical abnormalities in the urine or blood. Hypercalciuria is most common, while other abnormalities may include hypercalcemia, hyperuricemia, hyperuricosuria, hyperoxaluria, hypocitraturia, and either low or high urine pH.[10,11]

In many patients, both stones and biochemical abnormalities 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.[12,18-21]With respect to environmental factors, large observational studies have shown that low fluid intake, low calcium intake, and high fructose intake increase stone risk, while evidence is mixed for increased animal protein, increased sodium, increased sucrose, and low magnesium.[13-17] Risk of kidney stones also appears to vary by beverage type,[67,68] and 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.

Clinical Presentation of Nephrolithiasis

Kidney stones are often incidentally identified when patients undergo plain radiographs or computed tomographic imaging for another indication.[6] Stones may become symptomatic when they pass out of the renal pelvis into the ureter, with potential symptoms including renal colic with abdominal and flank pain; nausea and vomiting; urinary urgency and/or bleeding; urinary tract obstruction; infection; and acute though generally transient impairment in kidney function. While even stones as small as 1 mm in diameter may cause symptoms,[69] 90 percent of stones smaller than 5 mm pass through the urinary system without requiring intervention to aid expulsion. By comparison, approximately 50 percent of stones 5 to 10 mm in diameter require intervention to aid expulsion.[70] Large stones (e.g., struvite) also may remain in the renal pelvis and not cause pain. Studies have suggested that kidney stones may increase the risk of chronic kidney disease;[71,72] they may also may lead to hospitalizations and procedure-related morbidity.

Direct medical expenditures associated with kidney stones may exceed $4.5 billion annually in the United States.[1,8]

Laboratory Evaluation of Nephrolithiasis

Clinical guidelines recommend laboratory evaluation of patients who experience a kidney stone. Testing may include analysis of stone composition and biochemical evaluations of blood (e.g., calcium, albumin, creatinine, uric acid, potassium, bicarbonate, parathyroid hormone) and urine (e.g., pH, volume, calcium, creatinine, uric acid, oxalate, citrate, sodium, phosphate, sulfate, magnesium).[30] Clinicians may use laboratory evaluations to guide initial treatment selection, to assess treatment adherence or effectiveness, and to adjust pharmacological treatment dosing. It is not clear, however, whether pretreatment laboratory test results predict effectiveness of treatment on stone recurrence or other clinical health outcomes, or whether treatment tailored to pretreatment laboratory results is associated with reduced stone recurrence risk and better clinical health outcomes than empiric therapy. Neither do we know whether follow-up biochemical test results are valid surrogates for predicting stone recurrence. Current practice varies in the use of both initial and followup biochemical testing, particularly in patients who present as first-time stone formers.

Prevention of Recurrent Stone Disease

Many randomized controlled trials (RCTs) have examined dietary or pharmacological interventions to reduce risk of recurrent kidney stones. Yet, few of these RCTs are referenced by large clinical guidelines on the management of kidney stones, despite the fact that these guidelines include recommendations to modify various dietary components and to consider selected pharmacological therapies.[30,73]

Dietary Therapy for Prevention of Recurrent Stone Disease

Dietary interventions are designed to alter the concentration of one or more crystal-forming and/or crystal-inhibiting substance in the urine. Increasing water intake should increase urine volume and lower the urinary concentration of all crystal-forming substances. More narrowly targeted dietary interventions include reducing dietary oxalate to lower urinary oxalate and risk of calcium oxalate stones; reducing dietary animal protein and other purines to lower urinary uric acid and risk of uric acid stones; and maintaining normal dietary calcium to bind intestinal oxalate and thereby lower urinary oxalate and risk of calcium oxalate stones. Some demographic characteristics and comorbidities predict recurrent stone outcomes, but it is unclear how these factors affect relative effectiveness of treatments. It also is unclear how patient biochemical and stone characteristics affect treatment outcomes; nonetheless they are sometimes used to justify tailored dietary interventions.

Pharmacological Therapy for Prevention of Recurrent Stone Disease

Previous systematic reviews of RCTs of pharmacological therapies have reported that thiazide diuretics[24-26] and citrate therapy[26,27] reduce stone recurrence, but that evidence was insufficient regarding the efficacy of other pharmacological treatments.[24,26,28,29] These reviews did not include more recent RCTs. Nor did they evaluate evidence that compared different

pharmacological treatments with each other or combinations of pharmacological treatments versus monotherapy. Previous reviews also did not account for baseline fluid and diet intake or the effect of fluid and dietary co-interventions in pharmacological treatment trials. Further, previous reviews did not address the potential impact of patient demographics, comorbidities, biochemical measures, and stone characteristics on pharmacological treatment outcomes.

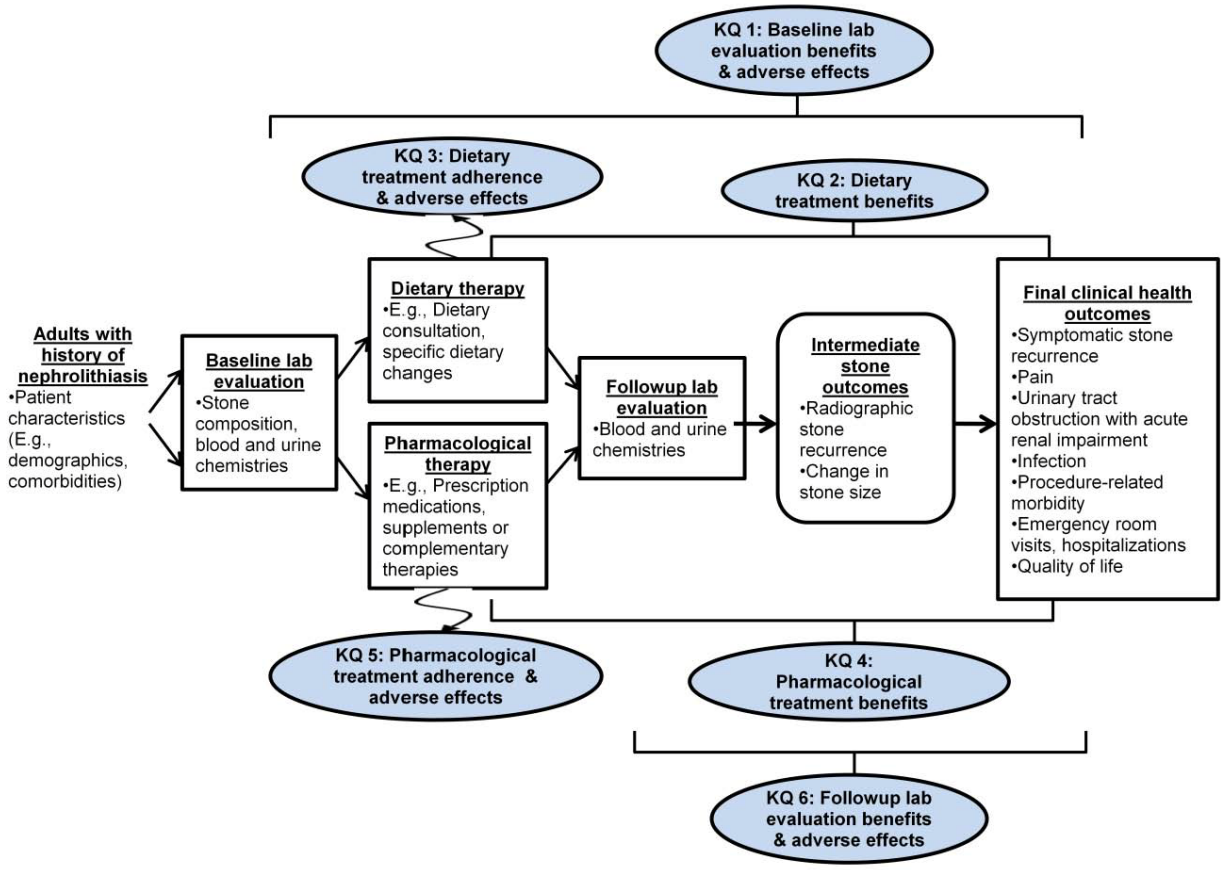
Purpose of Comparative Effectiveness Review

Current practice to prevent recurrent kidney stones varies significantly. 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. Our review and meta-analysis comprehensively addresses these questions to the degree possible with available data. Our findings should inform providers and patients making treatment decisions, organizations developing clinical guidelines, policymakers making coverage decisions, and researchers designing future studies to address remaining evidence gaps.

Analytic Framework and Key Questions

During this project's topic refinement, the topic nominator and other interested parties agreed that an independent, comprehensive review of the issues introduced above and as elaborated in the following analytic framework (Figure 1) and Key Questions would provide helpful guidance to clinicians and policymakers regarding prevention of recurrent kidney stones.

Figure 1. Analytic framework



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?

- Do effectiveness and adverse effects of treatment differ according to patient baseline stone composition and blood and urine biochemical measures?
- Does treatment tailored to the results of baseline stone composition and blood and urine chemistries improve final health outcomes and intermediate stone outcomes, and reduce adverse effects compared with empiric treatment?

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?

- Does effectiveness of diet therapy differ according to patient baseline demographic and comorbid characteristics?
- Does effectiveness of diet therapy differ according to patient baseline diet and fluid intake?

- Does effectiveness of diet therapy differ according to characteristics of stone history?

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?

- Does the risk of adverse effects differ according to patient baseline demographic and comorbid characteristics?
- Does the risk of adverse effects differ according to patient baseline diet and fluid intake?
- Does the risk of adverse effects differ according to characteristics of stone history?

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?

- Does effectiveness differ according to patient baseline demographic and comorbid characteristics?
- Does effectiveness differ according to patient baseline diet and fluid intake?
- Does effectiveness differ according to characteristics of stone history?

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?

- Does the risk of adverse effects differ according to patient demographic and comorbid characteristics?
- Does the risk of adverse effects differ according to patient baseline diet and fluid intake?
- Does the risk of adverse effects differ according to characteristics of stone history?

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?

- Does prediction of final health outcomes and intermediate stone outcomes differ according to the frequency or duration of followup biochemistry measurements?

Methods

Topic Refinement

The nominator of this topic proposed questions addressing the effectiveness and harms of dietary and medical treatments for prevention of recurrent kidney stones. We drafted Key Questions with input from representatives of the nominating organization. We discussed the Key Questions and project scope with a panel of key informants including researchers and clinicians (urology, nephrology, and dietary), patients, and payers. Based in part on their input, we submitted a revised Key Question document for Agency for Healthcare Research and Quality (AHRQ) approval. AHRQ then posted this document on the Effective Health Care (EHC) Web site for 4 weeks for public comment.

Comparative Effectiveness Review

After reviewing public comments with AHRQ and the nominator, we incorporated them as appropriate in a draft protocol. We then reviewed the draft protocol with a Technical Expert Panel (TEP) of researchers, clinicians, and representatives from the American Urological Association and the American College of Physicians. Based on TEP feedback, including on the relevance and scope of the review, we revised and finalized the protocol (including the Key Questions and proposed project methods) that ultimately was approved and posted by AHRQ on the EHC Web site.

Criteria for Inclusion/Exclusion of Studies in the Review

We developed criteria for inclusion and exclusion of studies based on patient populations, interventions, outcome measures, and evidence relevant to the Key Questions.

Population(s)

For all Key Questions, we restricted eligibility 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 order to distinguish the effect of secondary prevention from lithotripsy, we excluded studies comprising participants who had undergone lithotripsy within 90 days prior unless participants were documented as stone free at baseline.

Interventions

Diet

For Key Questions 2 and 3, we restricted the review to studies that evaluated individual diet interventions (e.g., intake of fluids, calcium, animal protein, sodium, fruit and fiber, purine, oxalate, potassium, soft drinks, citrus, others) or multicomponent diets. We also included empiric dietary interventions as well as those tailored according to patient demographics, comorbid conditions, baseline diet, baseline urine or blood biochemical testing, and/or stone type.

Pharmacological

For Key Questions 4 and 5, we restricted the review to studies that evaluated pharmacological agents currently approved by the U.S. FDA and available in the United States for prescription (e.g., hydrochlorothiazide, chlorthalidone, indapamide, potassium citrate, potassium magnesium citrate, sodium citrate, allopurinol, magnesium hydroxide, acetohydroxamic acid). We also considered as eligible trials of over-the-counter medications and supplements available in the United States and those that combined diet, pharmacological, 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/no treatment, or with other active treatments, including combination treatment and comparisons versus the same active treatment at varying dosages. Active pharmacological comparators were restricted to those currently approved by the U.S. 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, morbidity related to treatment for a recurrent stone, emergency room visits or hospitalizations for treatment of recurrent stones (e.g., for renal colic, acute renal failure), quality of life (general or urologic), and end-stage renal disease.

Also for Key Questions 1, 2, 4, and 6, 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, and hyperglycemia).

Measures of treatment adherence were those reported by the individual trials (e.g., self-report questionnaire, pill count, or as estimated by follow-up urine biochemical measures).

Timing

Eligible studies had to include followup of at least 12 months for final clinical health outcomes (e.g., stone recurrence), intermediate stone outcomes, and adherence, and at least 3 months for adverse effects. We felt that followup of fewer than 12 months would not likely be sufficient for treatments to impact recurrent stone outcomes, and that shorter trials would more likely focus on treatments to assist in stone expulsion. However, we considered 3 months sufficient for most treatment-related adverse effects to manifest.

Setting

We included studies conducted in all settings, including primary care, urology clinics, nephrology clinics, dietician 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 randomized control trials (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 very limited adverse effects data. Thus, for pharmacological treatments we expanded eligibility to RCTs of nephrolithiasis of at least 3 months in duration that reported only blood or urine biochemical outcome measures but not final clinical health outcomes or intermediate stone outcomes. Further, we included prospective observational studies of at least 3 months in duration in cohorts of at least 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 similar compositions to those of eligible trials; that dietary adverse effects seemed low; and that 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 limiting trials of medical treatments to those published in English.[74]

Searching for the Evidence: Strategies for Identifying Relevant Studies

We identified evidence for this review by searching relevant bibliographic databases, abstracts and conference proceedings, and trial registries. The primary bibliographic database search utilized MEDLINE® (January 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). Bibliographic database searches were supplemented by hand searching reference lists of included studies, previous systematic reviews, and relevant clinical guidelines. With Google Scholar, we performed forward citation searching of key included RCTs. We updated the literature search while the draft report was under public and peer review.

We searched several sources to identify unpublished RCTs, including ClinicalTrials.gov for relevant registered and completed trials, Web of Science for abstracts and conference proceedings, and industry scientific information packets for relevant regulatory documents and reports of conducted trials. Identified studies were then qualitatively evaluated and compared with published RCTs to assess potential outcomes-reporting bias.

Data Abstraction and Data Management

We screened identified studies in two stages. First, two independent investigators reviewed titles and abstracts, marking them “include,” “exclude,” or “full text needed” if a determination could not be made based on available information. We resolved the few differences in triage by group discussion. For all articles not excluded during the first stage, two investigators acting as primary and secondary abstractors/evaluators then assessed the full text for eligibility and extracted and verified data respectively into pretested tables for abstraction and evidence. Extracted data fields included: author; publication year; subject inclusion and exclusion criteria; intervention and control regimens; followup duration; participant baseline demographics, comorbidities, urine and blood test results; stone characteristics; followup urine and blood test

results; and event rates for final health outcomes, intermediate outcomes, adverse events, and adherence.

Assessment of Methodological Quality of Individual Studies

Primary and secondary abstractors/evaluators also reviewed each included RCT for quality using criteria recommended by the Cochrane Collaboration. These criteria included an assessment of the risk of bias within each study by specifically evaluating: (1) adequacy of allocation concealment;[31] (2) blinding methods (participant, investigator, and/or outcome assessor); (3) data completeness (inclusion of all randomized participants in outcomes analyses, i.e., intention-to-treat); and (4) whether reasons for dropouts/attrition were reported (to judge whether those reasons could be related to outcomes and were balanced between treatment groups.[32] Based on this evaluation, we assigned studies individual ratings of good, fair, or poor (Appendix C, Tables 7-8). A rating of good generally indicated that the trial reported adequate allocation concealment, blinding, analysis by intention-to-treat, and that reasons for dropouts/attrition were reported. We rated studies as poor if the method of allocation concealment was inadequate or not defined, blinding was not defined, analysis by intention-to-treat was not utilized, and reasons for dropouts/attrition were not reported and/or there was a high rate of attrition. We used a subset of questions from the McHarm Scale to evaluate the quality of RCTs and observational cohort studies reporting adverse events.[33] We resolved discrepancies in quality ratings by group discussion.

Data Synthesis

We qualitatively synthesized and summarized extracted study data in evidence summary tables relevant to the Key Questions. 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: patient demographic and comorbid characteristics (age, gender, race, baseline chronic kidney disease, obesity, pregnancy, solitary kidney, urinary tract anatomic abnormality, past bariatric surgery, history of renal transplant, or other comorbid conditions [e.g., cardiovascular disease, diabetes, gout, hypertension, heart failure]); baseline diet characteristics (intake of fluids, calcium, animal protein, sodium, fruit and fiber, purine, oxalate, potassium, soft drinks); 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); baseline biochemical measures from blood (uric acid, calcium, albumin, creatinine, potassium, bicarbonate) or urine (pH, volume, uric acid, oxalate, calcium, citrate, creatinine, sodium); study duration (e.g., 2 or more years versus <2 years); patient treatment adherence; followup blood and urine biochemical measures; and study quality.

Strength of Evidence for Key Questions

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 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.

We evaluated strength of evidence based on four required domains: (1) risk of bias (i.e., whether, based on study design and conduct, the studies for a given outcome or comparison have good internal validity; the risk of bias was rated low, medium, or high); (2) consistency (i.e., whether the included studies found a similar direction of effect; consistency was rated consistent, inconsistent, or, in cases when only a single study was evaluated, unknown/not applicable); (3) directness (i.e., reflecting a single, direct link between the intervention of interest and the outcome; directness was rated as either direct or indirect); and (4) precision (i.e., the degree of certainty surrounding an effect estimate of a given outcome; precision was rated either precise or imprecise, with a precise estimate being one that allowed a clinically meaningful conclusion). Examples when evidence is available, but strength of evidence 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, 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 cannot exclude either a clinically significant benefit or harm (e.g. lower CI bound <0.5 and upper CI bound >2).The 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. An overall rating of high strength of evidence implied that the included studies were RCTs with a low risk of bias with consistent, direct, and precise domains.

Assessing Applicability

We determined applicability of studies according to the PICOTS format. While some conditions that affect applicability of studies were used as exclusion criteria (i.e., short followup times), other study characteristics that could affect applicability were noted in evidence tables when possible by the study abstractors/evaluators. These characteristics included: non–U.S. settings; specialty clinic versus primary care settings; narrow study eligibility criteria; stone recurrence rates different from those described by population studies of nephrolithiasis; and drugs or dosages not typically used in current practice.

Results

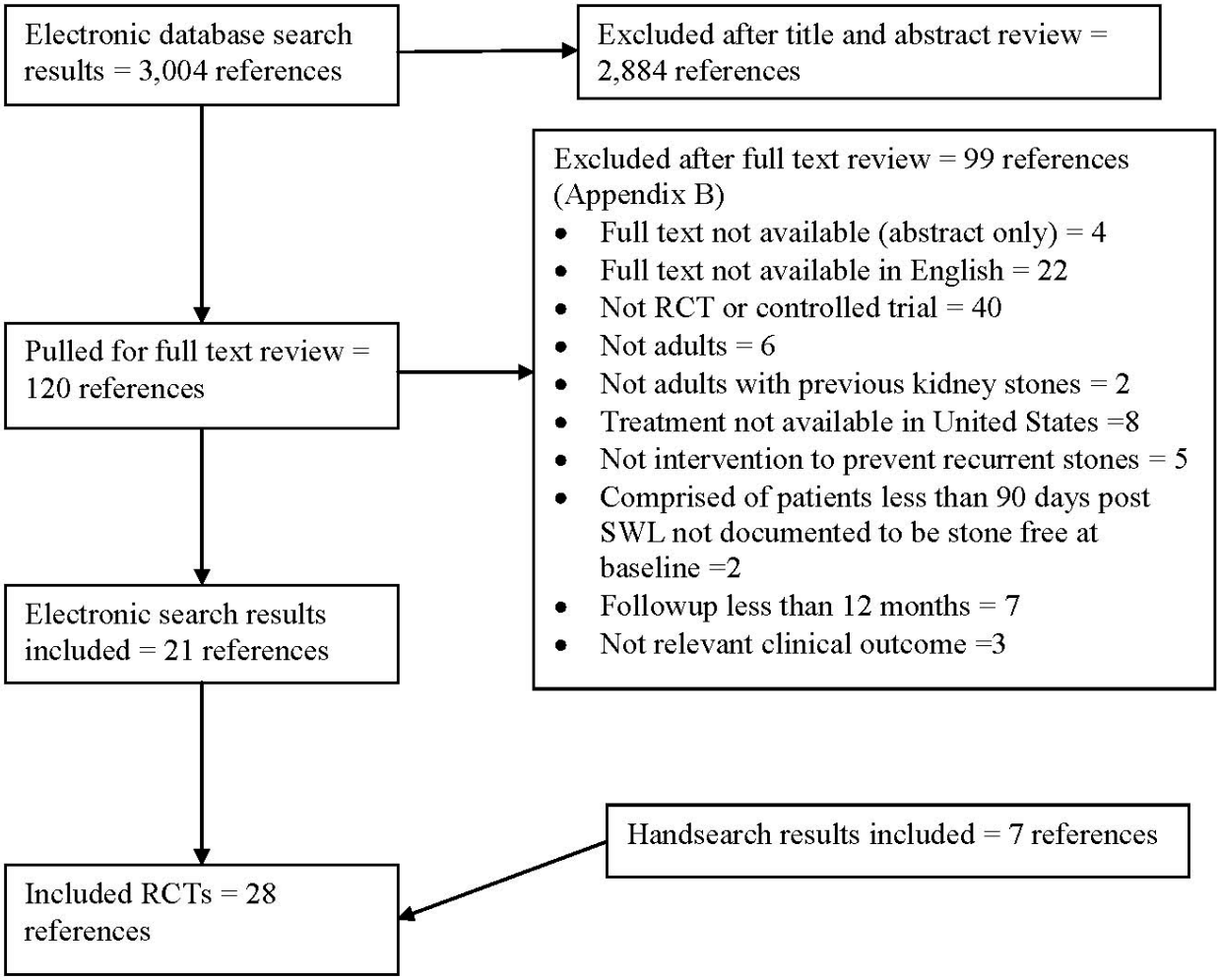
From our primary database search for RCTs of treatments to prevent recurrent nephrolithiasis that reported clinical efficacy outcomes (Figure 2), we identified 1,141 references from MEDLINE® and 2,770 references from Cochrane Central Register of Controlled Trials (CENTRAL), for a total of 3,004 unique references. Of these, we excluded 2,884 as ineligible during title and abstract review and 99 as ineligible during full-text review (Appendix B), leaving 21 that met eligibility criteria and were included. An additional seven references were identified by hand searching reference lists of included articles, systematic reviews, and clinical guidelines; all six met eligibility criteria and were included. Together, these sources generated 28 eligible RCTs of treatments to prevent recurrent nephrolithiasis (Figure 2).

We used Google Scholar to perform forward citation searching of key included RCTs and identified no additional published trials. We searched ClinicalTrials.gov for relevant registered and completed trials and identified 193 trials potentially meeting eligibility criteria. Of these, we excluded 179 as ineligible based on title review and nine as ineligible based on in-depth review. Of the five trials that appeared to meet study eligibility criteria, two were ongoing and had no results available (NCT01100580: increased fluid versus increased fluid plus low sodium; and NCT01349764: vitamin D supplementation versus control diet). We contacted authors of the three remaining, completed trials; one did not respond (NCT00004284: potassium citrate versus potassium phosphate), one reported that a final manuscript was under preparation (NCT00289120: cola versus control), and one informed us that final study results recently had been published (NCT01329042: potassium-sodium citrate versus no treatment). This article met eligibility criteria and was included. This brought the total number of eligible RCTs of treatments to prevent recurrent nephrolithiasis to 28, including eight dietary treatment studies and 20 pharmacological treatment studies. Twenty-six of the eligible RCTs were published in peer-reviewed English-language journals, while two were published as conference proceedings.[40,50]

To identify unpublished RCTs, we searched Web of Science for recent abstracts and conference proceedings, and we requested industry scientific information packets for relevant regulatory documents and reports of conducted trials. From Web of Science we identified 24 potentially relevant conference abstracts published since 2007. Of these, we excluded 17 as ineligible after title review and the rest after full abstract review. Our requests for industry scientific information packets to identify relevant regulatory documents and reports of conducted trials yielded no submissions.

From our supplemental MEDLINE® search for additional RCTs and prospective cohort studies of pharmacological treatments to prevent recurrent nephrolithiasis that reported adverse events, we identified 703 references, of which 485 were not previously identified. Of these, we excluded 466 during title and abstract review and the rest during full text review.

Figure 2. Literature search flowchart



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?

Overview

The majority of trials reported mean baseline biochemistry values and/or prevalence of one or more biochemical abnormalities, most often based on 24-hour urine collections. Additional RCTs based participant eligibility on the presence or absence of such abnormalities. Though many trials did not specify how biochemical abnormalities were defined, especially for hyperoxaluria, definitions reported were roughly similar between studies. Almost no RCTs reported and compared subsequent stone recurrence outcomes between treatments in subgroups stratified by baseline biochemistry levels. In comparisons between studies, results were mixed regarding whether stone characteristics or baseline biochemical measures predicted the

effectiveness of diet or pharmacological treatment relative to control in reducing risk of stone recurrence.

Stone Composition

Dietary Therapy Trials. One dietary therapy RCT allowed entry of participants with all stone types.[55] Otherwise, all were limited to individuals with calcium stones,[42,46,51,53,54,56,57] most of which included only those with calcium oxalate stones.[42,46,51,54,57] Consequently, we could not evaluate the effect of these dietary interventions in patients with other stone types.

Pharmacological Therapy Trials. All thiazide, allopurinol, and magnesium trials were limited to participants with calcium stones. Similarly, all AHA trials were performed in individuals with struvite stones, and all citrate trials but one that didn't specify stone type and reported only change in stone size as an outcome[63] were limited to participants with calcium stones. Consequently, we could not evaluate the effect of these interventions in patients with other stone types, including, notably, the effect of allopurinol in individuals with uric acid stones.

Blood and Urine Chemistry

Hypercalciuria

Dietary Therapy Trials. Of five dietary trials that reported prevalence of hypercalciuria or based participant eligibility on the presence or absence of hypercalciuria,[42,51,53,56,57] three defined it.[51,57,75] Respectively, reported definitions were >300 mg/day,[51] >300 mg/day in men or >250 mg/day in women,[57] and >0.1 mmol/kg/day.[56]

In the one dietary RCT limited to individuals with hypercalciuria, participants randomized to normal to high calcium, low animal protein, and low sodium diet had a significant reduction in risk of composite stone recurrence versus those assigned a low calcium diet (20 vs. 38 percent, p=0.03).[51] Adjustment for baseline characteristics, including urine calcium levels, did not significantly change these results.

In the one dietary RCT limited to participants without hypercalciuria, participants randomized to increased fluid intake had a significant reduction in risk of radiographically detected recurrent stones versus no treatment (8 vs. 56 percent, p<0.01),[42] a result qualitatively similar to that reported from a single trial comparing increased fluid intake with no treatment in participants unselected with regard to hypercalciuria (12 vs. 27 percent composite stone recurrence, p=0.008).[46] No trial evaluated any other dietary intervention in participants without hypercalciuria or in those who were unselected for hypercalciuria.

Pharmacological Therapy Trials. Of 12 pharmacological trials that reported prevalence of hypercalciuria or based participant eligibility on the presence or absence of hypercalciuria,[37,41,43,45,47-50,52,58,59,64] eight defined it.[37,41,45,47-49,52,64] Respectively, reported definitions were >300 mg/day (i.e., >7.5 mmol/day) in men and >250 mg/day (i.e., >6.2 mmol/day) in women,[64] $\geq$300 mg/day in men and $\geq$250 mg/day in women or >4 mg/kg in either gender,[37,47] >300 mg/day in men and >250 mg/day in women or >4 mg/kg or urine calcium/creatinine ratio >0.20 mg/dL in either gender,[41] >300 mg/day,[45] >6 mmol/day,[49] >276 mg/day or >6 mmol/day,[52] and >7.5 mmol/L/day in men and >6.25 mmol/L/day in women.[48]

In the one pharmacological RCT limited to individuals with hypercalciuria, participants randomized to thiazide had a significant reduction in risk of composite stone recurrence versus those assigned to control (RR, 0.33 [CI, 0.13 to 0.79]).[41] This result did not differ significantly from those in trials of thiazide versus control that were not limited to participants with hypercalciuria (p=0.29 for interaction).[47-50]

Two pharmacological RCTs enrolled only individuals without hypercalciuria. The first such trial reported no significant reduction in risk of composite stone recurrence in participants randomized to allopurinol versus control (RR, 0.49 [CI, 0.19 to 1.23]).[37] However, the estimate of effect did not differ significantly from that reported in a single study of allopurinol versus control in which participants with hypercalciuria were not excluded (RR, 0.61 [CI, 0.42 to 0.90])[38](p=0.65 for interaction). The second trial limited to participants without hypercalciuria reported a significant reduction in composite recurrent stone risk in those randomized to citrate versus control (RR, 0.35 [CI, 0.16 to 0.75]),[43] a result that did not differ significantly from results of two trials of citrate versus control that were not limited to participants without hypercalciuria (RR, 0.18 [CI, 0.07 to 0.44])[44,45](p=0.27 for interaction).

Several trials reported results stratified by or adjusted for hypercalciuria status. One RCT reported no significant difference in risk of composite recurrent stone between participants randomized to thiazide alone versus thiazide plus citrate overall (32 vs. 30 percent, p>0.05), nor in the subgroup of individuals with hypercalciuria (7 vs. 19 percent, p=0.36).[58] In a second trial, risk of composite stone recurrence in participants assigned thiazide and control, respectively, was 14 and 33 percent in the hypercalciuric subgroup (RR, 0.43 [CI, 0.10 to 1.81]) and 29 and 22 percent in the normocalciuric subgroup (RR, 1.29 [CI, 0.43 to 3.82])(p=0.23 for interaction between hypercalciuric and nonhypercalciuric subgroups).[48] A third trial reported that the effect of thiazide versus control on time to composite stone recurrence and on number of patients with new stones did not significantly differ between patients who had baseline hypercalciuria versus those who had normocalciuria (p>0.25 for interaction between hypercalciuria and normocalciuria groups for both outcomes).[49]

Hyperoxaluria

Dietary Therapy Trials. Of four dietary trials that reported prevalence of hyperoxaluria or based participant eligibility on the presence or absence of hyperoxaluria,[42,51,53,56]one defined hyperoxaluria (>500 micromol/day),[51] but not the threshold for exclusion.[51]

We identified no dietary treatment RCTs limited to participants with hyperoxaluria. However, two dietary treatment RCTs were limited to individuals without hyperoxaluria. The first trial reported no risk difference for composite recurrent stones between participants randomized to high fiber versus low animal protein versus a control diet.[56] No trial evaluated comparable interventions in participants not selected for the absence of hyperoxaluria. The second trial limited to individuals without hyperoxaluria reported a significant reduction in risk of radiographically detected recurrent stones in participants randomized to increased fluid intake versus no treatment (8 vs. 56 percent, p<0.01),[42] a result qualitatively similar to that reported from a single trial that compared increased fluid intake versus no treatment in participants unselected with regard to hyperoxaluria (12 vs. 27 percent composite stone recurrence, p=0.008).[46]

In addition, one dietary treatment RCT adjusted results for baseline urine oxalate. In this study, participants randomized to a low animal protein, low sodium, and normal to high calcium

diet were significantly less likely to have a recurrent composite stone outcome versus those assigned to a low calcium diet (20 vs. 38 percent, p=0.03). These results did not change significantly after adjustment for baseline characteristics, including urine oxalate.[51] No trials reported results stratified by baseline urine oxalate level.

Pharmacological Therapy Trials. Of four pharmacological trials that reported prevalence of hyperoxaluria or based participant eligibility on the presence or absence of hyperoxaluria,[43,52,58,64] two defined it.[52,64] Respectively, reported definitions were >40 mg/day,[64] and >46 mg/day or >0.48 mmol/L.[52]

In one pharmacological treatment RCT limited to participants with hyperoxaluria that also was just one year in duration, risk of symptomatic stone recurrence did not differ between the thiazide and control groups (RR, 1.04 [CI, 0.39 to 2.80]).[52] By comparison, risk of composite stone recurrence was significantly reduced in individuals randomized to thiazide versus control in two longer trials that excluded participants with hyperoxaluria (RR, 0.48 [CI, 0.24 to 0.94]).[47,50] We identified no additional pharmacological treatment RCTs limited to participants without hyperoxaluria.

In addition, one pharmacological treatment RCT adjusted results for baseline urine oxalate. This study reported a significant reduction in risk of composite stone recurrence in participants assigned to citrate versus control. Results were not significantly changed after adjustment for possible confounders including hyperoxaluria.[44] No trials reported results stratified by baseline urine oxalate level.

Hyperuricosuria and/or Hyperuricemia

Dietary Therapy Trials. Of two dietary trials that reported prevalence of hyperuricosuria or hyperuricemia, or based participant eligibility on the presence or absence of hyperuricosuria or hyperuricemia,[42,53] neither reported thresholds that defined abnormality.

We identified no dietary RCTs limited to participants with or without baseline hyperuricosuria or hyperuricemia, or that reported results adjusted for or stratified by baseline urine or blood uric acid level.

Pharmacological Therapy Trials. Of nine pharmacological trials that reported prevalence of hyperuricosuria or hyperuricemia, or based participant eligibility on the presence or absence of hyperuricosuria or hyperuricemia,[37,38,43,45,47,49,52,58,64] seven reported thresholds that defined abnormality,[37,38,45,47,49,52,64] Respectively, reported definitions of hyperuricosuria were $\geq$600 mg/day,[45,64] >763 mg/day,[52] >800 mg/day in men and >750 mg/day in women,[37,47] and >3.5 mmol/day.[49] Hyperuricemia was defined in one trial as >6 mg/dL[38] and in one trial as >6.48 mg/dL.[52]

Two pharmacological RCTs were limited to individuals with either baseline hyperuricosuria[37] or hyperuricemia.[38] Both of these trials enrolled only participants with calcium stones and compared allopurinol versus control. In pooled results, those randomized to allopurinol had a significantly reduced risk of recurrent composite stones versus control (33.3 vs. 55.4 percent; RR, 0.59 [CI, 0.42 to 0.84]). In participants with baseline hyperuricosuria, time to first composite stone recurrence was significantly greater in those assigned to allopurinol versus control (33.3 vs. 27.4 months, p<0.05), while absolute rate of composite stone recurrence was 0.12 versus 0.26 stones per patient year in the allopurinol and control groups, respectively.[37]

By comparison, in participants unselected for urine or serum uric acid levels and randomized to allopurinol versus control, we identified no pharmacological trials that reported a composite recurrent stone outcome. However, in two trials reporting, rate of symptomatic stone recurrence in the allopurinol and control groups, respectively, was 0.54 versus 0.58,[39] and 0.96 versus 0.66 stones per patient year.[40]

No pharmacological trials reported results stratified by baseline urine or blood uric acid level.

Hypocitraturia

Dietary Therapy Trials. The only dietary trial that reported prevalence of hypocitraturia or based participant eligibility on the presence or absence of hypocitraturia did not define it.[53]

We identified no dietary RCTs limited to participants with or without baseline hypocitraturia, or that reported results adjusted for or stratified by baseline urine citrate level.

Pharmacological Therapy Trials. Of six pharmacological trials that reported prevalence of hypocitraturia or based participant eligibility on the presence or absence of hypocitraturia,[43,45,52,58,59,64] four defined it.[43,45,52,64]Respectively, reported definitions were <273 mg/day,[52] <320 mg/day,[45,64] and <3.4 mmol/day.[43]

One pharmacological RCT was comprised entirely of participants with hypocitraturia, and those randomized to citrate versus control were significantly less likely to experience a composite stone recurrence outcome (RR, 0.35 [CI, 0.16 to 0.75]).[43] These results did not differ significantly from results in pharmacological trials of citrate versus control that were not restricted to participants with hypocitraturia (p=0.27 for interaction).[44,45] In addition, one pharmacological RCT that included a mix of hypocitraturic and normocitraturic participants and compared citrate versus control (overall RR, 0.20 [CI, 0.08 to 0.52]) reported that citrate's benefit on stone recurrence was not limited to the fewer than 20 percent of study participants with hypocitraturia; however, numerical stratified results were not reported.[44]

Other Biochemical Measures

Dietary Therapy Trials. One dietary treatment trial reported a significantly lower risk of composite stone recurrence in participants randomized to a low animal protein, low sodium, and normal to high calcium diet versus a low calcium diet (20 vs. 38 percent, p=0.03). Results were not significantly changed by adjustment for baseline characteristics, including urine volume, sodium, and calcium-oxalate product.[51] Otherwise, we identified no dietary RCT data addressing whether the effect of treatment on risk of recurrent stones differed according to baseline level of urine sodium, magnesium, phosphate, potassium, volume, pH, calcium-oxalate product, calcium-oxalate supersaturation, calcium-phosphate supersaturation, or uric acid supersaturation. No trials consisted entirely of participants with abnormal levels of any of these measures or reported results for stone recurrence stratified by any of these measures.

Pharmacological Therapy Trials. One pharmacological treatment trial reported a significant reduction in risk of composite stone recurrence in participants assigned to citrate versus control. The results were not significantly changed after adjustment for possible confounders including urine volume.[44] Otherwise, we identified no pharmacological RCT data addressing whether the effect of treatment on risk of recurrent stones differed according to baseline level of urine

sodium, magnesium, phosphate, potassium, volume, pH, calcium-oxalate product, calcium-oxalate supersaturation, calcium-phosphate supersaturation, or uric acid supersaturation. In no trials were all participants defined as having abnormal levels of any of these measures, and no trials reported results for stone recurrence stratified by any of these measures.

In one additional RCT, participants were randomized to an extensive biochemical evaluation and diet treatment tailored to address any biochemical abnormalities identified versus a limited biochemical evaluation and empiric diet treatment.[53] However, the study did not report results comparing outcomes for different diets within any biochemical subgroup.

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?

Overview

We found low strength of evidence (Table 1) that increased fluid intake to maintain urine output of >2 to 2.5 L/day significantly reduces risk of recurrent stones compared with a control diet. We found low strength of evidence that advice to reduce soft drink intake significantly reduces risk of recurrent stones compared with no treatment in men with high baseline soft drink consumption. We found low strength of evidence that decreased animal protein or increased fiber intake do not reduce risk of recurrent stones. We found low strength of evidence that an extensive biochemical evaluation followed by tailored diet treatment reduces risk of recurrent stones compared with a limited evaluation and empiric diet treatment. We found low strength of evidence that a multicomponent diet including normal to high calcium, low protein, and low sodium reduced risk of recurrent stones compared with a low calcium diet, but also low strength of evidence that a multi-component diet with low animal protein, high fruit, vegetables, and whole grains, increased bran and low purine increased risk of recurrent stones versus a control diet. We found no evidence regarding whether diets including increased calcium, low sodium, low oxalate, or low purine as isolated diet changes reduce risk of recurrent kidney stones. Results were based on trials conducted predominately in young to middle-aged men. Half of trials were performed in patients with only a single past calcium stone episode, including both trials of increased fluid intake versus no treatment, while the other half of trials included or were limited to participants with recurrent calcium stones. Nearly all studies relied on a composite definition of recurrent stone outcomes that included either symptomatic or radiographic recurrence. Few studies reported adherence. With the exception of one trial in which participants were recruited from primary care settings,[57] study subjects appeared to have been recruited from urology or nephrology clinics or specialty stone center**s.**

Study Characteristics

Study Design

Eight trials of dietary interventions met eligibility criteria (n=2294 participants, range 45 to 1009)[42,46,51,53-57] (Appendix C, Table 1; Appendix F, Table 1). All trials were published in peer-reviewed English-language journals. All trials indicated that they were randomized, although only two reported an adequate method of random allocation.[51,56] All trials used a parallel treatment group design. Treatment duration ranged from 19 to 60 months.

Treatment Groups

Among eligible trials, three compared treatment groups with regard to quantity or type of fluid intake (Appendix C, Table 1). One randomized participants to increase water intake to achieve >2 L/day urine volume versus no treatment (n=220) for 5 years,[46] one randomized participants to increase fluid intake to achieve > 2.5 L/day urine volume versus no treatment (n=45) for 2 to 3 years,[42] and a third randomized participants to consume 2 L/day water, as oligo-mineral water (15 mg/L calcium content) versus tap water (55 to 130 mg/L calcium content) (n=384).[54] A fourth trial randomized men with baseline soft drink consumption > 160 mL/day to advice to refrain from drinking soft drinks versus no treatment (n=1009).[55]

Four eligible trials evaluated the efficacy of multicomponent dietary interventions versus control diets. The first trial randomized 99 participants to a diet with low animal protein (56-64 gm/day), high fruit, vegetables, and whole grains, increased bran (1/4 cup/day), and low purine (75 mg/day) versus a control diet for 2 years. Both groups were advised to consume two dairy servings (or calcium carbonate supplements) and six to eight glasses of liquid daily.[57] In the second trial, 242 participants were randomized to a limited biochemical evaluation with general diet recommendations versus an extensive biochemical evaluation and diet tailored to identified abnormalities.[53] Among participants who underwent the extensive evaluation, those identified with hypercalciuria were assigned restricted animal protein and 750 to 1000 mg/day of dietary calcium; those identified with hyperuricosuria or hyperuricemia were assigned a low-purine diet and restricted to 80 gm/day of meat products with one to two meatless days per week; those identified with hyperoxaluria were assigned restricted oxalate intake, regular dairy intake, lemons, and increased fiber intake; those identified with magnesium deficiency were assigned increased fiber, regular dairy intake, and high magnesium mineral water; and those identified with hypocitraturia were assigned restricted animal protein, one to two servings of lemons or orange juice per day, and increased fruit and vegetables. For the control group, the general diet recommendations included 750 to 1000 mg/day of calcium, 100 to 120 gm/day of animal protein, oxalate restriction, increased fiber intake, and "moderate" sodium intake. In a third trial, 120 men were randomized to normal to high dietary calcium (1200 mg/day), low animal protein (52 gm/day), and low sodium (50 mmol/day) versus a control diet including low calcium (400 mg/day) for 5 years. Both groups were advised to drink 2 to 3 liters of water per day and decrease oxalate intake.[51] Last, in the fourth trial, 175 participants were randomized to a low protein diet ($\leq$ 3 meat or fish servings per week and $\leq$ 100 g/day of milk products) versus high fiber diet (increase baseline fiber consumption 25 g/day by increasing fruit, fiber, and whole grain intake) versus no treatment.[56]

Outcome Measures

All trials presented results in terms of the proportion with any stone recurrence, including one that reported symptomatic stone recurrence,[55] two that reported radiographic recurrence,[42,54] and five that reported a composite recurrence outcome defined by either symptomatic stone passage or radiographic detection.[46,51,53,56,57] In addition, one trial reported time to stone recurrence,[46] and another reported rate of recurrent stones per patient year of followup.[57] Last, one trial reported results for change in stone size, but did not report results separately by treatment group.[56]

Participant Characteristics

Demographics

Trial participants were predominately young (mean 42 years, range 32 to 45; 7 trials reporting) and male (80.9 percent) (Appendix C, Table 1). Two trials were restricted to males.[51,55] In the single trial that reported data on race, 77 percent of participants were Caucasian.[57] Six trials were conducted in Europe and two in the United States.[55,57] In nearly all trials, participants appeared to have been recruited from within a specialty stone center,[46,51,54] urology clinic,[53,55] or nephrology clinic.[56] By contrast, in one trial members of the Kaiser Permanente Medical Care Program with a history of a single calcium oxalate stone were recruited from their primary clinics.[57] One trial reported no participant recruitment source, but all had recently undergone shockwave lithotripsy and the authors were affiliated with the Department of Urology. Thus, it is likely that these individuals were recruited from a urology clinic setting.[42]

Medical History

Four trials reported baseline body mass index (BMI) or weight, with mean BMI 24.5 kg/m^2 [56,57] and mean weight 71.5 kg[46,51,56] (Appendix C, Table 1; Appendix F, Table 1). Two trials reported baseline renal function,[51,56] with mean serum creatinine of 1.0 mg/dL and respective mean creatinine clearances of 88 mL/min/1.73m^2 and 126 mL/min. One trial reported that no participants had urinary tract anatomic abnormalities.[51] No eligible trials reported prevalence of diabetes, although one study excluded participants with undefined severe diabetes.[54] No eligible trials reported prevalence of previous bariatric surgery, chronic kidney disease, solitary kidney, renal transplant, coronary artery disease, hypertension, or pregnancy. All but one trial excluded participants with conditions known to be associated with calcium nephrolithiasis.[55]

Stone History

Seven trials limited enrollment to participants with calcium stones, of which three were further restricted to those with pure calcium oxalate stones,[42,46,51] while four allowed mixed calcium oxalate and calcium phosphate stones[53,54,56,57] (Appendix C, Table 1). One trial included individuals with any stone type.[55] Four trials included only participants with a single past stone episode;[42,46,53,57] two trials included only participants with multiple past stone episodes;[51,54]and two trials included both groups.[55,56]

Three trials included only participants who were stone free at baseline, based, respectively, on abdominal radiography alone,[57] combined abdominal radiography and ultrasound,[54] or combined ultrasound and excretory urography.[46] In three trials that allowed entry of participants with residual stone fragments, 21 to 53 percent of participants had baseline stone fragments. Two of these studies determined presence of stone fragments based on combined abdominal radiography and ultrasound[51,53] and one based on combined abdominal radiography, ultrasound and renal tomography.[42] Two trials reported no data regarding the presence of residual stone fragments at baseline.[55,56] Two trials included only participants previously treated with extracorporeal shock wave lithotripsy, with one requiring that all participants be stone free at baseline[54] and the other reporting results in a subgroup that was stone free at baseline.[42]

Baseline Biochemistry

Among eight eligible diet studies, seven reported at least some baseline serum and/or urine biochemistry results[42,46,51,53,54,56,57] (Appendix H, Table 1). All urine biochemistries were based on 24-hour urine collections.

Five trials reported the proportion of participants with hypercalciuria, including 0 percent,[42] 18 percent,[57] 38 percent,[56] 100 percent,[51] and, finally, one trial in which 67 percent of participants in the multicomponent diet intervention group had hypercalciuria, but that reported no data for the control group.[53] Two trials had no participants with hyperoxaluria,[42,56] one trial included 18 percent of participants with mild hyperoxaluria,[51] and a fourth trial reported that 18 percent of the multicomponent diet intervention group had hyperoxaluria.[53] One trial had no participants with hyperuricosuria,[42] while a second reported that 27 percent of the multicomponent diet intervention group had hyperuricosuria.[53] Hypocitraturia (19 percent), hypomagnesuria (9 percent), hyperuricemia (10 percent), and hypomagnesemia (12 percent) each were reported only within the multicomponent diet intervention group from within a single trial that reported no data on the prevalence of these biochemical abnormalities in the control group.[53]

Six trials reported mean baseline values for at least some urine biochemistry measures (Appendix H, Table 1),[46,51,53,54,56,57] though one trial reported these results only for the multicomponent dietary intervention group and not for the control group.[53] All six trials reported urine calcium with a mean of 278 mg/24 hrs (range 204 to 451); other frequently reported baseline urine biochemistry results included mean oxalate 31 mg/24 hrs (range 29 to 41, n=5 trials), mean uric acid 596 mg/24 hrs (range 566 to 736, n=4 trials), mean sodium 4133 mg/24 hrs (range 3653 to 5379, n=4 trials), and mean citrate 565 mg/24 hrs (range 521 to 603, n=3 trials). Only one trial reported calcium-oxalate product,[51]and two trials reported calcium-oxalate supersaturation.[46,51] Five trials reported baseline urine volume, with a mean of 1.6 liters/24 hrs (range 1.0 to 2.4).[46,51,53,54,56]

Study Quality

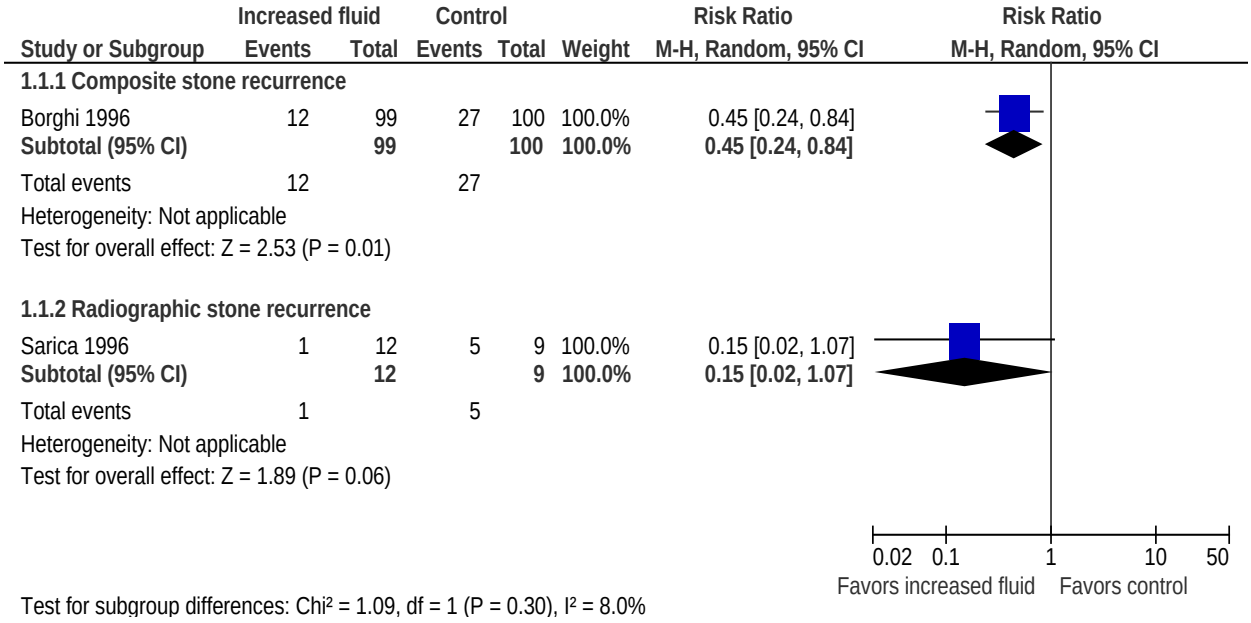
Among the eight eligible trials, one was rated good quality, five were rated fair quality, and two were rated poor quality (Appendix C, Table 7). Allocation concealment was adequate in two studies[51,56] and unclear in the rest. Four of the eight trials masked outcome assessors to participant treatment assignment.[51,55-57] Four trials performed intention to treat analysis.[42,51,55,57] Six of the eight trials adequately reported withdrawals,[42,51,54-57] which ranged from 0 to 58.3 percent.

Efficacy Outcomes Increased Fluid Intake Versus No Treatment

Stone Recurrence. Neither of two trials reported results for symptomatic stone recurrence; thus evidence is insufficient to directly address the effect of increased fluid intake on this outcome. In the single trial that reported composite stone recurrence, participants randomized to increased fluid intake to achieve urine volume > 2 L/day comparedwith no treatment were significantly less likely to experience stone recurrence (12.1 vs. 27.0 percent; RR, 0.45 [CI, 0.24 to 0.84])[46] (Figure 3; Appendix D, Table 1). Consistent with these results, mean time to first recurrence was greater in the increased fluid group compared with no intervention (38.7 vs. 25.1 months, p=0.016) (Appendix E, Table 1a). In the single trial that reported radiographic stone recurrence, participants who were stone free after shockwave lithotripsy were randomized to increased fluid intake to achieve urine volume > 2.5 L/day versus no treatment. Eight percent of the increased

fluid group experienced stone recurrence versus 55.6 percent of the no-treatment group (RR, 0.15 [CI, 0.02 to 1.07])[42] (Figure 3). Although the magnitude of benefit appeared large, this result was not statistically significant, possibly because of the small sample size. Nevertheless, because of thewide confidence intervals we are unable to conclude if increased fluid intake reduces radiographic stone recurrence.

Figure 3. Risk of stone recurrence, increased fluid intake versus no treatment



Other Clinical Outcomes. Neither of the two trials reported results for any other clinical health outcomes, including pain, urinary tract obstruction with acute renal failure, infection, procedure related morbidity, emergency room treatment or hospitalization related to stone recurrence, quality of life, or end-stage renal disease (Appendix E, Tables 1b-c).

Subgroup Results. Neither of the two trials reported efficacy outcomes within subgroups defined by demographic or comorbid characteristics or according to characteristics of stone history.

Adherence to Assigned Treatment. One of the two trials reported only that compliance was "good in the majority of the patients" assigned increased fluid intake, but provided no information regarding how compliance was defined.[42] Further, it did not report any data regarding the percentage of participants assigned increased fluid intake who maintained the goal level of daily urine output or their mean daily urine volume. In the second trial, participants assigned increased fluid intake had a mean urine volume of 1.1 L/day at baseline, 2.1 L/day at 1 year, 2.3 L/day at 2 years, and >2.5 L/day at the 3 through 5 year followup points.[46] By comparison, mean urine volume in the control group was 1.0 L/day at baseline, peaked at 1.3 L/day at 1 year, and otherwise remained similar to baseline at each followup point through 5 years. Followup urine volumes were available only in participants who had not withdrawn from the study.

Increased Oligomineral Water Intake Versus Increased Tap Water Intake

Stone Recurrence. In a single trial, all participants were assigned to drink >2 L of water per day, but were randomized to oligomineral water with 15 mg/L calcium versus tap water with 55 to 130 mg/L calcium content.[54] Stone recurrence was defined based on radiographic detection only. Seventeen percent of those randomized to oligomineral water had stone recurrence versus 22.9 percent of those allocated to tap water (RR, 0.73 [CI, 0.48 to 1.09]) (Appendix D, Table 1).

Other Clinical Outcomes. This trial did not report results for any other clinical health outcomes (Appendix E, Tables 1b-c).

Subgroup Results. This trial did not report efficacy outcomes within subgroups defined by demographic or comorbid characteristics or according to characteristics of stone history.

Adherence to Assigned Treatment. This trial reported no adherence data.

Decreased Soft Drink Intake

Stone Recurrence. One trial, conducted in stone-forming participants with baseline soft drink consumption >160 ml per day, reported a 7 percent absolute reduction in self-reported, physician-confirmed renal colic episodes (i.e., symptomatic recurrence) in those randomized to advice to abstain from soft drink intake versus no intervention for 3 years (33.7 vs. 40.6 percent; RR, 0.83 [CI, 0.71 to 0.98])[55] (Appendix D, Table 1). Total fluid intake was similar in both groups.

No data were reported for radiographic stone recurrence, a composite stone recurrence outcome, stone recurrence rate, change in stone size, or residual or stone fragment clearance (Appendix D, Table 1; Appendix E, Table 1a).

Other Clinical Outcomes. This trial reported no other clinical health outcomes (Appendix E, Tables 1b-c).

Subgroup Results. This trial reported that benefit appeared restricted to participants for whom the soft drink most frequently consumed at baseline was acidified solely by phosphoric acid (29.7 percent vs. 45.6 percent; RR, 0.65 [CI, 0.49 to 0.87], p=0.02 for interaction between baseline soft drink acidification types). The study reported no results within subgroups defined by baseline fructose consumption, demographic or comorbid characteristics, or according to characteristics of stone history.

Adherence to Assigned Treatment. The study determined that 43.1 percent of participants assigned to the low soft drink intake group were compliant at 6 months. Compliance was defined as self-report of drinking fewer than three 8-ounce glasses of soda (< 680 ml) per week during the most recent 6-month followup period. Reported compliance appeared constant over 3 years, though results were based only on participants who had not withdrawn from the study.

Multicomponent Dietary Interventions

Stone Recurrence. Three trials examined a multicomponent dietary intervention versus a control diet and reported conflicting results (Appendix D, Table 1; Appendix E, Table 1a).

In one trial that randomized participants to a low animal protein, high fiber, increased bran, and low purine diet versus a control diet for 2 years, and in which both groups were advised to increase fluid intake and consume regular dairy or supplemental calcium, 24.0 percent of participants randomized to the multicomponent diet had a composite stone recurrence versus 4.1 percent of those allocated to the control diet (p=0.004).[57] Participants allocated to the multicomponent diet group also had a higher composite stone recurrence rate (7.1 vs. 1.2 per 100 person-years, p=0.06). The study reported neither radiographic nor symptomatic stone recurrence as isolated outcomes, nor results for stone fragment clearance or change in stone size.

In a second trial that randomized participants to a limited biochemical evaluation with general (empiric) diet recommendations versus an extensive metabolic evaluation and diet recommendations tailored to the findings of the biochemical evaluation, fewer participants randomized to the extensive evaluation and tailored diet had a composite stone recurrence (6.2 vs. 19.1 percent; RR, 0.32 [CI, 0.14 to 0.74]).[53] The study reported no separate results for any biochemical abnormality subgroup or tailored diet type. The study also did not report radiographic or symptomatic stone recurrence as isolated outcomes, nor results for stone recurrence rate, stone fragment clearance, or change in stone size.

In a third trial that randomized participants to a diet including normal to high calcium, low animal protein, and low sodium versus a low calcium diet for 5 years, and in which both groups were advised to increase fluid and decrease oxalate intake, 20.0 percent of participants randomized to the multicomponent diet had a composite stone recurrence versus 38.3 percent of those allocated to the low calcium control diet (RR, 0.52 [CI, 0.29 to 0.95]).[51] The study reported neither radiographic nor symptomatic stone recurrence as isolated outcomes and no results for stone recurrence rate, stone fragment clearance, or change in stone size.

Other Clinical Outcomes. None of the multicomponent diet intervention trials reported results for any other clinical health outcomes (Appendix E, Tables 1b-c).

Subgroups. In one trial,[51] participants assigned a normal to high calcium, low animal protein, and low sodium diet versus a low calcium diet had a relative risk of stone recurrence of 0.81 (CI, 0.28 to 2.35) and 0.23 (CI, 0.08 to 0.67) in high-risk and low-risk subgroups, respectively (p=0.09 for comparison between risk subgroups). The study defined high-risk participants as those with five or more colic episodes in the year before randomization, 10 or more stones before randomization, or both, and all other study participants as low risk. Another trial that randomized participants to a low animal protein, high fiber, increased bran, and low purine diet versus a control diet reported a nonsignificantly greater rate of recurrent stones in a subgroup with lower mean protein intake (p=0.24 versus an unspecified comparison group).[57]

Adherence to Assigned Treatment. One of the three trials reported no information on adherence to assigned diet treatment.[53] In a second trial, participants allocated to the multicomponent dietary intervention group (low animal protein, low purine, high fiber, increased fluid intake) reported significantly lower mean intake of dietary protein and purine at 6 months compared with those assigned increased fluid intake only.[57] The relative reduction in protein

intake appeared attenuated with further followup. Treatment groups did not differ in mean fiber intake at any point except 42 months, by which time analyses were based on only 61 percent of originally randomized subjects. The study did not report the number of participants who met recommended goals for protein, purine, fiber, and fluid intake. The third trial reported that three participants assigned to the multicomponent dietary intervention group withdrew because they didn't want to continue the diet.[51] The study further reported no difference in dietary compliance between treatment groups, though it neither defined compliance nor reported compliance data.

High Fiber Intake

Stone Recurrence. Only one trial compared a high fiber diet (increase baseline fiber consumption 25 g/day by increasing fruit, fiber, and whole grain intake) independent of other dietary interventions with a control diet.[56] All study participants were advised to increase their water intake to > 2 L/day and to consume between 800-1000 mg/day of dietary calcium. As defined by a composite stone recurrence outcome, 63.0 percent of those randomized to high fiber intake had recurrent stones versus 47.8 percent of controls (RR, 1.18 [CI, 0.66 to 2.12]) (Appendix D, Table 1). The study reported neither radiographic nor symptomatic stone recurrence as isolated outcomes, nor results for stone recurrence rate or stone fragment clearance. Change in stone size was reported in three participants who had an asymptomatic increase of >50 percent, but authors did not report to which treatment group these participants were randomized (Appendix E, Table 1a).

Two additional trials assigned participants to high fiber as part of a multicomponent diet intervention versus a control diet.[53,57] Results for these studies were mixed, with the group assigned the multicomponent diet intervention containing high fiber experiencing a lower risk of recurrent stones in one trial[53]and a higher risk in one trial.[57]

Other Clinical Outcomes. None of the trials examining high fiber intake reported results for any other clinical health outcomes (Appendix E, Tables 1b-c).

Subgroups. None of the trials examining high fiber intake reported efficacy outcomes within subgroups defined by demographic or comorbid characteristics or according to characteristics of stone history.

Adherence to Assigned Treatment. Among participants randomized to a high fiber diet, 23.3 percent withdrew from the study during followup because of the assigned diet. By comparison, 15 percent of participants randomized to the control diet withdrew because of the assigned diet ($p=0.25$ between treatment groups). In addition, the study dietician assessed adherence every 4 months via participant phone interviews, during which the dietician also reinforced assigned dietary recommendations. Among participants assigned a high-fiber diet, mean fiber intake increased from 17 g/day at baseline to a peak of 27 g/day at 1 year ($p<0.01$ vs. baseline) and 23 g/day at 4 years ($p<0.01$ vs. baseline). By comparison, mean fiber intake in the control diet group was 17 g/day at baseline and did not change during followup. These results appeared to be derived from only those participants who had not withdrawn from the study.

Low Animal Protein Intake

Stone Recurrence. Only one trial compared a low animal protein diet (≤ 3 meat or fish servings per week and ≤ 100 g/day of milk products) independent of other dietary interventions with a control diet.[56] All study participants were advised to increase their water intake to > 2 L/day and to consume between 800-1000 mg/day of dietary calcium. Results did not differ between treatment groups in risk of composite recurrent stones, at 47.8 percent in both (RR, 1.00 [CI, 0.52 to 1.91]) (Appendix D, Table 1).

Three additional trials assigned participants to low animal protein as part of a multicomponent diet intervention versus a control diet.[51,53,57] Results for these studies were mixed, with the diet intervention group experiencing a lower risk of recurrent stones in two trials[51,53] and a higher risk in one trial[57] (Appendix D, Table 1).

Other Clinical Outcomes. No trial that evaluated low animal protein as an independent dietary intervention or as part of a multicomponent dietary intervention reported on other clinical health outcomes (Appendix E, Tables 1b-c).

Subgroups. Neither the trial that evaluated a low animal protein diet independent of other dietary interventions[56] nor the trials that included low animal protein as part of a multicomponent dietary intervention reported efficacy outcomes within subgroups defined by demographic or comorbid characteristics or according to characteristics of stone history. In one trial,[56] a subgroup of eight patients highly compliant with the low animal protein diet (decreased contribution of protein to total energy below 13 percent and significant decrease in 24-hour urea excretion) showed no difference in stone recurrence compared with the control group.

Adherence to Assigned Treatment. Of those assigned to low animal protein, 29.1 percent withdrew from the study during followup due to the diet. By comparison, 15 percent of participants randomized to the control diet withdrew due to the diet (p=0.07 between groups). In addition, based on phone interviews during which the study dietician assessed and encouraged adherence, participants assigned to low animal protein decreased mean total protein intake from 84 g/day at baseline (57 g/day animal protein) to 68 g/day at 1 year (38 g/day animal protein), a level that was maintained at 4 years ($p<0.001$ vs. baseline for both total protein and animal protein). By comparison, mean total protein intake in the control diet group was 84 g/day at baseline (55 g/day animal protein) and throughout followup. These results appeared to be derived from only those participants who had not withdrawn from the study. Followup urinary sulfate levels decreased from baseline at all points except 1 year in participants assigned a low animal protein diet. Within the subgroup of participants assigned a low animal protein diet who had baseline hypercalciuria, followup urine calcium and uric acid levels also decreased. No changes from baseline occurred in any of the followup urine biochemical measures in the control diet group.

Other Dietary Interventions

Stone Recurrence. No trials assessed the efficacy of diets with altered calcium, low sodium, low oxalate, or low purine independent of other diet changes. In one trial, fewer participants randomized to a multicomponent diet that included normal to high dietary calcium intake (1200

mg/day) had recurrent stones than the group assigned to a low dietary calcium (400 mg/day) control group[51] (Appendix D, Table 1) In a single trial, participants randomized to a multicomponent diet that included low dietary sodium intake (50 mmol/day vs. usual care)[51] were less likely to experience stone recurrence than those randomized to a control diet. Last, two trials that compared multicomponent dietary intervention trials that included low purine intake with control diets reported mixed results.[53,57]

Other Clinical Outcomes. None of the multicomponent diet intervention trials that include altered calcium, low sodium, low oxalate, or low purine reported results for any other clinical health outcomes (Appendix E, Tables 1b-c).

Subgroups. Because no trials assessed the efficacy of diets with altered calcium, low sodium, low oxalate, or low purine independent of other diet changes, there also are no efficacy data for these interventions within subgroups defined by demographic or comorbid characteristics or according to characteristics of stone history.

Adherence to Assigned Treatment. No trials assessed adherence to the diets.

Table 1. Strength of evidence for prevention of stone recurrence: Diet intervention trials

Intervention	Stone Recurrence Type	Number of Trials	Number of Randomized Subjects	Summary Statistics RR [95% CI]	Risk of Bias*	Directness**	Precision†	Consistency‡	Evidence Rating††
Increased fluid intake vs. control	Symptomatic	0	-	-	-	-	-	-	Insufficient
	Composite	1	220	0.45 [0.24 to 0.84]	medium	direct	precise	NA	Low
	Radiographic	1	21	0.15 [0.02 to 1.07]	medium	direct	imprecise	NA	Insufficient
Increased oligomineral water intake vs. increased tap water intake	Symptomatic	0	-	-	-	-	-	-	Insufficient
	Composite	0	-	-	-	-	-	-	Insufficient
	Radiographic	1	384	0.73 [0.48 to 1.09]	medium	direct	imprecise	NA	Low
Reduced soft drink intake vs. control	Symptomatic	1	1009	0.83 [0.71 to 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 to 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 to 2.12]	medium	direct	imprecise	NA	Low
	Radiographic	0	-	-	-	-	-	-	Insufficient
Multi-component diet (Borghi 2002)‡‡ vs. control	Symptomatic	0	-	-	-	-	-	-	Insufficient
	Composite	1	120	0.52 [0.29 to 0.95]	medium	direct	precise	NA	Low
	Radiographic	0	-	-	-	-	-	-	Insufficient
Multi-component diet (Hiatt 1996) § vs. control	Symptomatic	0	-	-	-	-	-	-	Insufficient
	Composite	1	99	5.88 [1.39 to 24.92]	medium	direct	precise	NA	Low
	Radiographic	0	-	-	-	-	-	-	Insufficient
Tailored diet§§ vs. empiric diet	Symptomatic	0	-	-	-	-	-	-	Insufficient
	Composite	1	242	0.32 [0.14 to 0.74]	medium	direct	precise	NA	Low
	Radiographic	0	-	-	-	-	-	-	Insufficient

Abbreviations: CI = confidence intervals; NA = not applicable; RR = relative risk

*Risk of bias rated low, medium, or high based on whether the design and conduct of the studies for a given treatment comparison and outcome indicate good internal validity.

**Directness indicated whether results reflect a single, direct link between the intervention of interest and the outcome and was rated as either direct or indirect.

†Precision indicated the degree of certainty surrounding an effect estimate of a given outcome and was rated either precise or imprecise, with a precise estimate being one that allowed a clinically meaningful conclusion.

‡Consistency indicated whether the included studies found a similar direction of effect and was rated consistent, inconsistent, or, in cases when only a single study was evaluated, unknown/not applicable.

††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
§§ Extensive laboratory evaluation followed by diet tailored to laboratory results versus limited laboratory evaluation followed by empiric diet (moderate intake of animal protein, sodium, and calcium; increased fiber; restricted oxalate)

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?

Overview

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.

Study Withdrawals and Adverse Events

Increased Fluid Intake Versus No Treatment. Withdrawals in the two trials that compared increased fluid intake to no treatment averaged 9.5 percent (range 0 to 10 percent) with similar proportions between intervention and control groups (Appendix G, Table 1). One trial reported zero withdrawals due to adverse events,[42] and one trial reported no data on withdrawals due to adverse events.[46] Neither trial reported any results regarding the number of participants with at least one adverse event or with any specific adverse event.

Increased Oligomineral Water Intake Versus Increased Tap Water Intake. The single trial that compared increased oligomineral water intake with increased tap water intake reported no withdrawals from either treatment group (Appendix G, Table 1). However, the study reported no 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 trial that compared decreased soft drink intake with no treatment reported that 8.7 percent of participants withdrew in the intervention group versus 5.5 percent in the control group[55] (Appendix G, Table 1). In each group, two participants withdrew due to adverse events in each group, and two participants died. No information was reported regarding the circumstances of the deaths. The trials reported no other adverse events data.

Multicomponent Dietary Interventions. Withdrawals in the three multicomponent dietary intervention trials averaged 16.4 percent (range 14.2 to 23.5 percent) and were no greater in the multicomponent dietary intervention group than the control group in the two studies that reported those outcomes separately[51,57] (Appendix G, Table 1). In the one trial reporting, withdrawals due to adverse events were 5.0 percent in the multicomponent dietary intervention group (hypertension, gout, and stroke each 1.7 percent) versus 11.7 percent in the control group (hypertension 11.7 percent).[51] In addition, two participants (3.3 percent) in the control group died during the study.[51]

High Fiber Intake. A single trial comparing a high-fiber diet with a control diet independent of other dietary interventions reported 55.0 percent withdrawals in the treatment group versus 61.7 percent for the control group after 4 years[56] (Appendix G, Table 1). This trial reported no data on withdrawals due to adverse events or regarding the number of participants with at least one adverse event or any specific adverse event.

Low Animal Protein Intake. The single trial that compared a low animal protein diet with a control diet independent of other dietary interventions reported 58.2 percent withdrawals in the low animal protein group versus 61.7 percent in the control group after 4 years[56] (Appendix G, Table 1). This trial reported no data on withdrawals due to adverse events or regarding the number of participants with at least one and/or any specific adverse event.

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?

Overview

In patients with multiple past calcium stones, we found moderate strength of evidence (Table 2) that treatment reduces risk of composite recurrent stones versus control for thiazide diuretics (RR, 0.53 [CI, 0.41 to 0.68], n=6 trials), citrate (RR, 0.26 [CI, 0.14 to 0.48], n=3 trials), and allopurinol (RR, 0.59 [CI, 0.42 to 0.84], n=2 trials). Among patients with a history of struvite stones, but no residual stones at baseline, we found insufficient strength of evidence that risk of radiographic stone recurrence was not significantly reduced in participants randomized to AHA versus placebo (RR, 0.81 [CI, 0.18 to 3.66], n=2 trials). We also found low strength of evidence that risk of a composite stone recurrence was nonsignificantly lower in individuals randomized to magnesium than in those assigned to placebo (RR, 0.65 [CI, 0.37 to 1.16], n=1 trial).

In trials that compared active treatments with each other, risk of composite stone recurrence was nonsignificantly higher in individuals randomized to magnesium than in those assigned to thiazide (RR, 2.06 [CI, 0.88 to 4.84], n=1 trial) (low strength of evidence). Further, the risk of a composite stone recurrence was not significantly different between individuals randomized to thiazide plus citrate versus thiazide alone (30.0 vs. 32.0 percent; RR, 0.94 [CI, 0.52 to 1.68]) (low strength of evidence), or between individuals randomized to thiazide plus allopurinol and those assigned to thiazide alone (12.5 vs. 15.8 percent; RR, 0.79 [CI, 0.18 to 3.49]) (insufficient strength of evidence).

Thiazide Diuretic Monotherapy Versus Placebo or Control

Study Characteristics

Study Design. Seven trials met all eligibility criteria and randomized participants with nephrolithiasis (n=565, range 41 to 150) to a thiazide diuretic versus placebo (n=3 trials)[47,49,52] or control treatment (n=4 trials)[41,48,50,58] (Appendix C, Table 2; Appendix F, Table 2). All trials were published in peer-reviewed English-language journals except for one published in a conference proceedings.[50] All trials indicated that they were randomized, although none reported an adequate method of random allocation of treatment assignment. All studies utilized a parallel group design, and three studies also compared historical pretreatment with post-treatment stone recurrence rates.[41,47,48] Mean study duration was 35 months (mean or median range 12 months to 4 years) and all but two studies were at least 3 years.

Treatment Groups. Among the trials that compared thiazide with placebo or control, five (n=365 participants) utilized hydrochlorothiazide, including studies that assigned participants to fixed doses of 25 mg twice daily,[49,50,52] 50 mg once daily,[58] and 50 mg twice daily[48] (Appendix C, Table 2). One trial randomized 124 participants to chlorthalidone versus placebo,[47] including treatment arms of 25 mg/day and 50 mg/day. In addition, one study randomized 75 participants to indapamide 2.5 mg/day versus control.[41] Among the seven eligible trials, six reported dietary co-interventions in both treatment and control arms, including increased fluid intake in six studies,[41,47-50,58] decreased oxalate intake in five studies,[41,47-50] decreased sodium intake in three studies,[41,47,49] decreased calcium intake in three studies,[41,48,49] increased calcium intake in one study,[47] decreased purine intake in two studies,[41,49] and decreased animal protein intake in one study.[47]

Outcome Measures. Five trials reported a composite outcome of stone recurrence defined by either stone passage or removal or by radiographic stone detection by x-rays and/or ultrasounds that were scheduled every 6 to 12 months.[41,47-49,58] In addition, one trial reported symptomatic stone recurrences only,[52] and one trial did not state how it defined incident recurrent stones.[50] No trials reported results for stones detected only by scheduled imaging, or for change in stone size.

Participant Characteristics

Demographics. The mean age of study participants was 45 years (range 35 to 48; n=6 trials), and men constituted 80 percent (range 61 to 88; n=6 trials) of all patients (Appendix C, Table 2; Appendix F, Table 2). In the single trial that reported data on race, 94 percent of participants were white.[47] Six trials were conducted in Europe (78 percent of participants) and one in the United States.[47] One trial recruited participants from general practice.[49] No other trials reported information on study setting.

Medical History. No trials reported baseline weight, BMI, or the prevalence of obesity (Appendix C, Table 2). One trial included only participants with normal renal function and morphology,[58] but no other studies reported inclusion, exclusion, or prevalence of participants with chronic kidney disease. In the single trial that reported baseline renal function, mean serum creatinine was 1.0 mg/dL.[41] In one trial reporting, 27 percent of participants had a history of hypertension.[41] All studies excluded patients with biochemical or other disorders that would predispose to stone disease. No eligible studies reported prevalence of previous bariatric surgery, solitary kidney, renal transplant, coronary artery disease, diabetes, or pregnancy. Several trials excluded participants with disorders that could predispose them to kidney stones, including exclusion of individuals with "endocrine disease,"[58] with "secondary causes" of kidney stones,[47] with primary hyperparathyroidism,[52] and inclusion only of participants with "idiopathic" stones.[41]

Stone History. All studies included only individuals with recurrent calcium stones, with four studies further restricting enrollment to those with calcium oxalate stones[41,47,50,58] (Appendix C, Table 2). Four trials required that stone episodes had occurred recently, ranging from at least one in the last[47,49] two[47,49] to [41] three[41] years, to at least two in the past 3 years.[58] One trial excluded participants with residual stones at baseline (ascertained by renal ultrasound and intravenous pyelography).[41] A second trial included both participants with (47 percent) and without residual

stones (ascertained by x-ray),[47] while the remaining studies reported no information regarding baseline presence of residual stones.

Baseline Biochemistry. All seven eligible thiazide studies reported at least some baseline serum and/or urine biochemistry results (Appendix H, Table 2). Five trials based urine biochemistry measures on 24-hour urine collections, and two did not specify how urine was collected.[50,58]

Forty-seven percent of study participants had hypercalciuria (range 12 to 100, n=7 trials), including one study entirely comprising participants with hypercalciuria.[41] Eleven percent of study participants had hyperoxaluria, including one study entirely comprising participants with hyperoxaluria,[31] three that excluded individuals with hyperoxaluria,[47,48,50]and one in which 2 percent of participants had hyperoxaluria.[58] Twelve percent of study participants had hyperuricosuria (range 0 to 37, n=5 trials), including two trials that excluded participants with hyperuricosuria.[48,50] Three trials reported on prevalence of hypocitraturia, including two that excluded participants with hypocitraturia[48,50] and one in which 15 percent of participants had hypocitraturia.[58]

Five trials reported mean baseline values for at least some urine biochemistry measures. (Appendix H, Table 2)[41,47-49,52] All trials reported urine calcium with a mean of 268 mg/24 hrs (range 185 to 384) in four trials and a calcium/creatinine ratio of 0.47 in one trial.[48] Other frequently reported baseline results included mean oxalate 25 mg/24 hrs (range 21 to 44, n=4 trials), mean uric acid 677 mg/24 hrs (range 532 to 757, n=4 trials), mean sodium 4552 mg/24 hrs (range 3230 to 4719, n=3 trials), and mean citrate 468 mg/24 hrs (range 348 to 564, n=2 trials). Only one trial reported calcium-oxalate product[52] and no trials reported calcium-oxalate supersaturation. Baseline urine volume was reported in four trials, with a mean of 1.61 liters/24 hrs (range 1.44 to 1.75).[41,47,49,52]

Study Quality

All seven eligible trials were rated fair quality (Appendix C, Table 8). Allocation concealment was unclear in all studies. Three trials reported that they were double-blinded,[47,49,52] two were open label studies,[41,50] and two reported no information on blinding.[48,58] Four trials performed intention to treat analysis.[48-50,58] All of the trials adequately reported withdrawals, which ranged from 0 to 46.3 percent.

Efficacy Outcomes

Stone Recurrence. Among the six trials that reported, pooled recurrence risk of composite stone outcome was significantly lower in individuals randomized to thiazide than to placebo or control treatment (24.9 vs. 48.5 percent; RR, 0.53 [CI, 0.41 to 0.68])[41,47-50,58] (Figure 4; Appendix D, Table 2). Results were similar in analyses in which the trial published in a conference proceeding was excluded (25.4 vs. 62.3 percent; RR, 0.48 [CI, 0.24 to 0.94]), and all further results reported include all eligible thiazide trials. The single trial that reported results for symptomatic stone recurrence, for which followup was limited to 1 year, found no difference in risk of recurrence between individuals randomized to thiazide versus placebo (24.0 vs. 23.1 percent; RR, 1.04 [CI, 0.39 to 2.80])[52] (Figure 5). Because the wide confidence intervals cannot exclude either a clinically significant benefit or harm, we judged the strength of this body of evidence as insufficient. No studies reported results for stone recurrence based on radiographic detection only.

The one trial that reported stone recurrence rates presented results not by treatment groups as a whole, but only by subgroups within treatment groups[48] (Appendix E, Table 2a). Stone recurrence rate appeared to drop in both treatment groups, without a greater reduction in those assigned to thiazide therapy. A second study reported a significant increase in time to stone recurrence from baseline among those treated with thiazide but among controls.[49]

Figure 4. Risk of composite stone recurrence, thiazide versus control treatment

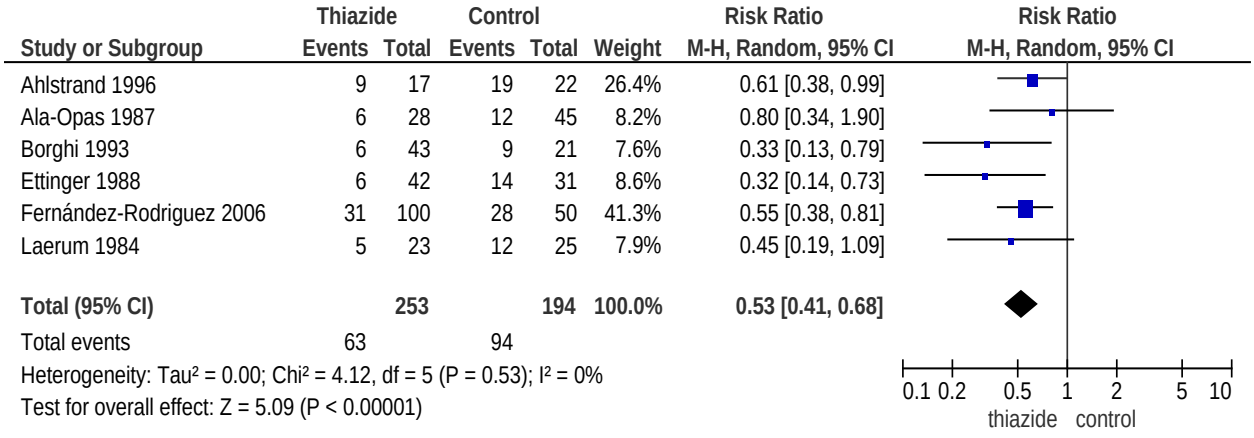
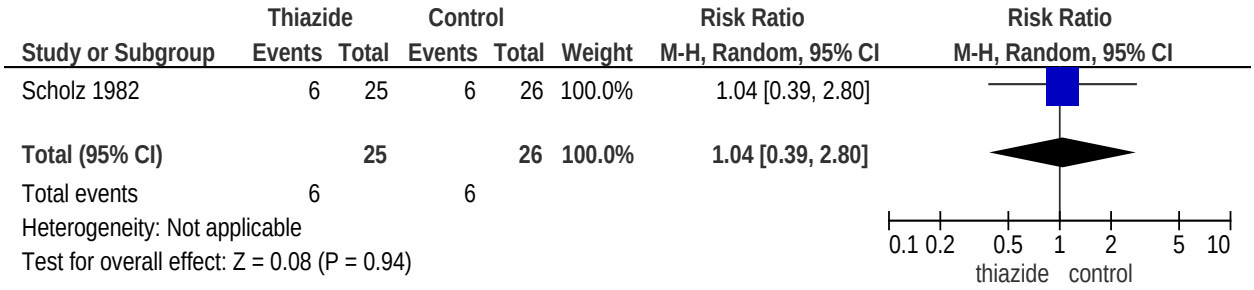


Figure 5. Risk of symptomatic stone recurrence, thiazide versus control treatment



Other Clinical Outcomes. One study reported a significantly lower risk of extracorporeal lithotripsy (8.0 vs. 26.0 percent, p=0.03) in participants randomized to thiazide compared with the placebo.[58] No trials reported results for any other clinical health outcomes (Appendix E, Tables 2b-c).

Subgroup Results. For the composite stone recurrence outcome, risk versus placebo or control was significantly reduced in each thiazide studied, including hydrochlorothiazide (RR, 0.58 [CI, 0.44 to 0.76]),[48-50,58] chlorthalidone (RR, 0.32 [CI, 0.14 to 0.73]),[47] and indapamide (RR, 0.33 [CI, 0.13 to 0.79])[41] (p=0.22 for interaction between thiazide types). In addition, there was no significant difference in risk of stone recurrence versus control based on total daily dose of hydrochlorothiazide (RR, 0.80 [CI, 0.31 to 1.90]) for 100 mg per day and (RR, 0.59 [CI, 0.45 to 0.77]) for 50 mg per day; p=0.50 for interaction)) or between trials that used 25 mg twice daily (RR, 0.63 [CI, 0.43 to 0.92]) and one that appeared to use 50 mg once daily (RR, 0.55 [CI, 0.38 to 0.81]) (p=0.66 for interaction). Similarly, efficacy for chlorthalidone 50 mg/day (RR, 0.29 [CI, 0.09 to 0.89]) was not significantly better than chlorthalidone 25 mg/day (RR, 0.35 [CI, 0.12 to 1.06]) (p=0.81 for interaction).

Thiazide treatment relative to placebo or control may be more effective in longer-term trials versus shorter term trials. In studies that reported a composite stone recurrence outcome, relative risk reduction in trials of at least 3 years (RR, 0.51 [CI, 0.39 to 0.66]) was not significantly greater than in a single 2-year trial (RR, 0.80 [CI, 0.34 to 1.90]) (p=0.32 for interaction between subgroups). By comparison, as noted above, a single 1-year trial found no difference in risk of symptomatic stone recurrence between treatment groups.[52]

Results also appeared similar to overall results in several additional subgroups defined by dietary co-interventions recommended to all treatment groups. These included five thiazide trials that advised all treatment groups to increase fluid and decrease oxalate intake alone or as part of a multicomponent dietary co-intervention (RR, 0.51 [CI, 0.37 to 0.70])(p=0.75 for interaction with single trial that reported no dietary co-intervention), and one trial that advised all treatment groups to increase dietary calcium as part of a multicomponent diet intervention (RR, 0.32 [CI, 0.14 to 0.73]).

None of the thiazide trials reported efficacy outcomes within subgroups defined by demographic or comorbid characteristics. Results in the single trial that reported recruitment of participants from a general practice setting (RR, 0.45 [CI, 0.19 to 1.09])[49] were similar to overall results. With regard to subgroups defined by characteristics of participant stone history, results in the single trial restricted to participants without residual stones at baseline were similar to overall results (RR, 0.33 [CI, 0.13 to 0.79]).[41] Because all participants in these trials had a history of recurrent calcium stones, no subgroup analyses for other stone types or for individuals who have experienced only one kidney stone were feasible.

Adherence to Assigned Treatment. One trial reported that compliance with medication was confirmed by regular pill counts, but compliance with diet instructions was not assessed. Further, approximately 15 percent of study participants discontinued the trial due to loss of interest.[47] A second trial reported that no participants discontinued therapy during the trial, but didn't report how adherence with thiazide treatment was monitored.[48] The remaining five trials reported no information regarding adherence.

Citrate Monotherapy Versus Placebo or Control

Study Characteristics

Study Design. Six trials met all eligibility criteria and randomized participants with nephrolithiasis (n=368, range 39 to 110) to citrate pharmacotherapy versus placebo (n=2 trials)[43,44] or control treatment (n=4 trials)[45,59,63,64] (Appendix C, Table 3). All trials were published in peer-reviewed English-language journals. All studies utilized a parallel group design, and two studies also compared historical pretreatment with post-treatment stone recurrence rates.[43,59] Mean study duration was 25 months, with the mean or median duration ranging from 12 to 37 months (Appendix F, Table 3).

Treatment Groups. Among the trials that compared citrate with placebo or control, two utilized fixed potassium citrate doses of 60 mEq/day[43,45] (Appendix C, Table 3). Three trials used sodium-potassium citrate, at 5-10 gm/day in one study,[63] at 30 gm/day initially followed by adjustments to keep urine pH between 7.0 and 7.2 in a second study,[59] and at 81 mEq/day in a third study.[64] Last, one trial used magnesium-potassium citrate (42 mEq/day potassium,

21 mEq/day magnesium, and 63 mEq citrate).[44] No trials assessed calcium citrate. Four trials reported dietary co-interventions in both treatment and control arms,[43,45,59,64] always including increased fluid intake. In addition, one study further advised all participants to decrease oxalate, animal protein, and sodium intake,[45] and one study advised all participants to decrease sodium intake.[43]

Outcome Measures. Four trials reported a composite outcome of stone recurrence defined by either stone passage or removal or by radiographic stone detection by x-rays and/or ultrasounds that were scheduled every 6 to 12 months.[43-45,64] In addition, one trial reported results for recurrent stones detected only by scheduled imaging.[59] No studies reported symptomatic stone recurrences only. One study reported results for radiographic change in stone size.[63]

Participant Characteristics

Demographics. The mean age of subjects was 47 years (range 42 to 55; n=5 trials), and men constituted 62 percent (range 44 to 78; n=6 trials) of all patients randomized (Appendix C, Table 3; Appendix F, Table 3). No trials reported data on race or ethnicity. Three trials were conducted in Europe (59 percent of participants),[43,45,59] one in the United States (17 percent of participants),[44] and two in Asia (24 percent of participants).[63,64]

Medical History. No trials reported baseline weight, BMI, or the prevalence of obesity (Appendix C, Table 3). Most trials excluded at least some participants with abnormal renal function and/or morphology, though exclusion criteria differed between studies. Two trials reported exclusion of participants with undefined abnormal kidney function or morphology, which were undefined in one trial[45] and were based on an intravenous pyelography performed at least 8 weeks prior to baseline in the second trial.[64] In addition, one trial excluded participants with serum creatinine greater than 1.8 mg/dl,[44] one trial excluded individuals with serum creatinine of 4.0 mg/dl or greater,[63]and one trial excluded those with undefined renal failure.[43] No trials reported any measure of baseline renal function. All studies excluded patients with biochemical abnormalities or other conditions that would predispose to stone disease. One trial excluded participants with diabetes or who were pregnant.[43] One trial excluded participants with coronary heart disease.[63] Otherwise, no study reported prevalence of previous bariatric surgery, solitary kidney, renal transplant, coronary artery disease, diabetes, hypertension, or pregnancy.

Stone History. Three trials included only individuals with recurrent calcium oxalate stones,[43,44,58,59] and one trial included only participants with a single calcium oxalate stone episode,[45] and one trial included participants with either one or multiple past calcium stones[64] (Appendix C, Table 3). By comparison, one trial reported no information regarding whether participants had single or multiple past stone episodes or their past stone composition.[63] Four trials required that stone episodes had occurred recently. One was limited to patients who had undergone extracorporeal shock wave lithotripsy (ESWL) or percutaneous nephrolithotomy (PCNL) 8 weeks earlier, with only the subgroup who were stone free considered eligible for this review.[64] Other trials required that participants had at least one stone episode in the last 2[44] to 3[59] years, to at least two episodes in the last 2 years.[43] One study was limited to participants with residual stones, which had to be a minimum of 10 mm in diameter as ascertained by ultrasound

alone.[63] Two other trials included 38 percent[45] and 72 percent[44] participants with residual stones, ascertained by x ray plus ultrasound or x ray alone, respectively.

Baseline Biochemistry. Five of six eligible citrate studies reported at least some baseline serum and/or urine biochemistry results[43-45,59,64] (Appendix H, Table 3). All of these trials based urine biochemistry measures on 24-hour urine collections.

Twenty percent of participants had hypercalciuria (range 0 to 44, n=3 trials),[43,45,59] including one study in which individuals with hypercalciuria were excluded.[43] Sixty-three percent had hypocitraturia (range 38 to 100, n=3 trials),[43,45,59] including one study in which only individuals with hypocitraturia were included.[43] Eighteen percent of participants had hyperuricosuria in one trial reporting.[45] No trials reported on prevalence of hyperoxaluria.

Three trials reported baseline urine citrate measurements (Appendix H, Table 3), including two that reported means of 365 mg/24hrs,[43] and 567 mg/24 hrs,[44] respectively, and one that reported 1.2 mmol/liter but provided no results for urine volume.[59] Otherwise, only one trial reported results for mean baseline urine calcium (257 mg/24 hrs), mean urine oxalate (36 mg/24 hrs), mean urine uric acid (708 mg/24 hrs), mean urine sodium (3865 mg/24 hrs), mean urine volume (1.86 liters/24 hrs), and mean urine calcium-oxalate product (1.59) (Appendix H, Table 3).[44] No trials reported calcium-oxalate supersaturation.

Study Quality. Among the six eligible trials, one was rated good quality,[44] and the remainder fair (Appendix C, Table 8). Allocation concealment was adequate in one study[44] and unclear in the rest. Two trials reported that they were double-blinded,[44,39]two others reported that the outcomes assessor was blinded,[45,63] and two reported no information on blinding.[59,64] One trial performed intention to treat analysis.[44] Five of the trials adequately reported withdrawals, ranging from 14.6 to 35.9 percent, while one did not report withdrawals separately for the eligible participants who were stone free at baseline.[64]

Efficacy Outcomes

Stone Recurrence. In four trials that reported a composite stone recurrence outcome,[43-45,64] pooled recurrence risk was significantly lower in individuals randomized to citrate than to either placebo or control (11.1 vs. 52.3 percent; RR, 0.25 [CI, 0.14 to 0.44]) (Figure 6; Appendix D, Table 3). In the single trial that reported results for radiographic stone recurrence only, risk did not differ between individuals randomized to citrate versus control (RR, 0.95 [CI, 0.62 to 1.44])[59] (Figure 7). No studies reported results for stone recurrence based on symptomatic detection only.

Two studies reported stone recurrence rates (Appendix E, Table 3a), with one noting a significant improvement with citrate therapy (0.1 stones/yr vs. 1.1 stones/yr, $p<0.001$),[43] and the other noting no difference between citrate and control (0.7 stones/yr vs. 0.9 stones/yr, $p=0.65$).[59] A single study that reported change in stone size found no significant difference between participants randomized to citrate versus *Orthosiphon grandiflorus* extract in the percentage reduction per year in stone diameter at 18 months (38.5 vs. 40.9 percent).[63]

Figure 6. Risk of composite stone recurrence, citrate versus control treatment

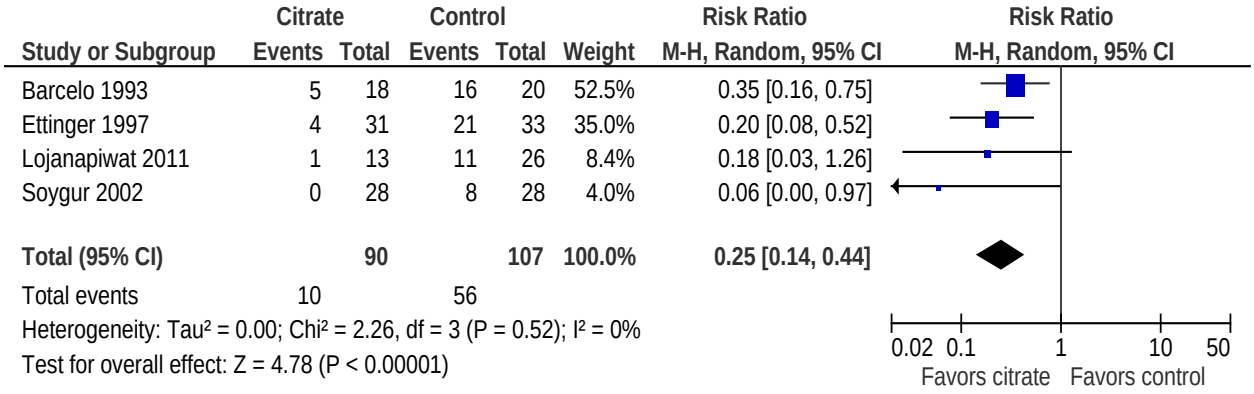
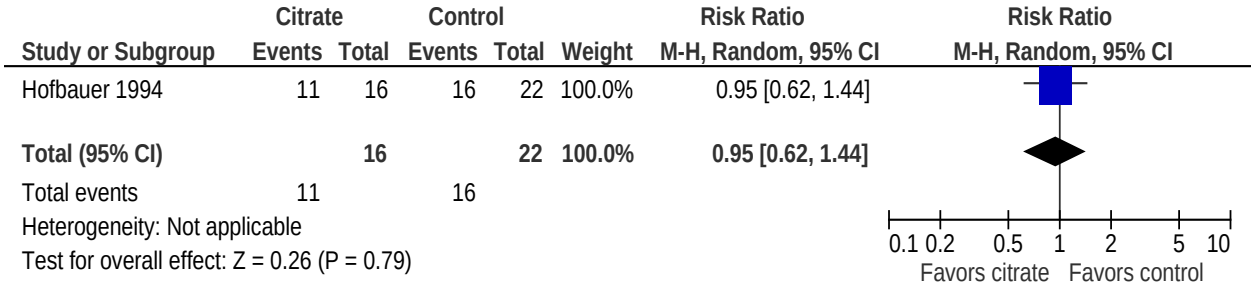


Figure 7. Risk of radiographic stone recurrence, citrate versus control treatment



Other Clinical Outcomes. One study reported that in participants with stone recurrence, spontaneous stone passage was significantly more likely to be painless in those assigned to citrate versus placebo (56 vs. 4 percent, p=0.001).[59] No trials reported results for any other clinical health outcomes (Appendix E, Tables 3b-c).

Subgroup Results. For the composite stone recurrence outcome, results appeared similar by type of citrate, including for potassium citrate (RR, 0.22 [CI, 0.04 to 1.21], n=2 trials),[43,45] potassium-magnesium citrate (RR, 0.20 [CI, 0.08 to 0.52], n=1 trial),[44] and potassium-sodium citrate (RR, 0.18 [CI, 0.03 to 1.26], n=1 trial)[64](p=0.99 for interaction). Both trials that used potassium citrate used similar doses (60 mEq/day and flexible dosing of 30 to 60 mEq/day) making it impossible to determine whether efficacy differed by dose.

Efficacy of citrate treatment relative to control appeared similar in short- and longer-term trials. Recurrence risk was significantly reduced both in the two studies that lasted at least 2 years (RR, 0.28 [CI, 0.15 to 0.51])[43,44] and in two studies that lasted 1 year (RR, 0.13 [CI, 0.03 to 0.62])[64,45](p=0.36 for interaction).

Again for the composite stone recurrence outcome, results appeared similar to overall results in several additional subgroups defined by dietary co-interventions recommended to all treatment groups. These included three citrate trials in which all treatment groups were advised to increase fluid (RR, 0.28 [CI, 0.13 to 0.59]),[43,45,64] in two cases as part of a multicomponent dietary co-intervention (p=0.94 for interaction with trials not reporting instructions to increase fluid intake). One of these multicomponent dietary trials also advised participants to reduce sodium intake (RR, 0.35 [CI, 0.16 to 0.75]),[43] and the other advised them to reduce sodium, oxalate, and animal protein intake (RR, 0.06 [CI, 0.00 to 0.97]).[45]

None of the citrate trials reported efficacy outcomes within subgroups defined by demographic or comorbid characteristics. With regard to subgroups defined by characteristics of participant stone history, a single trial found a significant reduction in recurrent stone risk in participants with only a single past stone episode and who had no residual stones (RR, 0.06 [CI, 0.00 to 0.97]).[45] Because all participants in these trials had a history of calcium stones, subgroup analyses by stone composition was not possible.

Adherence to Assigned Treatment. One trial reported no information regarding adherence.[63] Among trials that reported adherence, one reported median compliance by pill count of 89 percent in the citrate group and 87 percent in the placebo group, with 81 percent of the citrate group and 73 percent of the placebo group being more than 70 percent compliant.[44] A second trial categorized participants who took an average of fewer than six of 12 scheduled study tablets per day as noncompliant, and reported 29 percent noncompliance for participants assigned to citrate and 28 percent for those assigned to placebo.[43] A third study reported that four participants were excluded from analyses due to "reluctance to receive medication" and that compliance with citrate as determined by urinary citrate and potassium levels was "good in all patients."[45] A fourth study reported only that one participant was excluded from analyses due to "unsatisfactory compliance with medication."[64] Last, a study that assessed treatment compliance using participant urinary pH self-monitoring reported that 12 percent of control group participants "refused to comply with regular follow-ups" and 25 percent of citrate group participants "were not followed up due to noncompliance."[59] It was not clear whether "refused regular followups" referred to pH monitoring, study visits, or other measures.

Allopurinol Monotherapy Versus Placebo or Control

Study Characteristics

Study Design

Four trials met all eligibility criteria and randomized participants with nephrolithiasis (n=240, range 15 to 132) to allopurinol monotherapy versus placebo[37,40] or control[38,39] (Appendix C, Table 4). All trials but one were published in peer-reviewed English-language journals except for one published in a conference proceedings.[40] All studies utilized a parallel group design and also compared historical pretreatment with post-treatment stone recurrence rates. Study duration was reported as 24 and 36 months in two studies,[37,40] and up to 60 months in two other studies.[38,39]

Treatment Groups

All trials utilized an allopurinol dosage of 300 mg/day throughout the treatment period except for one in which participants assigned allopurinol were prescribed 300 mg/day for 1 week, then 100 mg/day for the remainder of the study[38] (Appendix C, Table 4). Three of the four trials reported dietary co-interventions in both treatment and control arms, always including increased fluid intake.[37,38,40] In addition, one study further advised all participants to decrease calcium and purine intake.[40] A second study advised all participants to take sodium bicarbonate as needed to keep urine pH above 6.5, a co-intervention investigators stated was to prevent the theoretical formation of xanthine stones.[38]

Outcome Measures

Two trials reported a composite outcome of stone recurrence defined either by stone passage or removal or by radiographic stone detection.[37,38] One of these trials scheduled x rays every 12 months and excluded participants who had symptomatic stone recurrences less than 6 months after baseline from analyses.[37] The second trial reported no type or frequency of the radiographic imaging used for identification of incident stones.[38] In addition, three trials reported symptomatic stone recurrences only,[37,39,40] and one reported results for recurrent stones detected by scheduled radiographic imaging.[37] One study reported results for radiographic growth in stone size.[37]

Participant Characteristics

Demographics. In single studies reporting, the mean age of subjects was 48 years[37] and men constituted 100 percent of all patients[39] (Appendix C, Table 4). No study reported race or ethnicity.

Medical History. In a single trial reporting,[37] baseline BMI was 27.8 kg/m^2(Appendix C, Table 4). One trial excluded participants with renal failure,[37] but no other studies reported inclusion, exclusion, or prevalence of participants with chronic kidney disease, or reported a baseline measure of renal function. Two studies limited inclusion to individuals without biochemical abnormalities or other secondary causes that would predispose to stone disease.[37,39] An additional trial excluded participants on uricosuric medications.[38] No study reported prevalence of previous bariatric surgery, solitary kidney, renal transplant, coronary artery disease, diabetes, hypertension, or pregnancy.

Stone History. All trials were limited to participants with recurrent stones comprised entirely or predominately of calcium oxalate (Appendix C, Table 4). Three trials required that stone episodes had occurred recently, including at least one in the last 2 years,[37] at least four in the past 3 years,[38] and an average of at least two stones per year for the last 3 years.[40] One trial included both participants with (47 percent) and without residual stones (ascertained by x-ray),[37] while the remaining studies reported no information regarding baseline presence of residual stones.

Baseline Biochemistry. Three of four eligible allopurinol studies reported at least some baseline serum and/or urine biochemistry results;[37,38,40] the fourth trial reported that testing was performed but reported no results[39] (Appendix H, Table 4). Two trials based urine biochemistry measures on 24-hour urine collections,[37,40] and the others did not specify.

One trial excluded participants with hypercalciuria,[37] and no other trials reported prevalence of hypercalciuria. One trial included only participants with hyperuricosuria,[37] another included only participants with hyperuricemia,[38] and no other studies reported the prevalence of either condition. No studies reported prevalence of hyperoxaluria, hypocitraturia, or any other baseline biochemical abnormality.

Two trials reported mean baseline values for at least some urine biochemistry measures. (Appendix H, Table 4).[37,40] Mean urine calcium was 221 mg/24 hrs (range 201 to 224), mean urine uric acid was 874 mg/24 hrs (range 470 to 975), mean serum uric acid was 5.8 mg/dl (range 4.4 to 6.1), and mean urine volume was 1.66 liters/24 hrs (range 1.37 to 1.74). No trials reported calcium-oxalate product, calcium-oxalate supersaturation, or uric acid supersaturation.

Study Quality

All four eligible trials were rated fair quality (Appendix C, Table 8). Allocation concealment was adequate in one study[37] and unclear in the rest. Three trials reported that they were double-blinded,[37,38,40] and one reported no information on blinding.[39] None of the trials performed intention to treat analysis. Two of the trials adequately reported withdrawals.[37,38] Two additional studies reported preliminary results in a portion of randomized participants and were unclear regarding whether any participants not included in the analyses had withdrawn.[39,40] Withdrawals in the studies ranged from 16.7 to 47.0 percent.

Efficacy Outcomes

Stone Recurrence. In the two trials that reported a composite stone recurrence outcome, we found moderate strength of evidence that recurrence risk was significantly lower in individuals randomized to allopurinol than in those assigned to placebo (33.3 vs. 55.4 percent; RR, 0.59 [CI, 0.42 to 0.84])[37,38] (Figure 8; Appendix D, Table 4). In one study reporting, we found low strength of evidence that allopurinol does not reduce risk of recurrent symptomatic stones versus control (10.3 vs. 29.0 percent; RR, 0.36 [CI, 0.11 to 1.19]) (Figure 9), and insufficient strength of evidence that allopurinol does not reduce risk of recurrent radiographic stones (RR, 1.07 [CI, 0.16 to 7.10]) (Figure 10).[37] Results for radiographic stones were judged insufficient because of the small number of recurrent stone events and because the wide confidence intervals could not exclude either a clinically significant benefit or harm. These results were reported only in peer-reviewed allopurinol trials.

Results were inconsistent in the three trials that reported stone recurrence rates (Appendix E, Table 4a), perhaps related to differences in the type of stone recurrence they reported. The absolute rate of stone recurrence appeared lower in participants assigned to allopurinol versus control in one study that reported a rate of composite stone recurrence (0.12 vs. 0.26 stones per patient year),[37] but not in two studies that reported a rate of symptomatic stone recurrence (0.54 vs. 0.58,[39] and, in the only allopurinol trial published as a conference proceeding, 0.96 vs. 0.66 stones per patient year;[40] none of these studies reported a test for statistical significance. One trial also reported a significant increase in time to first composite stone recurrence in participants assigned allopurinol versus placebo (33.3 vs. 27.4 months, $p<0.05$).[37]

Figure 8. Risk of symptomatic stone recurrence, allopurinol versus control treatment

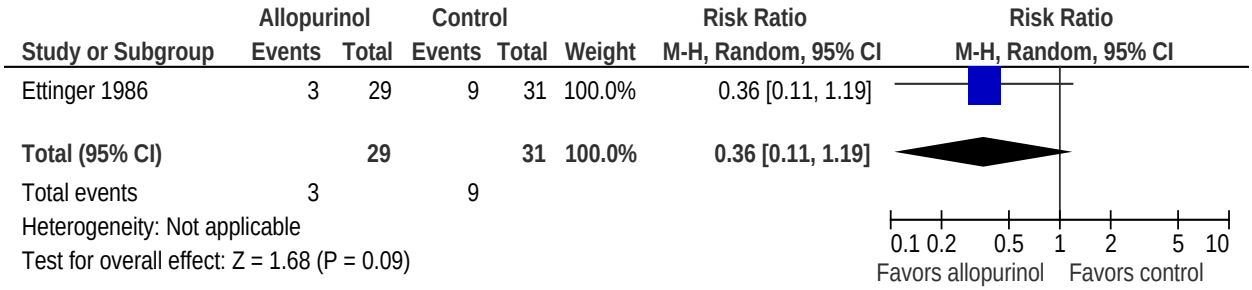


Figure 9. Risk of composite stone recurrence, allopurinol versus control treatment

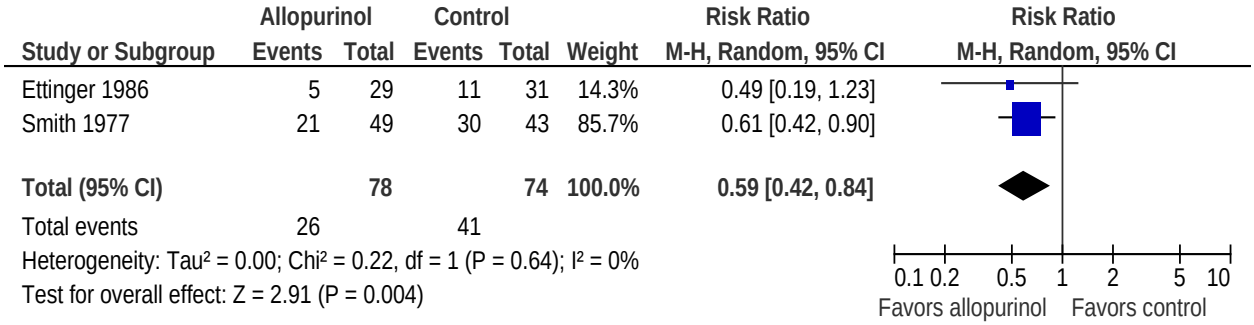
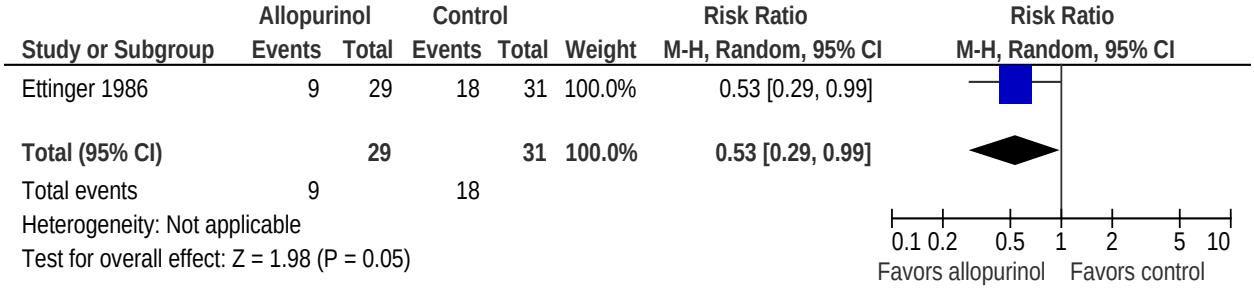


Figure 10. Risk of radiographic stone recurrence, allopurinol versus control treatment



Other Clinical Outcomes. No trials reported results for any other clinical health outcomes (Appendix E, Tables 4b-c).

Subgroup Results. Regarding dosage, a single study that dosed allopurinol at 100 mg/day rather than 300 mg/day throughout all but the first week of the treatment period[38] found better results for allopurinol versus control (RR, 0.61 [CI, 0.42 to 0.90]) and appeared similar to the overall results.

Regarding study duration, reduction in composite stone recurrence risk appeared similar between a single trial of up to 5 years duration (RR, 0.61 [CI, 0.42 to 0.90])[38] and in a single study of 2 years in duration (RR, 0.49 [CI, 0.19 to 1.23]).[37]

Regarding dietary co-interventions, all composite stone recurrence results were derived from trials that assigned participants in both treatment and control groups to increased fluid intake. A single allopurinol monotherapy trial in which additional dietary co-interventions were instituted (reduced calcium and purine intake), found no difference in the rate of symptomatic stone recurrence between treatment groups.[40]

None of the allopurinol trials reported efficacy outcomes within subgroups defined by demographic or comorbid characteristics. With regard to subgroups defined by characteristics of participant stone history, all participants in these trials had a history of recurrent calcium stones, thus we could not perform subgroup analyses by stone composition and number of past stone episodes.

Adherence to Assigned Treatment. One trial reported 88 percent compliance for allopurinol and 89 percent compliance for placebo as ascertained by pill counts conducted every 3 months.[37] A second trial reported that pill counts were performed prior to issuance of each new medication

refill, but provided no count results.[38] The remaining three studies reported no information regarding adherence.

Acetohydroxamic Acid Versus Control

Study Characteristics

Study Design. Three trials met all eligibility criteria and randomized participants with recurrent struvite kidney stones (n=343, range 39 to 210) to acetohydroxamic acid (AHA) versus placebo[60-62] (Appendix C, Table 5). All trials were published in peer-reviewed English-language journals. All studies utilized a parallel group design and ranged in duration from up to 24 months to up to 32 months. Mean study duration was reported in two trials as 18 months.[61,62]

Treatment Groups. Two trials dosed AHA at 15 mg/kg/day,[61,62] while the third trial utilized 500 to 1000 mg/day depending on participant weight and renal function[60] (Appendix C, Table 5). One trial treated all participants in both groups with suppressive antibiotics throughout the study,[62] while the other trials left use of antibiotics to the discretion of the physician.

Outcome Measures. All studies reported a radiographic definition of stone recurrence based on abdominal x-rays every 3 to 12 months, though one trial reported results only for the AHA group and not for the control group. All studies also reported the outcome of stone growth, defined variably as an increase from baseline in stone area of at least 10 percent,[60] at least 25 percent,[61] or at least 100 percent.[62] Though none of the trials reported results for symptomatic stone recurrence, one reported an outcome for participants who underwent surgery for obstruction or infection. No trials reported a composite recurrent stone outcome, defined as occurrence of either radiographic or symptomatic stones.

Participant Characteristics

Demographics. The mean age of participants was 49 years (range 48 to 49; n=2 trials), and men constituted 77 percent (range 18 to 100; n=3 trials) of all patients (Appendix C, Table 5; Appendix F, Table 5). No trial reported information on race or ethnicity. All trials were conducted in the United States.

Medical History. In a single trial reporting, baseline weight was 76.3 kg[60] (Appendix C, Table 5). In two trials reporting, 85 percent of participants had a history of spinal cord injury, including all individuals in one trial[60] and half the participants in a second trial.[61] In two trials reporting, 50 percent of participants had undergone prior supravesical diversion (range 18 to 64).[61,62] In one trial, 8 percent of participants had a history of neurogenic bladder. All studies excluded patients with significant renal insufficiency, with the cutpoints ranging from serum creatinine $\geq$2.5 mg/dL[61] to $\geq$3 mg/dL.[60,62] However, only one trial reported a baseline measure of renal function, with a mean serum creatinine of 1.0 mg/dL.[60] Two trials included only participants considered not to be candidates for surgical stone removal.[60,61] One trial excluded participants who were pregnant. Otherwise, no study reported prevalence of previous bariatric surgery, solitary kidney, renal transplant, coronary artery disease, diabetes, or hypertension.

Stone History. All trials were limited to participants with struvite stones in the setting of chronic urea-splitting urinary tract infections (Appendix C, Table 5). Two trials reported inclusion of only participants with multiple past stone episodes,[61,62] while the third trial reported no information on the number of past stones.[60] In the two trials reporting, residual stone fragments were present in 88 percent (by excretory urogram)[60] and 89 percent (by x ray)[61] of participants, respectively.

Baseline Biochemistry. Although two of the three trials reported that they measured multiple urine chemistries from baseline 24-hour urine collections, neither reported any of these results.[60,62] The third trial reported that baseline urine chemistries were not measured.[61]

Study Quality

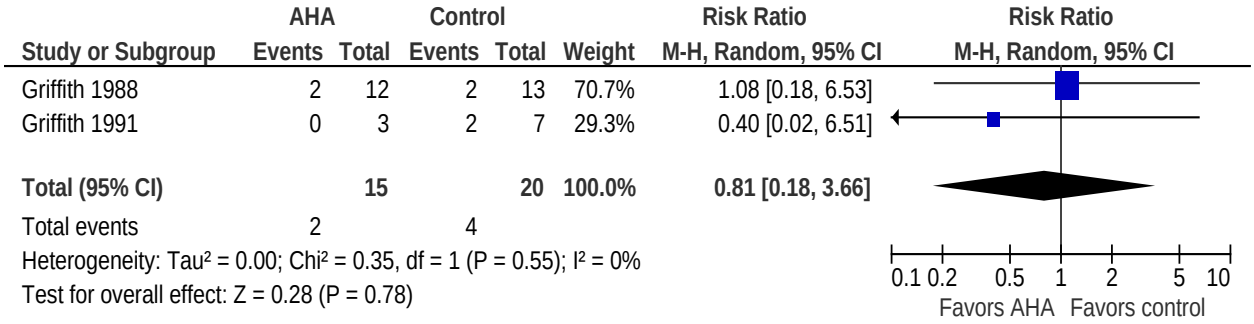
We rated all three trials as fair quality (Appendix C, Table 8). Allocation concealment was adequate in two studies[60,62] and unclear in one.[61] All three trials reported that they were double-blinded. Only one of three trials performed intention to treat analysis.[61] All of the trials adequately reported withdrawals, which ranged from 30.0 to 69.1 percent.

Efficacy Outcomes

Stone Recurrence. Two trials reported radiographic stone recurrence,[60,61] and among participants with no residual stones at baseline, recurrence occurred in 13.3 percent of those randomized to AHA compared with 20 percent of those assigned to placebo (RR, 0.81 [CI, 0.18 to 3.66]) (Figure 11; Appendix D, Table 5). We judged strength of evidence for this comparison and outcome as insufficient because of the small number of recurrent stone events and because the wide confidence intervals could not exclude either a clinically significant benefit or harm. No trials reported results for symptomatic stone recurrence, but one reported that two participants assigned to the placebo group and none assigned to AHA underwent surgery for obstruction or infection.[62] No trials reported results for composite stone recurrence or for stone recurrence rate.

All trials reported results for stone growth (Appendix E, Table 5a). One study reported a significantly lower risk of a >100 percent increase in stone area in participants randomized to AHA versus those assigned placebo (0 percent vs. 39 percent, p=0.008).[62] A second study reported a significantly lower risk of a >25 percent increase in stone area (19.0 vs. 50.0 percent, p<0.05).[61] By comparison, a third study reported a significantly lower risk of >10 percent increase in stone area at 1 year (33.3 vs. 60.5 percent, p=0.017) but not at 2 years (41.7 vs. 60.0 percent, p=0.26), with some participants in both treatment groups reaching this endpoint at 1 year and thus excluded from the 2-year analyses.[60] Last, one trial reported no significant difference in stone fragment clearance between AHA and placebo after either 1 or 2 years.[60]

Figure 11. Risk of radiographic stone recurrence, acetohydroxamic acid versus control treatment



Other Clinical Outcomes. None of the trials reported results for any other clinical health outcomes (Appendix E, Tables 5b-c).

Subgroup Results. Due to the small number of study participants for whom data were reported for recurrent stones in both AHA and control treatment groups, no subgroup analyses were performed.

Adherence to Assigned Treatment. One trial defined compliance by whether fewer than 20 percent of the pills prescribed at the previous study visit remained at the next study visit; compliance during the study ranged from 79 to 91 percent in the AHA group and from 84 to 94 percent in the placebo group.[60] One trial reported only that few if any participants in the treatment group received their medications 100 percent of the time, but that close monitoring resulted in a high (>80 percent) degree of compliance.[61] The third trial reported that compliance was verified by pill counts and urine screening for AHA, and that participants determined by either measure to be taking less than 50 percent of their medication were withdrawn from the study. Although 16 percent of participants assigned to AHA and 5 percent of those assigned to placebo were not included in analyses after 7 to 10 months of treatment because of noncompliance, the study did not report compliance over its full duration.[62]

Magnesium Monotherapy Versus Placebo or Active Treatment

Study Characteristics

Study Design. One trial met all eligibility criteria and randomized participants with recurrent kidney stones to magnesium (n=51) versus placebo (n=31) versus thiazide diuretic (n=42)[37,47] (Appendix C, Table 6). This study was published in a peer-reviewed English-language journal. It utilized a parallel group design and also compared historical pretreatment with post-treatment stone recurrence rates. Study duration was 36 months.

Treatment Groups. This trial included two different magnesium hydroxide fixed-dose groups (650 mg/day and 1300 mg/day), two different thiazide fixed-dose groups (chlorthalidone 25 mg/day and 50 mg/day), and a placebo group (Appendix C, Table 6). Participants in all treatment and placebo groups were instructed to follow a dietary co-intervention, consisting of drinking sufficient fluid to achieve a urine output of 2L/day, and restricting dietary salt, animal

protein, and high oxalate foods. They further were instructed to increase intake of cereal fiber, avoid vitamin C, and consume two or fewer dairy servings/day.

Outcome Measures. This trial reported a composite outcome of stone recurrence defined by either passage of a previously unrecognized stone at least 3 months after baseline or radiographically detected stone growth or detection of a new stone as ascertained by annual x-ray.

Participant Characteristics

Demographics. Participant mean age was 47 years, and men constituted 88 percent of all patients (Appendix C, Table 6). Ninety-four percent of study participants were categorized as white, and the study was conducted in the United States.

Medical History. This trial reported no information on baseline BMI or weight (Appendix C, Table 6). In addition, it did not report inclusion or exclusion based on renal function, prevalence of participants with chronic kidney disease, or any measure of baseline renal function. Participants with secondary causes of kidney stones were excluded. Otherwise, the study reported no information on baseline prevalence of bariatric surgery, solitary kidney, renal transplant, coronary artery disease, diabetes, hypertension, or pregnancy.

Stone History. This trial was limited to participants with recurrent stones predominately comprising calcium oxalate (Appendix C, Table 6). Participants must have had at least one stone in the past 2 years and at least two stones in the past 5 years. The study included both participants with (47 percent) and without residual stones (ascertained by x-ray).

Baseline Biochemistry. Urine biochemistry measures were based on 24-hour urine collections. Among participants randomized to magnesium or placebo, 35 percent had hypercalciuria and 32 percent had hyperuricosuria. Mean baseline urine calcium was 252 mg/24 hrs, mean oxalate was 26 mg/24 hrs, mean uric acid was 758 mg/24 hrs, mean magnesium was 94 mg/24 hrs, and mean urine volume was 1.66 liters/24 hrs (Appendix H, Table 5).

Among participants randomized to magnesium or thiazide, 40 percent had hypercalciuria and 41 percent had hyperuricosuria. Mean baseline urine calcium was 274 mg/24 hrs, mean oxalate was 25 mg/24 hrs, mean uric acid was 797 mg/24 hrs, mean magnesium was 94 mg/24 hrs, and mean urine volume was 1.74 liters/24 hrs.

The study reported neither prevalence of baseline hyperoxaluria or hypocitraturia nor mean baseline citrate or sodium levels.

Study Quality

We rated the single magnesium trial as fair quality (Appendix C, Table 8). Because the study assigned treatment based on medical record number but used identical appearing tablets for magnesium and placebo, the adequacy of allocation concealment was unclear. The trial was double-blinded, but performed no intention to treat analysis. Withdrawals were adequately reported as 19.5 percent.

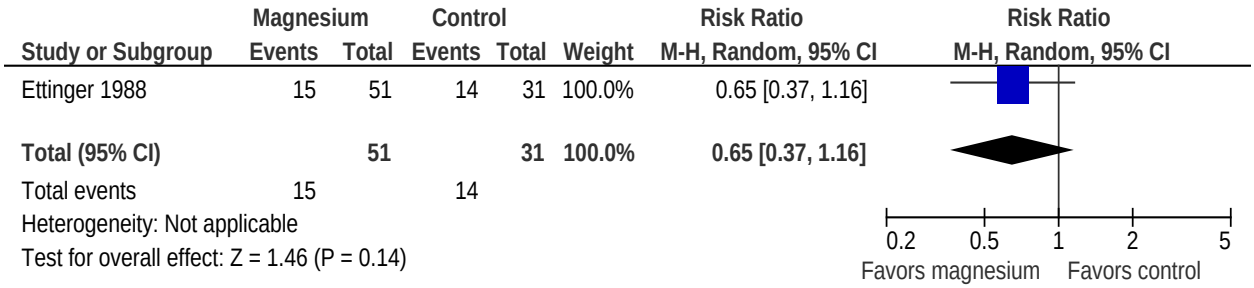
Efficacy Outcomes

Stone Recurrence. Risk of a composite stone recurrence was nonsignificantly lower in individuals randomized to magnesium than in those assigned to placebo (29.4 vs. 45.2 percent) (RR, 0.65 [CI, 0.37 to 1.16]) (Figure 12; Appendix D, Table 6).

Risk of composite stone recurrence was nonsignificantly higher in individuals randomized to magnesium than in those assigned to thiazide (29.4 vs. 14.3 percent) (RR, 2.06 [CI, 0.88 to 4.84]).

This study reported no results for symptomatic stones, radiographically detected stones, stone recurrence rate, or stone growth as isolated outcomes (Appendix D, Table 6; Appendix E, Table 6a).

Figure 12. Risk of composite stone recurrence, magnesium versus placebo treatment



Other Clinical Outcomes. This trial did not report results for any other clinical health outcomes (Appendix E, Tables 6b-c).

Subgroup Results. The effect of magnesium on risk of recurrent stones relative to placebo and relative to thiazide appeared similar at 650 mg/day and 1300 mg/day. Compared wth 45.2 percent of individuals assigned to placebo and 14.3 percent of individuals assigned to thiazide who experienced a recurrent stone, the proportion with a recurrent stone was 26.7 percent in the magnesium 650 mg/day group (p=0.15 vs. placebo and p=0.20 vs. thiazide) and 33.3 percent in the 1300 mg/day group (p=0.41 vs. placebo and p=0.08 vs. thiazide), respectively.

This study reported no efficacy outcomes within subgroups defined by demographic or comorbid characteristics, or by characteristics of stone history.

Adherence to Assigned Treatment. The study reported that medication compliance was assessed by regular pill counts, but reported no results of these assessments.

Thiazide Diuretic Plus Citrate Versus Thiazide Monotherapy

Study Characteristics

Study Design. One trial met all eligibility criteria and randomized participants with recurrent kidney stones (n=100) to thiazide plus citrate versus thiazide monotherapy[58] (Appendix C, Tables 2-3). This trial was published in a peer-reviewed English-language journal. It utilized a parallel group design. Mean study duration was 36 months.

Treatment Groups. Participants were randomized to hydrochlorothiazide 50 mg/day plus potassium citrate 20 mEq/day versus hydrochlorothiazide 50 mg/day monotherapy (Appendix C, Tables 2-3). The study reported no information regarding dietary co-interventions, including whether all participants were advised to increase fluid intake.

Outcome Measures. This trial reported a composite outcome of stone recurrence defined either by stone passage or removal or by radiographic stone detection by x-rays scheduled every 6 months. The study reported no results for recurrent symptomatic stones, for recurrent stones detected only by scheduled radiographic imaging, or for change in stone size.

Participant Characteristics

Demographics. The study included participants between 18 and 65 years of age, but reported no mean or median age (Appendix C, Tables 2-3). Nor did the study report information on gender distribution, race, or ethnicity. It was conducted in Europe.

Medical History. The study reported no information on baseline weight, BMI, or the prevalence of obesity (Appendix C, Tables 2-3). It excluded participants with undefined abnormal kidney function or morphology, but reported no measure of baseline renal function. The study also excluded patients with biochemical abnormalities or other conditions that would predispose to stone disease, but did not report prevalence of previous bariatric surgery, solitary kidney, renal transplant, coronary artery disease, diabetes, hypertension, or pregnancy.

Stone History. This trial included only individuals with recurrent calcium oxalate stones, including at least two stones in the past 3 years (Appendix C, Tables 2-3). The study did not report whether participants had residual stones.

Baseline Biochemistry. The study did not report how the urine utilized for biochemical measurements was collected. Among participants randomized to thiazide plus citrate versus thiazide alone, 35 percent had hypercalciuria, 15 percent had hypocitraturia, 4 percent had hyperuricosuria, and 1 percent had hyperoxaluria (Appendix H, Tables 2-3). No mean levels were reported for any baseline urine biochemical measure or for urine volume.

Study Quality

We rated the study as fair quality (Appendix C, Table 8). Allocation concealment was unclear and the study reported no information regarding blinding. However, the study performed intention to treat analysis and reported that there were no withdrawals.

Efficacy Outcomes

Stone Recurrence. The risk of a composite stone recurrence did not differ significantly between individuals randomized to thiazide plus citrate versus thiazide alone (30.0 vs. 32.0 percent; RR, 0.94 [CI, 0.52 to 1.68]) (Appendix D, Tables 2-3). The study reported no results for recurrent symptomatic stones, for recurrent stones detected only by scheduled radiographic imaging, or for change in stone size (Appendix E, Tables 2a and 3a).

Other Clinical Outcomes. This study reported no difference in risk of extracorporeal lithotripsy between treatment groups, at 8.0 percent in both. This study reported results for no other clinical health outcomes (Appendix E, Tables 2b-c and 3b-c).

Subgroup Results. This trial reported no efficacy outcomes within subgroups defined by treatment duration, participant demographic or comorbid characteristics, or by characteristics of stone history. Because the study did not describe any dietary co-interventions, subgroup analyses based on these factors were not feasible.

Adherence to Assigned Treatment. This study reported no adherence information.

Thiazide Diuretic Plus Allopurinol Versus Thiazide Monotherapy

Study Characteristics

Study Design. One trial met all eligibility criteria and randomized participants with nephrolithiasis (n=50) to a thiazide diuretic plus allopurinol versus thiazide diuretic monotherapy[41] (Appendix C, Tables 2 and 4). This study was published in a peer-reviewed English-language journal. While it reported that it was randomized, it did not report an adequate method of random allocation of treatment assignment. The study utilized a parallel group design, but also compared historical pretreatment with post-treatment stone recurrence rates. Mean study duration was 36 months.

Treatment Groups. This study randomized 50 participants to indapamide 2.5 mg/day plus allopurinol 300 mg/day versus indapamide 2.5 mg/day alone (Appendix C, Tables 2 and 4). In addition, participants in both treatment groups were advised to increase fluid intake, and to decrease dietary intake of oxalate, sodium, calcium, and purine.

Outcome Measures. This trial reported a composite outcome of stone recurrence defined either by stone passage or removal or by radiographic stone detection by x-rays scheduled every 6 to 12 months. The study reported no results for recurrent symptomatic stones, for recurrent stones detected only by scheduled radiographic imaging, or for change in stone size.

Participant Characteristics

Demographics. The mean age of study participants was 46 years and men constituted 78 percent of all patients randomized (Appendix C, Tables 2 and 4). The study reported no data for ethnicity or race. It was conducted in Europe.

Medical History. Mean baseline weight was 72.8 kg (Appendix C, Tables 2 and 4). Participants were neither included nor excluded based on presence of chronic kidney disease and its prevalence was not reported. Mean serum creatinine was 1.0 mg/dL. The study excluded participants with disorders that could predispose them to kidney stones, limiting enrollment to participants with “idiopathic” stones. Otherwise, it did not report prevalence of previous bariatric surgery, solitary kidney, renal transplant, coronary artery disease, diabetes, or pregnancy.

Stone History. The study included only individuals with recurrent calcium oxalate stones, including at least one in the past 3 years (Appendix C, Tables 2 and 4). It excluded participants with residual stones at baseline (ascertained by renal ultrasound and intravenous pyelography).

Baseline Biochemistry. The study based urine biochemistry measures on 24-hour urine collections. The study enrolled only participants with hypercalciuria and reported no information on the baseline prevalence of hyperoxaluria, hyperuricosuria, or hypocitraturia. Mean baseline urine calcium was 412 mg/24 hrs, mean oxalate was 31 mg/24 hrs, mean uric acid was 731 mg/24 hrs, mean sodium was 4828 mg/24 hrs, mean citrate was 521 mg/24 hrs (range 348 to 564, n=2 trials), and mean baseline urine volume was 1.88 liters/24 hrs (Appendix H, Table 2). The study indicated that it obtained results for calcium-oxalate supersaturation, calcium-phosphate supersaturation, and uric acid supersaturations, but it did not report them.

Study Quality

This study was rated fair quality (Appendix C, Table 8). Allocation concealment was unclear and the study was conducted as open label. Analysis was not conducted as intention to treat. Withdrawals were adequately reported as 14 percent.

Efficacy Outcomes

Stone Recurrence. Risk of composite stone recurrence did not differ between the thiazide plus allopurinol group and the thiazide only group (12.5 vs. 15.8 percent; RR, 0.79 [CI, 0.18 to 3.49]) (Appendix D, Tables 2 and 4). We judged strength of evidence for this comparison and outcome as insufficient because of the small number of recurrent stone events and because the wide confidence intervals could not exclude either a clinically significant benefit or harm. This study reported no results for symptomatic stone recurrence, recurrence based only radiographic detection, recurrence rates, or stone growth (Appendix D, Tables 2 and 4; Appendix E, Tables 2a and 4a).

Other Clinical Outcomes. This study reported no results for any other clinical health outcomes (Appendix E, Tables 2b-c and 4b-c).

Subgroup Results. This trial reported no efficacy outcomes within subgroups defined by participant demographic or comorbid characteristics, or by characteristics of stone history. Because all participants in this trial had a history of recurrent calcium stones and received the same dietary co-intervention, no subgroup analyses by these factors were feasible.

Adherence to Assigned Treatment. This study reported no adherence information.

Table 2. Strength of evidence for prevention of stone recurrence: pharmacological intervention trials

Intervention	Stone Recurrence Type	Number of Trials	Number of Randomized Subjects	Summary Statistics, RR [95% CI]	Risk of Bias*	Directness**	Precision†	Consistency‡	Evidence Rating††
Thiazide vs. placebo or control	Symptomatic	1	51	1.04 [0.39 to 2.80]	medium	direct	imprecise	NA	Insufficient
	Composite	6	387	0.53 [0.41 to 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 to 0.44]	medium	direct	precise	consistent	Moderate
	Radiographic	1	50	0.95 [0.62 to 1.44]	medium	direct	imprecise	NA	Low
Allopurinol vs. placebo or control	Symptomatic	1	72	0.36 [0.11 to 1.19]	medium	direct	imprecise	NA	Low
	Composite	2	204	0.59 [0.42 to 0.84]	medium	direct	precise	consistent	Moderate
	Radiographic	1	72	1.07 [0.16 to 7.10]	medium	direct	imprecise	NA	Insufficient
AHA vs. placebo or control	Symptomatic	0	-	-	-	-	-	-	Insufficient
	Composite	0	-	-	-	-	-	-	Insufficient
	Radiographic	2	304	0.81 [0.18 to 3.66]	medium	direct	imprecise	consistent	Insufficient
Magnesium vs. placebo	Symptomatic	0	-	-	-	-	-	-	Insufficient
	Composite	1	82	0.65 [0.37 to 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 to 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 to 3.49]	medium	direct	imprecise	NA	Insufficient
	Radiographic	0	-	-	-	-	-	-	Insufficient

Abbreviations: CI = confidence intervals; AHA = Acetohydroxamic acid; NA = not applicable; RR = relative risk

*Risk of bias was rated low, medium, or high based on whether the design and conduct of the studies for a given outcome or comparison indicate good internal validity.

**Directness indicated whether results reflect a single, direct link between the intervention of interest and the outcome and was rated as either direct or indirect.

†Precision indicated the degree of certainty surrounding an effect estimate of a given outcome and was rated either precise or imprecise, with a precise estimate being one that allowed a clinically meaningful conclusion.

‡Consistency indicated whether the included studies found a similar direction of effect and was rated consistent, inconsistent, or, in cases when only a single study was evaluated, unknown/not applicable.

††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).

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?

Overview

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, those that reported only biochemical efficacy data, or from prospective cohort studies.

Thiazide Diuretics Versus Placebo or Control

In seven eligible RCTs of at least 1 year in duration, 17 percent (range 0 to 59) of participants randomized to thiazide withdrew versus 8 percent (range 0 to 38) of those assigned to placebo or control[41,47-50,52,58] (Appendix G, Table 2). Eight percent (range 0 to 29) of participants randomized to thiazide withdrew due to adverse events versus 1 percent (range 0 to 4) of those assigned to placebo or control. Four of seven studies reported adverse events as a composite outcome.[47,49,50,52] Adverse events in these different composite measures included orthostatic reactions, gastrointestinal upset, erectile dysfunction, fatigue and muscle symptoms, though no two studies reported the same list. Otherwise, no individual adverse event (e.g., hypokalemia, hypotension) was reported in more than a single individual in any trial.

We identified no additional withdrawal or adverse events data comparing thiazide diuretics with control or placebo from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies of 3 months or longer.

Citrates Versus Placebo or Control

In five eligible RCTs of at least 1 year in duration, 25 percent of randomized participants withdrew, and 7 percent withdrew due to adverse events[43-45,59,63] (Appendix G, Table 3). Among the four of these trials that reported results separately by treatment group, 36 percent (range 21 to 48) of participants randomized to citrate withdrew versus 20 percent (range 8 to 31) of those assigned to placebo or control.[43,44,59,63] Further, 15 percent (range 7 to 21) of participants randomized to citrate withdrew due to adverse events versus 2 percent (range 0 to 3) of those assigned to placebo or control. In two trials reporting, incidence of any adverse event occurred in 24 percent of participants randomized to citrate versus in none of those assigned to placebo or control.[59,63] Four trials reported incidence of gastrointestinal complaints, which occurred in 26 percent (range 16 to 42) of participants randomized to citrate and 17 percent (range 0 to 39) of those assigned to placebo or control.[43-45,59]

We identified no additional withdrawal or adverse events data comparing citrates with control or placebo treatment from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies of 3 months or longer.

Allopurinol Versus Placebo or Control

Among four eligible RCTs of at least one year in duration,[37-40] two reported withdrawals, in which 31 percent (range 19 to 37) of participants randomized to allopurinol withdrew versus 42 percent (range 14 to 57) of those assigned to placebo[37,38] (Appendix G, Table 4). In data limited to these same two trials, 4 percent (range 3 to 6) of participants randomized to allopurinol withdrew due to adverse events versus 8 percent (range 6 to 9) of those assigned to placebo. No trials reported incidence of any adverse event, and only two reported specific adverse events. Reported adverse events included rash in two or fewer participants per treatment group in two trials,[37,38] and, in one trial, acute gout in 5 percent and leukopenia in 2 percent of the allopurinol group, but not reported in the placebo group.[38]

In one additional prospective study that compared allopurinol with control, but in which it was unclear whether participants were randomly assigned, withdrawals were reported in 6 percent of those treated with allopurinol but no withdrawal data were reported for the control group.[76] Similarly, this study reported rash in 6 percent of participants in the allopurinol group but did not report whether rash occurred in the control group. We identified no additional withdrawal or adverse events data comparing allopurinol with control or placebo treatment from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies of 3 months or longer.

Acetohydroxamic Acid Versus Placebo

In three eligible RCTs of at least one year in duration, 59 percent (range 30 to 64, n=3 trials) of participants randomized to AHA withdrew versus 46 percent (range 31 to 73, n=2 trials) of those assigned to placebo[60,61] (Appendix G, Table 5). While all three trials reported withdrawals due to adverse events in participants randomized to AHA (range 10 to 27 percent), only two of them reported withdrawals due to adverse events in those randomized to placebo (5 to 6 percent).[60,61] All three trials reported results for incidence of any adverse event, which occurred in 64 percent (range 45 to 78) of participants randomized to AHA compared with 32 percent (range 5 to 49) of those assigned to placebo. Anemia and headache were each reported in two trials, with anemia occurring in 2 to 25 percent of AHA participants and in 0 to 12 percent of those assigned to placebo,[60,61] and headache occurring in 5 to 9 percent of AHA participants,[60,61] and, in the only study reporting, in 4 percent of those assigned placebo.[61] Additional adverse events reported included alopecia (9 vs. 2 percent in 1 trial),[61] tremulousness (25 percent, reported only for the AHA group in 1 trial),[62] deep vein thrombosis (16 percent, reported only for the AHA group in 1 trial),[62] and phlebitis (2 percent in both treatment groups, reported in 1 trial).[61]

We identified no additional withdrawal or adverse events data comparing acetohydroxamic acid with control or placebo treatment from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies of 3 months or longer.

Magnesium Versus Placebo

In the single eligible RCT of at least 1 year in duration, 18 percent of participants randomized to magnesium withdrew versus 17 percent of those assigned placebo[47] (Appendix G, Table 6). Thirteen percent of participants randomized to magnesium 1300 mg/day withdrew due

to adverse events (all due to diarrhea) versus 3 percent of those assigned to placebo (all due to gastrointestinal upset). The study did not report any withdrawals due to adverse events in the magnesium 650 mg/day group. The study did not report the proportion of participants with any or with specific types of adverse events, overall or by treatment group.

We identified no additional withdrawal or adverse events data comparing magnesium with control or placebo treatment from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies of 3 months or longer.

Thiazide Plus Citrate

In a single eligible RCT, there were no withdrawals in either the thiazide plus citrate or thiazide treatment groups (Appendix G, Tables 2-3). The study did not report results for adverse events.

We identified no additional withdrawal or adverse events data comparing thiazide plus citrate with thiazide or control treatment from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies of 3 months or longer.

Thiazide Plus Allopurinol

In a single eligible RCT, withdrawals were reported in 4 percent of participants randomized to thiazide plus allopurinol, 24 percent of those assigned to thiazide, and 16 percent of those assigned to control (Appendix G, Tables 2 and 4). Withdrawals due to adverse events were reported in no participants randomized to thiazide plus allopurinol, 8 percent of those assigned to thiazide, and none of those assigned to control. 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.

We identified no additional withdrawal or adverse events data comparing thiazide plus citrate with thiazide or control treatment from RCTs of 3 to less than 12 months in duration to prevent stone recurrence, RCTs of 3 months or longer that reported only biochemical efficacy data, or from prospective cohort studies of 3 months or longer.

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?

Overview

Although many RCTs reported results of followup biochemistry measures, most often based on 24-hour urine collections, none reported and compared subsequent stone recurrence outcomes between treatments stratified by followup biochemistry levels or by changes in these measures from pretreatment baseline. Therefore, eligible RCTs provided no direct data regarding whether followup biochemistry measures prospectively predict the effectiveness of ongoing treatment in preventing later stone recurrence.

However, RCT followup biochemistry data and recurrent stone outcomes data reported for treatment groups as a whole suggest that decreased urine calcium-oxalate supersaturation, uric

acid supersaturation, and calcium-phosphate supersaturation might be able to predict reduced risk of subsequent stones with increased fluid intake[46] and with at least one studied multicomponent diet intervention.[51] As none of the eligible pharmacological RCTs reported followup urine supersaturation levels, no RCT data exist for whether changes in these measures may 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 stone recurrence. Though the association of a decline in urine calcium with reduced recurrent stone risk may be greatest in patients randomized to thiazide treatment, even in these trials the significantly reduced urine calcium in two trial control groups suggests its limited specificity.[41,48] Further, its improvement only in the subgroup of participants with baseline hypercalciuria in one trial may be indicative of regression to the mean.[48,65] We could not determine whether a reduction in serum or urine uric acid levels may be able to predict allopurinol effectiveness in reducing stone recurrence.[37]

Dietary Therapy Trials

Five eligible RCTs that compared an intervention diet with a control diet reported both followup urine biochemistry measures (range 1 week to 12 months) and recurrent stone outcomes (Appendix H, Table 1).[46,51,53,56,57] Among these, one trial that compared increased fluid intake with no treatment and reported a reduction in composite stone recurrence after 5 years of followup also reported significantly increased urine volume and significantly decreased urine calcium-oxalate supersaturation and uric acid supersaturation at one year versus baseline in the increased fluid intake group only.[46] In addition, calcium-phosphate supersaturation was significantly decreased only in the increased fluid group at all followup time points from 2 to 5 years after baseline. These data suggest that changes in these urine measures might predict risk of subsequent recurrent stones.

A trial that compared a low animal protein diet with a high fiber diet and a control group showed no significant change from baseline in urinary volume, or urine calcium, oxalate, citrate or sodium in any of the three treatment groups.[56] Another trial compared a low animal protein, low sodium, and normal to high calcium diet versus a low calcium diet.[51] This study reported a greater reduction versus baseline in levels of urinary sodium, oxalate, calcium-oxalate product, and calcium-oxalate supersaturation in participants assigned the multicomponent diet than in those assigned a low calcium diet. There was no difference in the change from baseline between treatment groups in urinary calcium or urine volume. Next, a trial that compared a diet low in animal protein and purine, and high in fiber and bran with a usual diet reported no difference between treatment groups in followup urine volume, calcium, oxalate or uric acid.[57] These three trials were heterogeneous in their interventions, stone outcomes and followup urine biochemistries except that all reported no change in followup urine calcium or urine volume. The one trial that reported a significant reduction in recurrent stones with the intervention diet was the only trial that reported reductions in followup urine oxalate, sodium, calcium-oxalate product, and calcium-oxalate supersaturation.[51] The two trials that reported no reduction in stone recurrence[56] and an increase in risk of stone recurrence,[57] respectively, both reported no change in followup urine oxalate and neither reported results for urine calcium-oxalate product or any urine supersaturation measure. Collectively, these trials suggest that for these diet interventions followup urine calcium is unlikely to be a useful predictor of stone recurrence and reductions in urine oxalate, calcium-oxalate product, and calcium-oxalate supersaturation might better predict reduced risk of subsequent recurrent stones.

Last, a trial that compared an extensive biochemical evaluation and tailored diet with a limited evaluation and empiric diet reported that the tailored diet group had an increase compared with baseline in urine calcium and magnesium, and no change in urine oxalate, citrate, and urine volume.[53] Because the tailored diet group followup urine biochemistries were derived from participants assigned a heterogeneous mix of diet instructions, with no followup biochemistry data reported separately by biochemical or dietary subgroups, and no followup biochemistry data reported for the control group, it was not possible to correlate the reported urine changes with stone outcomes.

Since a reduction in stone recurrence did not occur in all trials that reported an increase in urine citrate, the value of this followup biochemical measure for predicting reduced stone recurrence with citrate or control treatment is unknown.

No trials reported results for recurrent stones outcomes as a function of the followup level or the change from baseline in any biochemistry measure.

Pharmacological Therapy Trials

Thiazide Versus Placebo or Control

Six eligible RCTs that compared thiazide with placebo or control reported both followup urine biochemistry measures (range 6 to 24 months) and recurrent composite or radiographic stone outcomes (Appendix H, Table 2).[41,48,49,52,58] Among these six trials, five reported significantly reduced urinary calcium at followup in participants assigned to thiazide,[41,47,49,52,58] and the other trial reported a significant reduction in followup urinary calcium only in the subgroup of thiazide participants that had high baseline urine calcium.[48] Though thiazides also significantly reduced risk of recurrent composite calcium stones, it is uncertain whether a reduction in urine calcium in treated patients will predict future reduction in risk of stone recurrence. No trials reported whether differences in followup urine calcium levels within the thiazide treatment group participants were associated with differences in risk of recurrent stones. Further, one of these six thiazide trials reported a significant reduction in urinary calcium in participants assigned to its control group overall,[41] and a second trial reported a significant reduction only in the subgroup of controls that had high baseline urine calcium.[48] These results suggest that a reduction in urine calcium is a nonspecific marker and could represent 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] The only trial that reported followup results for urine calcium-oxalate product found a significant reduction from the baseline level in both thiazide and placebo treatment groups.[52] No other followup biochemistry measure reported was consistently changed from baseline in these trials, though none of the trials reported followup results for calcium-oxalate supersaturation or calcium-phosphate supersaturation.

Citrate Versus Placebo or Control

Three eligible RCTs that compared citrate with placebo or control reported both followup urine biochemistry measures (range 3 to 36 months) and recurrent composite or radiographic stone outcomes (Appendix H, Table 3).[43,44,59] However, none reported results for recurrent stones outcomes as a function of the followup level or the change from baseline in any biochemistry measure. All trials reported significantly increased urine citrate at followup in participants randomized to citrate, but not in those assigned to control treatment. One trial that utilized

potassium-magnesium-citrate also reported increased followup levels of urine potassium, magnesium and oxalate in the citrate group only,[44] and another trial that utilized potassium citrate reported an increased followup level of urine potassium and pH, again in the citrate group only.[43] Though no followup biochemistry measure other than urine citrate was reported in all three citrate trials (and urine calcium-oxalate supersaturation, uric acid supersaturation, or calcium-phosphate supersaturation were not reported in any trials), among results reported, no other urine biochemistry measure was changed from baseline in any trial citrate group. Further, no trial reported a significant change in any followup biochemical measure in its control group. While citrate treatment consistently increased urinary citrate levels, the three trials were inconsistent in stone recurrence outcomes, with two trials reporting a significant reduction in composite stone recurrence versus control (pooled RR, 0.26 [CI, 0.14 to 0.48])[43,44] and the third reporting no difference in risk of radiographic stone recurrence versus control (RR, 0.95 [CI, 0.62 to 1.44]).[59] Since a reduction in stone recurrence did not occur in all trials that reported an increase in urine citrate, accuracy of an increase in urinary citrate for predicting reduced stone recurrence with citrate or control treatment is unknown. From the limited data available, we could not determine whether this pattern was in part attributable to differences in the baseline prevalence of hypocitraturia between trials.

Allopurinol Versus Placebo or Control

Two eligible RCTs that compared allopurinol with placebo or control reported both followup blood and/or urine biochemistry measures and recurrent composite stone outcomes (Appendix H, Table 4).[37,40] Both trials were limited to participants with calcium stones. In one trial, relative to placebo, participants randomized to allopurinol had a significant reduction after 3 months in serum and urine uric acid levels but not in urine calcium.[37] In 24 months followup, this study also reported a nonsignificant reduction in risk of recurrent composite stones (RR, 0.49 [CI, 0.19 to 1.23]). In a second trial that collected followup biochemistry measures every 3 months but didn't indicate the time at which those reported were collected, there was no significant difference between treatment groups in followup serum uric acid, urine calcium, or urine uric acid levels.[40] In 36 months followup, the rate of recurrent composite stones was not lower in the allopurinol group (0.96 per person year) than the placebo group (0.66 per person year). Considering both trials, we could not determine whether a reduction in uric acid levels might predict allopurinol effectiveness in reducing stone recurrence.

Acetohydroxamic Acid Versus Placebo

None of the three AHA trials reported followup blood and/or urine biochemistry measures.

Magnesium Versus Placebo

The one eligible RCT that compared magnesium with placebo reported both followup urine biochemistry measures and recurrent composite stone outcomes (Appendix H, Table 5).[47] Participants randomized to magnesium had a significant increase in mean urine magnesium level at 24 months (148 vs. 97 mg/24 hrs, $p<0.001$) compared with no significant change from baseline in the placebo group. There was no change from baseline to followup in either treatment group in mean urine calcium, oxalate, or uric acid levels. In 36 months followup, the trial reported no significant difference in risk of composite recurrent stones between participants in the magnesium and placebo treatment groups overall. It did not report stone recurrence results for the period after the first reported followup biochemistry measurements, let alone compared

between treatments or stratified by followup magnesium levels or by changes in magnesium levels from pretreatment baseline.

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 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 with citrate, thiazide with allopurinol, or citrate with 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 risk 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 RCT data addressing whether the effect of any dietary or pharmacological 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 were predominately comprised of 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 3 summarizes the areas needing future research based on the gaps identified in this review.

Table 3. 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. • Modeling studies to estimate the benefits and harms of different kidney stone evaluation, treatment and followup strategies were outside the scope of this report.	• 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. • 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.

Table 3. Future research recommendations (continued)

Research Gaps	Future Research Recommendations
	• 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. • 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	• 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. • 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.

Table 3. Future research recommendations (continued)

Research Gaps	Future Research Recommendations
more effective in preventing stone recurrence in patients with hypercalciuria than in those without or unselected for hypercalciuria.	
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. o Does low dietary calcium increase recurrent stone risk? Does higher dietary calcium lower risk? o 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. o 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.
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	• 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.

Table 3. Future research recommendations (continued)

Research Gaps	Future Research Recommendations
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 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.
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.

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

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Acronyms and Abbreviations

AHA	Acetohydroxamic acid
ACP	American College of Physicians
AUA	American Urological Association
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
dL	Deciliter
EHC	Effective Health Care
FDA	Food and Drug Administration
KQ	Key Questions
kg	Kilogram
mg	Milligram
PICOTS	Population, intervention, comparator, outcome, timing, setting
RCT	Randomized controlled trial
RR	Relative risk
TEP	Technical Expert Panel

Appendix A. Search Strategy

Ovid MEDLINE Search Strategy

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) Search Strategy

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 B. Excluded Studies

1. Yuruk E, Binbay M, Sari E, et al. A prospective, randomized trial of management for asymptomatic lower pole calculi. Journal of Urology. 2010 Apr;183(4):1424-8. 20172565. *not treatment to prevent recurrent stones*
2. Yuan ZY. [Oral administration of magnesium and vitamin B6 in patients with renal calculi]. Chinese Journal of urology. 1987(2):91-3. CN-00366933. *not available in English*
3. Yoshioka K, Ohashi Y, Sakai T, et al. A multicenter trial of mizoribine compared with placebo in children with frequently relapsing nephrotic syndrome. Kidney International. 2000 Jul;58(1):317-24. 10886577. *not adults*
4. Wolf H, Brocks P, Transbol I. Do thiazides prevent recurrent idiopathic renal calcium oxalate stones? Results of a randomized, controlled clinical trial [abstract]. Kidney international. 1983(3):426. CN-00644376. *not controlled trial*
5. Wolf H, Brocks P, Dahl C. Do thiazides prevent recurrent idiopathic renal calcium oxalate stones? Proceedings of the European Dialysis & Transplant Association. 1983:477-80. CN-00644307. *not eligible treatment*
6. Van Reen R, Valyasevi A, Dhanamitta S. Studies of bladder stone disease in Thailand. XII. The effect of methionine and pyridoxine supplements on urinary sulfate. American Journal of Clinical Nutrition. 1970 Jul;23(7):940-7. 4917073. *not adults*
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8. Tiselius HG, Ackermann D, Alken P, et al. Guidelines on urolithiasis. European Urology. 2001 Oct;40(4):362-71. 11713390. *not controlled trial*
9. Tiselius H-G. Editorial comment on: Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. European Urology. 2009 Jul;56(1):80. 19321254. *not controlled trial*
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11. Thomas M, Caring for Australians with Renal I. The CARI guidelines. Clinical diagnosis of kidney stones. Nephrology. 2007 Feb;12 Suppl 1:S1-3. 17316269. *not controlled trial*
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14. Srinivasan S, Jenita X, Kalaiselvi P, et al. Salubrious effect of vitamin E supplementation on renal stone forming risk factors in urogenital tuberculosis patients. Renal Failure. 2004(2):135-40. CN-00516213. *not adults with previous kidney stones*

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16. Smith MJ. Allopurinol and calcium-stone formers. Lancet. 1973 Feb 10;1(7798):315. 4119188. *not controlled trial*

17. Siener R, Hesse A. Comparison of the effect of variations in dietary purine on risk of uric acid stone formation. American Journal of Clinical Nutrition. 1999(35):631s. CN-00495618. *not adults with previous kidney stones*

18. Sidabutar, Lumenta NA, Suling RC. Chlorthalidone in prevention of urinary calcium stone. Journal of the Medical Association of Thailand. 1978(Suppl 1):195-204. CN-00507294. *not controlled trial*

19. Segura JW, Preminger GM, Assimos DG, et al. Nephrolithiasis Clinical Guidelines Panel summary report on the management of staghorn calculi. The American Urological Association Nephrolithiasis Clinical Guidelines Panel. Journal of Urology. 1994 Jun;151(6):1648-51. 8189589. *not controlled trial*

20. Segura JW, Preminger GM, Assimos DG, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. Journal of Urology. 1997 Nov;158(5):1915-21. 9334635. *not controlled trial*

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Appendix C. Evidence Tables

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
Dussol 2008[1] Location: France Funding Source: none stated	Inclusion Criteria: • idiopathic calcium stone formers, regardless of the number of stone-forming episodes they had experienced • over age 18 and under 70 Exclusion Criteria: • systemic disease (including primary hyperparathyroidism, sarcoidosis,vitamin D excess, bowel disease of any kind, renal tubular acidosis, primary hyperoxaluria or urinary tract infections). • hereditary or acquired anatomical disorders of the kidney or the urinary drainage system, except medullary sponge kidney	N=175 Age (yr): 44 Gender (Male %): 65 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: BMI 24, weight 152 lbs Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): 1 mg/dL Estimated GFR (ml/min/1.73m^2): NR but creatinine clearance was 88 ml/min/1.73m^2 Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	<u>Stone characteristics:</u> Stone type: calcium oxalate or a mixture of calcium phosphate and oxalate Number of past stone episodes: NR but included patients regardless of number of past stone episodes. Residual stones/ fragments: NR Urine analysis: Hypercalciuria 38%; Hypocitraturia NR; Hyperuricosuria NR; Hyperoxaluria 0%; Mixed NR; No metabolic disorder; NR Blood analysis: abnormalities were not stated	1. Low animal protein diet, decrease intake of animal protein by limiting consumption of meat and fish to 3 servings per week and to not exceed 100 g/day of milk products. The target was to obtain a daily contribution of protein to energy of <13% (n=55). 2. High fiber diet, increase intake of fruits and vegetables and to substitute their usual cereals with whole grain dietary products in order to limit the increase in energy. The target was to obtain a 25-g/day increase in fiber intake. Subjects were not instructed to exclude fruits and vegetables particularly rich in oxalate (n=60). 3. Controls (usual diet) (n=60) Study dietician reinforced assigned dietary recommendations during every 4 month participant phone calls.	1. Allocation Concealment: adequate 2. Blinding: assessor 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* No adverse events reported :

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
				Followup period: 48 mos Study withdrawals (%): 58 (n=102) at month 48 Assessment of compliance and adherence to treatment: 23.3% of high fiber group, 29.1% of low animal protein group, and 15% of controls withdrew because of the assigned diet (p=NS). In high fiber group, mean fiber intake increased from 17 g/day at baseline to 27 g/day at 1 year (p<0.01 vs baseline) and 23 g/day at 4 years (p<0.01 vs baseline). Mean fiber intake in control diet group did not change during follow-up. In low protein group, mean total protein intake increased from 84 g/day at baseline (57 g/day animal protein) to 68 g/day at 1 year (38 g/day animal protein), a level that was maintained at 4 years (p<0.001 versus baseline for both total	

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
				protein and animal protein). By comparison, mean total protein intake in the control diet group was 84 g/day at baseline (55 g/day animal protein) and did not change during follow-up. Setting (e.g., medicine, urology): Nephrology clinic Follow up biochemical measures collected: (y/n): yes	
Sarica 2006[2] Location: Turkey Funding Source: none stated	Inclusion Criteria: • renal stone subjects who underwent shock wave lithotripsy 3 months prior • calcium oxalate stones located in the renal pelvis without any urinary tract infection Exclusion Criteria: • other types of calculi • patient with previous stone disease history with stone passage • no metabolic abnormality (including hyperoxaluria, hypercalciuria, hyperuricosuria, and hyperparathyroidism) could be demonstrated,	N=21 (of 45 total) stone free patients Age (yr): 32(mean reported as 32 yrs) Gender (Male %): 64 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	<u>Stone characteristics:</u> Stone type: calcium oxalate 100% Number of past stone episodes: single 100%, multiple 0% Residual stones/ fragments: 53% by plain abdominal X-ray (including renal tomography) and kidney sonography (n=24) Urine analysis: Hypercalciuria 0%; Hypocitraturia NR; Hyperuricosuria 0%; Hyperoxaluria 0%; Mixed NR; No metabolic disorder 100%	1. Forced fluid to achieve urinary output of >2.5 liters (n=12 (of 25) that were stone free) 2. No treatment (n=9/20 that were stone free) Followup period: 24-36 mos Study withdrawals (%): 0 Assessment of compliance and adherence to treatment: Reported 'good compliance' in majority of participants in the intervention	1. Allocation Concealment: unclear, not specified 2. Blinding: none stated 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: none reported *Quality of harms reporting:* No adverse events reported

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
	and no prior intervention		Blood analysis: no metabolic disorder 100%	group Setting (e.g., medicine, urology): none stated, authors noted to be affiliated with department of urology Follow up biochemical measures collected: (y/n): no	
Borghi 2002[3] Location: Italy Funding Source: non-industry	Inclusion Criteria: • idiopathic hypercalciuria (urinary calcium excretion, >300 mg per day on an unrestricted diet • recurrent formation of calcium oxalate stones (≥ 2 documented events colic episodes with expulsion of stones or radiographic evidence of retained stones) Exclusion Criteria: • presence of condition commonly associated with calcium nephro-lithiasis (e.g., primary hyperparathyroidism, primary hyperoxaluria, enteric hyperoxaluria, bowel resection, inflammatory bowel disease, renal tubular acidosis, sarcoidosis, or sponge kidney) • previous visit to a stone disease center	N=120 Age (yr): 45 Gender (Male %): 100 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: 171 lbs Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): 1.1 Estimated GFR (ml/min/1.73m^2) NR but creatinine clearance was 126 ml/min Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: 0% Pregnancy: NA History of CAD: NR History of DM: NR History of HTN: NR	<u>Stone characteristics:</u> Stone type: calcium oxalate 100% Number of past stone episodes: Single 0%; Multiple 100% Residual stones/ fragments: 27% by ultrasound and radiography Urine analysis: Hypercalciuria100%; Hypocitraturia NR; Hyperuricosuria NR; Hyperoxaluria 18% with “mild hyperoxaluria”; Mixed NR; No metabolic disorder 0% Blood analysis: no metabolic disorder 0%	1. Low calcium diet (<10 mmol) (n= 60) 2. Low protein (<93 g) and low sodium (50 mmol) diet (n=60) Both diets included daily increases in water intake to 2-3 liters. Followup period: 60 mos Study withdrawals (%): 14 (n=17) Assessment of compliance and adherence to treatment: Mean urine volume increased from 1.1 L/d at 1 year to > 2.5L/d in intervention group compared to a maximum of 1.3L/d at 1 year in the control group	1. Allocation Concealment: adequate 2. Blinding: outcomes assessor only 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: yes 3. Number of participants with adverse events reported for each study group: yes 4. Number of participants with each type of adverse event reported for each study group: yes 5. Number of participants that withdrew/lost to followup adequately described: yes

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
	• current treatment for the prevention of recurrent stones except for the advice to increase water intake			Setting (e.g., medicine, urology): not stated; authors affiliated with departments of clinical sciences and internal medicine and nephrology Follow up biochemical measures collected: (y/n): yes	
Di Silverio 2000[4] Location: Italy Funding Source: none stated	Inclusion Criteria: • received ESWL for idiopathic calcium kidney stone. • episodes of recurrence (3 recurrences within the last 4 years or 2 recurrences within the last 3 years). • free from clinically evident residual stones or fragments Exclusion Criteria: • patients with severe diabetes, gout or urinary infections.	N=384 Age (yr): 39 Gender (Male %): 60 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: NR Pregnancy: NR History of CAD: NR History of DM: NR (“severe” diabetes excluded) History of HTN: NR *No data provided regarding what proportion of participants underwent ESWL in the prior 90 days versus more than 90 days before baseline.	<u>Stone characteristics:</u> Stone type: calcium 100% Number of past stone episodes: Single 0%; Multiple 100% Residual stones/ fragments: 0% by X-ray and abdominal echographic studies Urine analysis: Hypercalciuria NR but mean baseline calcium levels were above the thresholds defined for hypercalciuria; Hypocitraturia NR; Hyperuricosuria NR; Hyperoxaluria NR; Mixed NR; No metabolic disorder; NR Blood analysis: none stated	1. “Fiuggi water’” oligo-mineral water with a calcium content of 15 mg/l, 2 liters within a 24-hour period (n=192) 2. tap water with a calcium content between 55 and 130 mg/l, 2 liters within a 24-hour period (n=192) A varied diet with a mean calcium content of 600 mg/day was prescribed for all patients. Followup period: 19 mos Study withdrawals (%): 0 Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine,	1. Allocation Concealment: unclear, not specified 2. Blinding: none stated 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: none reported *Quality of harms reporting:* No adverse events reported

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
				urology): stone centers Follow up biochemical measures collected: (y/n): yes	
Kocvara 1999[5] Location: Czech Republic Funding Source: non-industry	Inclusion Criteria: • first idiopathic calcium kidney stone. Exclusion Criteria: • primary hyperpara-thyroidism • primary hyperoxaluria • renal tubular acidosis, with struvite, uric acid and cystine stones • medullary sponge disease	N=242 (number randomized per arm unclear) Age (yr): range 18-72 Gender (Male %): 46 (those completing trial) Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	<u>Stone characteristics:</u> Stone type: calcium 100% (primarily oxalate and some mixed with phosphate) Number of past stone episodes: single 100%, multiple 0% Residual stones/ fragments: 21% by ultrasound and radiography (n=43) Urine analysis: (Tailored diet only): Hypercalciuria 67% ; Hypocitraturia 19%; Hyperuricosuria 27%; Hyperoxaluria 18%; Hypomagnesuria 9%; Blood analysis (Tailored diet only): Hyperuricemia 10%; Hypomagnesemia 12%	Tailored diet: 1. Hypercalciuria: Restriction of animal proteins. Regular intake of calcium-rich food (0.75-1.0 g Ca) divided into small doses during the day 2. Hyperuricosuria/ hyperuricemia: Restriction of meat products to 80 g/day; 1-2 meatless days per week 3. Mild hyperoxaluria (up to 0.8 mmol/day): Firm restriction of oxalate-rich diet. Regular dairy intake in main meal. Lemons, increased fiber intake. 4. Magnesium deficiency: Increased fiber intake, especially bran. Regular intake of dairy products. High magnesium mineral water. 5. Hypocitraturia: Animal protein restriction. 1-2 lemons/day (orange juice in normal oxaluria). Increase fruit & vegetables	1. Allocation Concealment: unclear, not specified 2. Blinding: none stated 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: no *Quality of harms reporting:* No adverse events reported

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
				(depending on oxaluria) <u>General diet recommendations</u> moderate intake (100–120 g) of animal proteins, restriction of oxalate-rich foods, an adequate calcium intake (0.75–1.0 g), increased fibre intake, and a moderate sodium intake. (n= 94 completers) Followup period: 36 mos Study withdrawals (%): 14 (n=35) Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): department of urology Follow up biochemical measures collected: (y/n): yes	
Borghi 1996[6] Location: Italy Funding Source:	Inclusion Criteria: • treatment for first idiopathic calcium kidney stone • absence of other retained calculi	N=220 Age (yr): 41 Gender (Male %): 67 (those completing trial) Race/Ethnicity (%): NR BMI, weight, or percent with	<u>Stone characteristics:</u> Stone type: calcium oxalate 100% Past stone episodes: single 100%, multiple 0%	1. Achieve urine volume >2 liters/day. Urine volume to be measured every 2 months to ensure high volume (n=110)	1. Allocation Concealment: unclear, not specified 2. Blinding: none stated 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: no

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
none stated	• absence of arterial hypertension or other metabolic pathology that requires regular dietary measures or drug therapy Exclusion Criteria: none provided	obesity: 154 lbs BMI, weight, or percent with obesity: NR Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Residual stones/ fragments: 0% by plain abdominal x-ray, renal echography, and infusion excretory urography Urine analysis: Hypercalciuria NR; Hypocitraturia NR; Hyperuricosuria NR; Hyperoxaluria NR; Mixed NR; No metabolic disorder; NR Blood analysis: none stated	2. No treatment (n=110) Followup period: 60 mos Study withdrawals (%): 10 (n=21) Assessment of compliance and adherence to treatment: Reported that 3 participants withdrew as they did not want to comply with the diet. Also reported no difference in dietary compliance but did not give specific information Setting (e.g., medicine, urology): stone center Follow up biochemical measures collected: (y/n): yes	*Quality of harms reporting:* No adverse events reported
Hiatt 1996[7] Location: United States Funding Source: non-industry	Inclusion Criteria: • documented single calcium oxalate kidney stone analyzed as ≥ 65 percent calcium oxalate • aged between 20-60 years • abdominal radiograph (x-ray film) with negative results within the previous 6 months.	N=99 Age (yr): 43 Gender (Male %): 79 Race/Ethnicity (%): 77 white, 13 Asian, 5 Hispanic, 4 black BMI, weight, or percent with obesity: BMI 25.5 Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR	<u>Stone characteristics:</u> Stone type: calcium oxalate 100% Number of past stone episodes: single 100% Residual stones/ fragments: 0% by radiography Urine analysis: Hypercalciuria 18%;	1. Low animal protein and high fiber diet: Decrease intake of animal protein (56 to 64 gm/day) and purine containing foods (75 mg/day); increase fruits, vegetables, and whole grains; and add 1/4 cup bran/day (n= 51, 50 included in study, 1 excluded post	1. Allocation Concealment: unclear, not specified 2. Blinding: assesor 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: no *Quality of harms reporting:* No adverse events reported

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
	Exclusion Criteria: • known metabolic explanation for stone formation (e.g., renal tubular acidosis, hyperparathyroidism, acromegaly, Cushing's syndrome) • chronic urosepsis, creatinine ≥1.8 mg/dl (137 unol/liter) • chronic small or large bowel disease	Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Hypocitraturia NR; Hyperuricosuria NR; Hyperoxaluria NR; Mixed NR; No metabolic disorder; NR Blood analysis: none stated	randomization) 2. Standard advice instructed on fluid intake and calcium intake (n=51, 49 included in study 2 excluded post randomization) Subjects advised to consume 2 servings of dairy products or 500 mg of calcium carbonate daily. Followup period: 48 mos Study withdrawals (%): 24 (n=24) Assessment of compliance and adherence to treatment: Self reported reduction in dietary protein and purine at 6 mos in intervention group Setting (medicine, urology): NR Followup biochemical measures collected: (y/n): y	
Shuster 1992[8] Location: United States	Inclusion Criteria: • male • aged 18-75 years • physician-confirmed	N=1009 Age (yr): 43 Gender (Male %): 100 Race/Ethnicity (%): NR	<u>Stone characteristics:</u> Stone type: All stone types Number of past stone	1. Intervention group: Asked to refrain from soft drinks, educated about the link between	1. Allocation Concealment: unclear, not specified 2. Blinding: controls were blinded and telephone contact was

Appendix C. Table 1. Evidence table: Diet trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/Biochemistry	Intervention/ Duration	Study Quality
Funding Source: non-industry	urinary stone episode. Exclusion Criteria: • Soft drink consumption <160 mL daily	BMI, weight, or percent with obesity: NR Previous bariatric surgery: NR Chronic kidney disease: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney: NR History of renal transplant: NR Urinary tract anatomic abnormality: NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	episodes: single 37% ;multiple 63% Residual stones/ fragments: NR Urine analysis: Hypercalciuria NR; Hypocitraturia NR; Hyperuricosuria NR; Hyperoxaluria NR; Mixed NR; No metabolic disorder; NR Blood analysis: none stated	soft drink consumption and stone formation (n= 504) 2. No intervention (n=505) Followup period: 36 mos Study withdrawals (%): 7 (n=72) Assessment of compliance and adherence to treatment: 43.1% at 6 months: defined as self reported consumption of < 680mL soda/week Setting (e.g., medicine, urology): urology clinics Follow up biochemical measures: (y/n): n	masked for the treatment group 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* No adverse events reported

Abbreviations: CAD = coronary artery disease; DM = diabetes mellitus; ESWL = extracorporeal shock wave lithotripsy; HTN = hypertension; NR = not reported; UTI = urinary tract infection

Appendix C. Table 2. Evidence table: Thiazide trials for recurrent nephrolithiasis

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Fernández-Rodriguez, 2006[9] Location: Spain Funding Source: none stated	Inclusion Criteria: • aged 18-65 years (male and female); • more than one prior episode of calcium stones in the past 36 months, resolved after stone passage, ESWL, or surgery (endoscopic and/or open); • normal renal function and morphology; • absence of endocrine disease. Exclusion Criteria: NR	N=150 Age (yr): NR, range 18-65 Gender (Male %): NR Race/Ethnicity (%): NR BMI: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): 0 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): 0 History of renal transplant (%): 0 Urinary tract anatomic abnormality (%): 0 Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR *No data provided regarding how many participants previously underwent ESWL and how many, if any, underwent ESWL in the prior 90 days.	Stone type: calcium oxalate 100% Past stone episodes: single 0%, multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria 35%; hypocitraturia 15%; hyperuricosuria 4%; hyperoxaluria 2%; mixed 16%; no metabolic disorder 29% Blood analysis: NR Diet characteristics: NR	1. Hydrochlorothiazide 50 mg/d (n=50) 2. Potassium citrate 20 mEq/d + hydrochlorothiazide 50 mg/d + (n=50) 3. No treatment (n= 50) Followup period: 36 months Study withdrawals (%): • Overall: 0 • due to adverse events: 0 • due to loss to follow-up: 0 Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): yes	1. Allocation Concealment: unclear, not specified 2. Blinding: not specified 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: none reported *Quality of harms reporting:* [No adverse event data reported] 1. Adverse events predefined: no 2. Adverse events reported for all participants:no 3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: none

Appendix C. Table 2. Evidence table: Thiazide trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Ahlstrand, 1995[10] Location: Sweden Funding Source: none stated	Inclusion Criteria: • calcium oxalate stone formers with hypercalicuria or hypomagnesium Exclusion Criteria: • none stated	N=41 Age (yr): 35 Gender (Male %): 83 Race/Ethnicity (%): NR BMI: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Stone type: calcium oxalate 100% Past stone episodes: multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria 90%; hypocitraturia 0%; hyperuricosuria 0%; hyperoxaluria 0%; mixed 0%; hypomagnesuria 10%; no metabolic disorder 0% Blood analysis: NR Diet characteristics: NR	1. Hydrochlorothiazide 25 twice daily (n=17) 2. No treatment (n= 24) (An additional 16 subjects randomized to combined hydrochloro-thiazide + Mg aspartate HCl, which isn't included in analyses since Mg aspartate HCL is ineligible treatment) All patients to increase fluids and decrease oxalate intake Followup period: mean 47 mos (up to 60) • Study withdrawals (%) overall: 19 (46) • due to adverse events: Thiazode, 5 (12), none in control • loss to follow-up: NR Assessment of compliance/ adherence to treatment: NR Setting (e.g., medicine, urology): NR, authors affiliated with department of urology Follow up biochemical measures collected: (y/n): yes	1. Allocation Concealment: unclear, not specified 2. Blinding: open-label 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: no 3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: yes
Borghi, 1993[11] Location: Italy Funding Source:	Inclusion Criteria: • Idiopathic recurrent stone formers (pure CaOx or with less than 20% of CaP);	N=75 Age (yr): 45 Gender (Male %): 79 Race/Ethnicity (%): NR BMI: NR	Stone type: calcium oxalate 100% (stones could be all CaOx or mix of CaOx + CaP) Past stone episodes:	1. Indapamide 2.5 mg/d (n=25). 2. Allopurinol 300 mg/d + Indapamide 2.5 mg/d (n=25).	1. Allocation Concealment: unclear, not specified 2. Blinding: open-label 3. Intention to Treat Analysis: no

Appendix C. Table 2. Evidence table: Thiazide trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
non-industry (University of Parma)	• hypercalciuric (urine Ca > 300 mg/d in men >250 mg/d in women or >4 mg/kg or Ca/creatinine >0.20 mg/dL for both); • formed at least 1 stone in the previous 3 years; • calculi free before treatment. Exclusion Criteria: NR	Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): 1.0 Estimated GFR (ml/min/1.73m^2): Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: 26.6%	multiple 100% Residual stones/ fragments: 0% on intravenous pyelography and renal echography) Urine analysis: Hypercalciuria 100%; hypocitraturia NR ; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder 0% Blood analysis: Hyperuricemia NR Diet characteristics: NR	3. Control (diet/increased fluid treatment) (n=25) All groups to increase fluid intake; limit sodium, calcium, oxalate and purine intake. Followup period: 36 mos Study withdrawals (%): • overall: 11 (15) • due to adverse events:2(3) 0 • due to loss to follow-up: 0 Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): yes	4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Harms predefined: no 2. Harms specified as ALL events collected: no 3. Number of participants that withdrew/lost to follow up adequately described: yes 4. Total number of participants affected by harms specified for each study group: yes 5. Number for each type of harm event specified for each study group: yes
Ettinger, 1988[12] Location: US Funding Source: Industry and non-industry	Inclusion Criteria: • recurrent calculous disease; • calculous composition exceeding 79% calcium oxalate; • 2 or more calculi within the previous 5 years and at least 1 calculus within the previous 2 years. Exclusion Criteria:	N=124 Age (yr): 47 Gender (Male %): 88 Race/Ethnicity (%): white 94 BMI: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant	Stone type: calcium oxalate 100% (stones could be all CaOx or mix of CaOx + CaP) Past stone episodes: single 0%, multiple 100% Residual stones/ fragments:47% on X-ray Urine analysis: Hypercalciuria 36%; hypocitraturia %; NR hyperuricosuria 37%; hyperoxaluria NR;	1. Chlorthalidone 25 mg/d (n=19) 2. Chlorthalidone 50 mg/d (n=23) 3. Magnesium hydroxide 650 mg/d (n=30) 4. Magnesium hydroxide 1300 mg/d (n=21) 5. Placebo (n=31) All groups to drink fluid for urine output of 2L/day; restrict salt, animal protein, and high oxalate foods; increase cereal fiber; avoid	1. Allocation Concealment: inadequate (medical record number) 2. Blinding: double, outcomes assessor 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: yes

Appendix C. Table 2. Evidence table: Thiazide trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
	• secondary causes for nephrolithiasis.	(%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	mixed hypercalciuria and hyperuricosuria 23%; Blood analysis: NR Diet characteristics: NR	vitamin C; consume ≤2 dairy servings/day. Followup period: 36 mos Study withdrawals (%): • overall: ~32* (possibly 26) • due to adverse events: unclear, range was 3.2% (placebo) to 22.6% (Chlorthalidone 25 mg). None reported for Magnesium hydroxide 650 mg • due to loss to follow-up: 0 Setting (e.g., medicine, urology): NR Assessment of compliance and adherence to treatment: Pill counts, no results reported. Approximated 13-18% of the study population dropped out due to loss of interest Follow up biochemical measures collected: (y/n): yes * Approximate estimate based on the percentages provided in the text by each treatment arm. Actual number of subjects not reported (and it was difficult to calculate the number of patients withdrawing due to	3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: yes

Appendix C. Table 2. Evidence table: Thiazide trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
				the discrepancies between the reported percentages and the numbers in each arm that were reported).	
Ala-Opas, 1987[13] Location: Finland Funding Source: none stated	Inclusion Criteria: • recurrent urinary calcium stones. Exclusion Criteria: NR	N=73 Age (yr): 48 Gender (Male %): 82 Race/Ethnicity (%): NR BMI: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Stone type: calcium 100% Past stone episodes: single 0%, multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria 44%; hypocitraturia NR; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder 56% Blood analysis: NR Diet characteristics: NR	1. Hydrochlorothiazide 50 mg twice daily for first 5 months (+ bran) (n=28) 2. Control (bran) (n=45) Both groups to drink ≥2.5 L/day fluid; diet of 40 gm/d bran, low calcium, low oxalate. Followup period: 24 mos Study withdrawals (%): • overall: 0 • due to adverse events: 0 • due to loss to follow-up: 0 Assessment of compliance and adherence to treatment: Self reported questionnaire on calcium intake. Results report no discontinuation of therapy Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): yes	1. Allocation Concealment: unclear, not specified 2. Blinding: open-label 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: none reported *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: no 3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: none, no withdrawals
Laerum, 1984[14] Location: Norway Funding Source:	Inclusion Criteria: • at least 15 years of age with or without hypercalciuria (> 6 mmol/24 hr) and/or hyperuricosuria (>	N=50 Age (yr): 44 Gender (Male %): 76 Race/Ethnicity (%): NR BMI: NR Previous bariatric surgery	Stone type: calcium stones 100% Past stone episodes: single 0%, multiple 100% Residual stones/	1. Hydrochlorothiazide 25 mg twice daily + potassium chloride 1.2 gm/d (n=25) 2. Placebo (n=25) Both groups to drink fluid	1. Allocation Concealment: unclear, not specified 2. Blinding: double 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts

Appendix C. Table 2. Evidence table: Thiazide trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Industry	3.5 mmol/24 hr); • two or more stones totally formed if the most recent stone, associated with renal colic, had occurred during the last 2 years and was verified by X-ray examination, surgery, or stone passage. Exclusion Criteria: • chronic and/or active UTI; • pyelographically verified urinary obstruction; • uric acid and triple phosphate stones; • chronic diseases such as heart congestion, cancer and sarcoidosis.	(%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	fragments: NR Urine analysis: Hypercalciuria 26%; hypocitraturia NR%; hyperuricosuria 24%; hyperoxaluria NR%; mixed NR%; no metabolic disorder NR% Blood analysis: NR Diet characteristics: NR	for urine output ≥2L/day; restrict salt, calcium, oxalate and purine-rich foods. Followup period: 40 mos Study withdrawals (%): • overall: 2 (4) • due to adverse events: 0 • due to loss to follow-up: 0 Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): "general practice" Follow up biochemical measures collected: (y/n): yes	adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: yes 3. Number of participants with adverse events reported for each study group: yes 4. Number of participants with each type of adverse event reported for each study group: yes 5. Number of participants that withdrew/lost to followup adequately described: yes
Scholz, 1982[15] Location: Germany Funding Source: none stated (industry supplied thiazide and placebo)	Inclusion Criteria: • metabolically active calcium stone formation. Exclusion Criteria: • primary hyperparathyroidism.	N=51 Age (yr): 44 Gender (Male %): 61 Race/Ethnicity (%): NR BMI: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): NR Solitary kidney (%): NR History of renal transplant (%): NR	Stone type: calcium 100% Past stone episodes: single 0%, multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria 12%; hypocitraturia NR%; hyperuricosuria NR%; hyperoxaluria 100%; mixed NR%; no metabolic disorder 0%	1. Hydrochlorothiazide 25 mg twice daily (n=25) 2. Placebo (n=26) "Additional potassium" given to those with K <3 mEq/L during study. Followup period: 12 mos Study withdrawals (%): • overall: 3 (6) • due to adverse events: 3 (6) • due to loss to follow-up: 0	1. Allocation Concealment: unclear, not specified 2. Blinding: double, statistical analysis was done independently 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: yes 3. Number of participants with

Appendix C. Table 2. Evidence table: Thiazide trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
		Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Blood analysis: NR Diet characteristics: NR	Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): yes	adverse events reported for each study group: yes 4. Number of participants with each type of adverse event reported for each study group: yes 5. Number of participants that withdrew/lost to followup adequately described: yes

Abbreviation: NR = not reported

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
Lojanapiwat, 2011[16] Location: Thailand Funding Source: NR	Inclusion Criteria: • Stone-free or had residual stones <4 mm diameter at 8 weeks after ESWL or percutaneous nephrolithotomy (PCNL) • Normal renal function and normal renal anatomy Exclusion Criteria: • UTI • Anatomic abnormalities • Clinical history of urologic stone surgery	N=39 stone-free patients (80 total were enrolled (data for 76 of completed trial) and 37 had residual stone fragments) *Demographics for stone-free only unless noted)* Age (yr): 52, range 28-75 Gender (Male %): 62 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: 23.8 (all patients) Previous bariatric surgery (%): NR Chronic kidney disease (%): 0 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): 0% (normal renal morphology) History of renal transplant (%): 0% (normal renal function and morphology) Urinary tract anatomic abnormality: 0% (normal renal morphology) Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Stone type: calcium 100% Past stone episodes: NR Residual stones/ fragments: 49% (37/76 study completers) with fragment(s) (<4 mm diameter at baseline) 8 weeks after completion of ESWL or PCNL by KUB radiography Urine analysis for all patients (stone-free and residual stones): Hypercalciuria 14%; hypocitraturia 46%; hyperuricosuria 1%; hyperoxaluria 18%; mixed NR; no metabolic disorder NR Blood analysis: NR Diet characteristics: NR	1. Sodium- potassium citrate 81 mEq/d (n=13 *stone-free only, 39 total*) 2. No treatment (n=26 *stone-free only, 37 total*) Diet and/or fluid modification: patients were instructed to have sufficiently high fluid intake throughout the study Followup period: 12 mos Study withdrawals reported only for all patients and not broken out for baseline stone-free group (%): • overall: 4 (5) • due to adverse events: 0 • due to loss to follow-up: 3 (4) • noncompliance: 1 (1) Assessment of compliance and adherence to treatment: 1 subject was excluded from analyses due to unsatisfactory compliance with medication	1. Allocation Concealment: unclear, not specified 2. Blinding: not specified 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting: No harms data reported* 1. Adverse events predefined: no 2. Adverse events reported for all participants: no 3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: yes

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
Fernández-Rodriguez, 2006[9] Location: Spain Funding Source: NR	Inclusion Criteria: • aged 18-65 years • more than one prior episode of calcium stones in the past 36 months, resolved after stone passage, ESWL (time since ESWL not specified), or surgery (endoscopic and/or open);normal renal function and morphology; • absence of endocrine disease. Exclusion Criteria: NR	N=150 Age (yr): NR, range 18-65 Gender (Male %): NR Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): 0 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): 0% (normal renal morphology) History of renal transplant (%): 0% (normal renal function and morphology) Urinary tract anatomic abnormality: 0% (normal renal morphology) Pregnancy: NR History of CAD: NR History of DM: 0% (absence of endocrine disease) History of HTN: NR	Stone type: calcium oxalate 100% Past stone episodes: single 0%, multiple 100% (time since ESWL not reported) Residual stones/ fragments: NR Urine analysis: Hypercalciuria 35%; hypocitraturia 15%; hyperuricosuria 4%; hyperoxaluria 2%; mixed 16%; no metabolic disorder 29% Blood analysis: NR Diet characteristics: NR	1. Potassium citrate 20 mEq/d + hydrochlorothiazide 50 mg/d (n=50) 2. Hydrochlorothiazide 50 mg/d (n=50) 3. No treatment (n=50) Diet and/or fluid modification: NR Followup period: 36 mos Study withdrawals (%): • overall: 0 • due to adverse events: 0 • due to loss to follow-up: 0 Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): yes	1. Allocation Concealment: unclear, not specified 2. Blinding: not specified 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: none reported *Quality of harms reporting: No harms data reported* 1. Adverse events predefined: no 2. Adverse events reported for all participants: no 3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: no withdrawals occurred
Soygur, 2002[17] Location: Turkey Funding Source: none stated	Inclusion criteria: • Patients with lower caliceal calcium oxalate stones who underwent SWL mono-therapy; • stone free or with fragments <5 mm diameter on plain	N=110 Age (yr): 42 (18 to 63) Gender (Male %): 67 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery: NR Chronic kidney disease (%): 0	Stone type: calcium oxalate 100% Past stone episodes: single 100%, multiple 0% Residual stones/ fragments: 38% with fragment(s) (<5 mm	1. Potassium citrate 60 mEq/d (n=46) 2. Control (n=44) Diet and/or fluid modification: Both groups to drink fluid to achieve 2.1 liters/d	1. Allocation Concealment: unclear, not specified 2. Blinding: outcomes assessor 3. Intention to Treat Analysis: no, non-compliant patients, patients with epigastric discomfort, and patients unwilling to receive medication were excluded from

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
	abdominal films and renal ultrasounds 4 weeks later; • Patients with simple renal lithiasis in the presence of normal renal morphology and functions. Exclusion criteria: • UTI; • anatomic abnormality of urinary tract • history of urologic surgery, or urolithiasis prior to most recent stone episode; • definitive metabolic disease such as hyper-parathyroidism or renal tubular acidosis.	Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): 0 Urinary tract anatomic abnormality (%): 0 Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	diameter at baseline) 4 weeks after completion of SWL by radiography (abdominal plain films) and ultrasound. Urine analysis: Hypercalciuria 20%; hypocitraturia 38%; hyperuricosuria 18%; hyperoxaluria NR; mixed NR; no metabolic disorder NR Blood analysis: NR Diet characteristics: NR	urine output; avoid oxalate rich and salty foods; limit meat intake; increase fiber. Followup period: 12 mos Study withdrawals (%): • overall: 20 (18) • due to adverse events: 6 (5) • due to loss to follow-up: 14 (13), including 10 "noncompliance with follow-up" and 4 reluctant to take medication Assessment of compliance and adherence to treatment: 4 patients excluded because of "reluctance to receive medication" (treatment groups not reported). Compliance with citrate determined by urinary citrate and potassium reported as "good in all patients" Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): no	analysis 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: no 3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: yes

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
Premgamone, 2001[18] Location: Thailand Funding Source: non-industry (Institute of Thai Traditional Medicine and Ministry of Public Health)	Inclusion Criteria: • Subjects with at least 1 kidney stone ≥10 mm, serum creatinine ≤ 4 mg/dL, no heart disease. Exclusion Criteria: NR	N=48 Age (yr): NR, range 20 to 60 Gender (Male %): 48 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: 0% (no heart disease) History of DM: NR History of HTN: NR	Stone type: not stated Past stone episodes: not stated Residual stones/ fragments: 100% with retained stone/ fragment(s) >10mm diameter by ultrasound. Urine analysis: Hypercalciuria NR; hypocitraturia NR; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder NR Blood analysis: NR Diet characteristics: NR	1. Sodium-potassium citrate 5-10gm/d (n=24) 2. *Orthosiphon grandiflorus* extract 5 g/d (n=24) Diet and/or fluid modification: NR Follow up period: 18 mos Study withdrawals (%): • overall: 7 (15) • due to adverse events: 5 (10) • due to loss to follow-up: 2 (4) Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): home and private clinic Follow up biochemical measures collected: (y/n): yes	1. Allocation Concealment: unclear, not specified 2. Blinding: outcomes assessor 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: yes 3. Number of participants with adverse events reported for each study group: yes 4. Number of participants with each type of adverse event reported for each study group: yes 5. Number of participants that withdrew/lost to followup adequately described: yes
Ettinger, 1997[19] Location: US Funding Source: non-industry (US	Inclusion criteria: • Active, recurrent calculous disease; • no secondary cause for nephrolithiasis; • two or more calculi in last 5 years and at least 1 in last 2 years.	N=64 Age (yr): 48 Gender (Male %): 78 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR	Stone type: calcium oxalate 100% Past stone episodes: single 0%, multiple 100% Residual stones/ fragments: 72% by X-ray.	1. Potassium (42 mEq/d)-magnesium (21 mEq/d) citrate (63 mEq/d) (n=31) 2. Placebo (n=33) Diet and/or fluid modification:	1. Allocation Concealment: adequate 2. Blinding: double, outcomes assessor 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: yes

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
Public Health Service Research)	Exclusion criteria: • obstructive uropathy; • chronic urosepsis; • renal failure (serum creatinine >1.8mg/dl, normal 1.5 or less); • renal tubular acidosis; • lithotripsy treatment within the previous 6 months.	Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR (≤1.8) Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Urine analysis: Hypercalciuria NR; hypocitraturia NR; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder NR Blood analysis: NR Diet characteristics: NR	Restricted salt, oxalate, refined sugar and animal protein. Allowed up to 2 servings/day dairy Followup period: 37 mos Study withdrawals (%): • overall: 23 (36) • due to adverse events: 6 (9) • due to loss to follow-up: NR Assessment of compliance and adherence to treatment: Medication compliance assessed by pill counts; diet compliance not assessed. Median compliance 86.9% for placebo and 89.0% for citrate group. >70% compliance in 73.1% of placebo group and 80.8% of citrate group. Setting (e.g., medicine, urology): none stated Follow up biochemical measures collected: (y/n): yes	*Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: yes 3. Number of participants with adverse events reported for each study group: yes 4. Number of participants with each type of adverse event reported for each study group: yes 5. Number of participants that withdrew/lost to followup adequately described: no

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
Hofbauer, 1994[20] Location: Austria Funding Source: none stated	Inclusion criteria: • patients with recurrent idiopathic calcium oxalate urolithiasis; • at least one stone annually over the previous 3 years. Exclusion criteria: • primary hyperparathyroidism; • renal tubular acidosis (type I); • UTI; • hypercalcemia or diseases of the gastrointestinal tract.	N=50 Age (yr): 55 Gender (Male %): 62 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Stone type: calcium oxalate 100% Past stone episodes: single 0%, multiple 100% Residual stones/ fragments: not stated Urine analysis: Hypercalciuria 44%; hypocitraturia 69%; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder NR Blood analysis: NR Diet characteristics: NR	1. Sodium-potassium citrate 30 gm/d initially, then adjusted to keep urine pH 7.0-7.2 (n=25) 2. Control (n=25) Diet and/or fluid modification: Both groups to perform "abundant liquid intake," make unspecified diet restrictions. Followup period: 36 mos Study withdrawals (%): • overall: 12 (24) • due to adverse events: 4 (8) • due to loss to follow-up: 8 (16); appeared 3 were patient refusal to regularly follow-up and 5 investigators stopped follow-up due to participant noncompliance Assessment of compliance and adherence to treatment: Reported assessed by participant urinary pH self-monitoring. Noncompliance in 3/25	1. Allocation Concealment: unclear, not specified 2. Blinding: not specified 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: no 3. Number of participants with adverse events reported for each study group: yes 4. Number of participants with each type of adverse event reported for each study group: yes 5. Number of participants that withdrew/lost to followup adequately described: yes

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
				control group participants ("refused to comply with regular follow-ups" though not specified if this referred to pH monitoring, or other). "Noncompliance" in 5/25 in citrate group. Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): yes	
Barcelo, 1993[21] Location: Spain Funding Source: none stated	Inclusion criteria: • active calcium nephrolithiasis concomitant with idiopathic hypocitraturia; • moderately severe active lithiasis (≥2 stones formed during the previous 2 years composed of calcium oxalate or a mixture of calcium oxalate and calcium phosphate)l • low (<2 mmol/day) or low normal (<3.4 mmol/day) urinary citrate. Exclusion criteria: • 3 or more stones in same kidney, in whom stone number was difficult to quantitate; • metabolic abnormalities,	N=57 Age (yr): 44 Gender (Male %): 44 Race/Ethnicity (%): NR BMI, weight, or percent with obesity Previous bariatric surgery (%): NR Chronic kidney disease (%): NR but no renal failure Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: 0% History of CAD: NR History of DM: 0% History of HTN: NR	Stone type: calcium oxalate or calcium oxalate + phosphate Past stone episodes: single 0%, multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria 0%; hypocitraturia 100%; hyperuricosuria 0%; hyperoxaluria 0%; mixed 0%; no metabolic disorder 0% Blood analysis: NR Diet characteristics: NR	1. Potassium citrate scheduled 60 mEq/d, but included in analysis if took 30-60 mEq/d (n=28) 2. Placebo (n=29) Diet and/or fluid modification: Both groups to increase fluid intake to 2-3L/day, and limit sodium intake Followup period: 36 mos Study withdrawals (%): • overall: 19 (33) • due to adverse events: 3 (5) • loss to follow-up: 16 (28)	1. Allocation Concealment: unclear, not specified 2. Blinding: double 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: no 3. Number of participants with adverse events reported for each study group: yes 4. Number of participants with each type of adverse event reported for each study group: yes 5. Number of participants that withdrew/lost to followup adequately described: yes

Appendix C. Table 3. Evidence table: Citrate trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/ Duration	Study Quality
	such as hypercalciuria, hyperuricosuria or hyperoxaluria; • diabetes mellitus, renal failure, hyperkalemia, active UTI infection, gastrointestinal diseases, medication for stone disease; • pregnancy or lactation			Assessment of compliance and adherence to treatment: Noncompliance defined as taking fewer than 6 of 12 tablets/day due to inconvenience of dosing regimen (ascertained by interview and pill count). 8/28 noncompliant in potassium citrate group and 8/29 in placebo group. Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): yes	

Abbreviations: CAD = coronary artery disease; DM = diabetes mellitus; ESWL = extracorporeal shock wave lithotripsy; HTN = hypertension; NR = not reported; UTI = urinary tract infection

Appendix C. Table 4. Evidence table: Allopurinol trials for recurrent nephrolithiasis

Study/Region/ Funding Source	Inclusion/ Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Borghi, 1993[11] Location: Italy Funding Source: non-industry (University of Parma)	Inclusion Criteria: • idiopathic recurrent stone formers • Stone type pure CaOx or with less than 20% of CaP, • Hypercalciuria (urine Ca > 300 mg/d in men >250 mg/d in women or >4 mg/kg or Ca/creatinine >0.20 mg/dL for both) • formed at least 1 stone in the previous 3 years • calculi free before treatment. Exclusion Criteria: NR	N=75 Age (yr): 45 Gender (Male %): 79 Race/Ethnicity (%): NR Weight (mean, kg): control 74.0, Indapamide 69.1, Indapamide + Allopurinol 76.4 Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): 1.0 Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: 26.6%	Stone type: <20% Calcium phosphate, remainder calcium oxalate Past stone episodes: multiple 100% Residual stones/ fragments: 0% on i.v. pyelpgraphy and renal USG Urine analysis: Hypercalciuria 100%; hypocitraturia NR ; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder 0% Blood analysis: Hyperuricemia NR Diet characteristics: NR	1. Allopurinol 300 mg/d + Indapamide 2.5 mg/d (n=25). 2. Indapamide 2.5 mg/d (n=25). 3. Control (n=25) Diet and/or fluid modification: All groups instructed to increase fluid intake; limit sodium, calcium, oxalate and purine intake. Follow up period: 36 mos Study withdrawals (%): • overall n=11 (15%) • due to adverse events 0 • loss to follow-up 0 Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): Yes	1. Allocation Concealment: unclear, not specified 2. Blinding: open-label, no placebo given to control group 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Harms predefined: No 2. Harms specified as ALL events collected: No 3. Number of participants that withdrew/lost to followup adequately described: Yes 4. Total number of participants affected by harms specified for each study group: Yes 5. Number for each type of harm event specified for each study group: Yes

Appendix C. Table 4. Evidence table: Allopurinol trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/ Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Ettinger, 1986[22] Location: US Funding Source: Industry and non-industry	Inclusion Criteria: • calculous composition exceeding 79% calcium oxalate • recurrent calculous disease • ≥2 calculi within the previous 5 years and at least 1 calculus within the previous 2 years. Exclusion Criteria: • secondary causes of nephrolithiasis (chronic UTI and obstruction, renal failure, renal acidification defects, disorders of calcium metabolism, chronic GI disorders or the use of drugs that could effect calculous disease)	N=72 Age (yr): 48 Gender (Male %): NR Race/Ethnicity (%): NR BMI (mean): placebo 28.1, treatment 27.4 Obesity (%): study stated was present "in half the subjects" without specifying treatment group Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy (%): NR History of CAD (%): NR History of DM (%): NR History of HTN (%): NR	Stone type: 100% of patients with stones comprised of at least 79% calcium oxalate Past stone episodes: multiple 100% Residual stones/ fragments: 42% Allopurinol and 52% placebo groups on abdominal X-ray Urine analysis: Hypercalciuria 0%; hypocitraturia NR ; hyperuricosuria 100%; hyperoxaluria NR; mixed NR no metabolic disorder 0% Blood analysis: Hyperuricemia NR Diet characteristics: NR	1. Allopurinol 300 mg/d (n=36) 2. Placebo (n=36) Diet and/or fluid modification: Both groups to "increase fluid intake." Follow up period: 24 mos Study withdrawals (%): • overall 12 (17%) • due to adverse events 0 • due to loss to follow-up 0 Assessment of compliance and adherence to treatment: By pill count, 89% for placebo, 88% for allopurinol Setting (e.g., medicine, urology): none stated Follow up biochemical measures collected: (y/n): yes	1. Allocation Concealment: adequate, block randomization 2. Blinding: double blind 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Harms predefined: NR 2. Harms specified as ALL events collected: NR 3. Number of participants that withdrew/lost to follow up adequately described: yes 4. Total number of participants affected by harms specified for each study group: yes 5. Number for each type of harm event specified for each study group: yes

Appendix C. Table 4. Evidence table: Allopurinol trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/ Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Miano, 1985[23] Location: Italy Funding Source: none stated	Inclusion Criteria: • minimum recurrence rate of 2 stone episodes per year for at least 3 years. Exclusion Criteria: • none provided.	N=30, preliminary data on 15 completing 3 years follow up. Age (yr): NR Gender (Male %): NR Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy (%): NR History of CAD (%): NR History of DM (%): NR History of HTN (%): NR	Stone type: calcium oxalate 100% Past stone episodes: multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria NR; hypocitraturia NR ; hyperuricosuria NR; hyperoxaluria NR; mixed NR no metabolic disorder: NR Blood analysis: Hyperuricemia NR Diet characteristics: NR	1. Allopurinol 300 mg/d (n=8) 2. Placebo (n=7) Data on other 15 subjects not reported Diet and/or fluid modification: Both groups to consume ≥1500 mL water daily; limit calcium and purine intake Follow up period: 36 mos Study withdrawals (%): none reported (preliminary data) Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): none stated, authors noted to be affiliated with department of urology Follow up biochemical measures collected: (y/n): yes	1. Allocation Concealment: unclear, not specified 2. Blinding: double blind 3. Intention to Treat Analysis: no (preliminary results) 4. Withdrawals/Dropouts adequately described: unclear; not stated whether any of 15 not completing 3 years followup were dropouts. *Quality of harms reporting:* 1. Harms predefined: NR 2. Harms specified as ALL events collected: NR 3. Number of participants that withdrew/lost to follow up adequately described: NR 4. Total number of participants affected by harms specified for each study group: NR 5. Number for each type of harm event specified for each study group: NR

Appendix C. Table 4. Evidence table: Allopurinol trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/ Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Robertson, 1985[24] Location: UK Funding Source: none stated	Inclusion Criteria: • recurrent idiopathic calcium stone-formers Exclusion Criteria: • secondary calcium stones, or with cystine, uric acid or infection stones during pre-treatment observation period.	N=120, preliminary data on 45 participants who first entered the trial. Age (yr): NR Gender (Male %): 100 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy (%): NR History of CAD (%): NR History of DM (%): NR History of HTN (%): NR	Stone type: calcium oxalate 100% Past stone episodes: multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria NR; hypocitraturia NR ; hyperuricosuria NR; hyperoxaluria NR; mixed NR no metabolic disorder: NR Blood analysis: Hyperuricemia NR Diet characteristics: NR	1. Allopurinol 300 mg/d (n=12) 2. Control (n=9) 24 patients made up 2 more ineligible arms of the study Follow up period: up to 60 mos Study withdrawals (%): none reported (preliminary data) Assessment of compliance and adherence to treatment: NR Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): NR	1. Allocation Concealment: unclear, not specified 2. Blinding: not specified 3. Intention to Treat Analysis: no (preliminary results) 4. Withdrawals/Dropouts adequately described: unclear; not stated whether any of 75 not included in analyses were dropouts *Quality of harms reporting:* 1. Harms predefined: NR 2. Harms specified as ALL events collected: NR 3. Number of participants that withdrew/lost to follow up adequately described: NR 4. Total number of participants affected by harms specified for each study group: NR 5. Number for each type of harm event specified for each study group: NR
Smith, 1977[25] Location: US Funding Source: none stated	Inclusion Criteria: • not on uricosuric drugs • had passed or had had a minimum of 4 renal calculi in the preceding 3 years, of which there must have been at least 1 crystallographic analysis confirming calcium oxalate • serum uric acid >6mg/dl).	N=132 Age (yr): NR Gender (Male %): NR Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality	Stone type: calcium oxalate 100% Past stone episodes: multiple 100% Residual stones/ fragments: NR Urine analysis: Hypercalciuria NR; hypocitraturia NR ; hyperuricosuria NR; hyperoxaluria NR; mixed NR no metabolic disorder:	1. Allopurinol (300 mg/d x 1 week, then 100 mg/d) + sodium bicarbonate as needed to keep urine pH >6.5 (n=65) 2. Placebo + sodium bicarbonate as needed to keep urine pH >6.5 (n=67) Diet and/or fluid modification: Both groups to drink adequate fluids, given “simple diet”.	Allocation Concealment: adequate (pharmacy controlled) Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix C. Table 4. Evidence table: Allopurinol trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/ Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
		(%): NR	0%		
	Exclusion Criteria: • none provided	Pregnancy (%): NR History of CAD (%): NR History of DM (%): NR History of HTN (%): NR	Blood analysis: Hyperuricemia 100% Diet characteristics: NR	Follow up period: up to 60 mos Study withdrawals (%): • overall 40 (30%) • due to adverse events 8 (6.1%) • due to loss to follow-up 13 (9.8%) Assessment of compliance and adherence to treatment: Number of remaining pills counted by pharmacy before refills Setting (e.g., medicine, urology): none stated, authors noted to be affiliated with department of urology Follow up biochemical measures collected: (y/n): NR	

[a]Total number randomized unclear.
[b] Number randomized to each treatment group unclear.
[c] Total number of withdrawals unclear
Abbreviation: NR = Not reported

Appendix C. Table 5. Evidence table: Acetohydroxamic acid (AHA) trials for recurrent nephrolithiasis

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Griffith, 1991[26] Location: USA Funding Source: Government	Inclusion Criteria: • presence or history of infection calculi in association with chronic, urea-splitting urinary infection that was recalcitrant to permanent eradication by antimicrobial agents; • serum creatinine <2.5 mg/dL (225 µmol/L); • not suitable for surgical removal of calculi and antimicrobial therapy Exclusion Criteria: NR	N=94 Age (yr): 79% in age range 25-75y Gender (Male %): 51 Race/Ethnicity (%): NR Spinal cord injury: 50% BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): 64% with prior urinary diversion (ileal conduits) Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Stone type: Struvite 100% Past stone episodes: multiple 100% Residual stones/ fragments: 89% by X-ray. Urine analysis: Hypercalciuria NR; hypocitraturia NR; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder NR Blood analysis: Hyperuricemia NR Diet characteristics: NR	1. AHA 15 mg/kg/d every 6-8 hours (n=45) 2. Placebo (n=49) Other: Antibiotics were prescribed according to the physicians as clinically indicated Follow up period: 6-32 mos Study withdrawals (%): • overall 65 (69) • due to adverse events 15 (15.9) • due to loss to follow-up 11 (11.7) Assessment of compliance and adherence to treatment: Overall > 80% medication compliance as assessed by study nurse Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): NR	1. Allocation Concealment: unclear, not specified 2. Blinding: double blind and radiologist who reviewed radiographs 3. Intention to Treat Analysis: yes 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Harms predefined: No 2. Harms specified as ALL events collected: No 3. Number of participants that withdrew/lost to follow up adequately described: Yes 4. Total number of participants affected by harms specified for each study group: Yes 5. Number for each type of harm event specified for each study group: Yes

Appendix C. Table 5. Evidence table: Acetohydroxamic acid (AHA) trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/Duration	Study Quality
Griffith, 1988[27] Location: USA Funding Source: Government	Inclusion Criteria: • non-progressive spinal cord injury • chronic urinary tract infection with urea-splitting organisms • serum creatinine < 3 mg/dL • acceptance of the logistical requirements of 3-month follow up visits for 2 years • acceptance of the double-blind investigational format. Exclusion Criteria: • progressive neuropathy • candidates for surgical lithotomy • nonfunctioning stone-containing kidneys • major coexistent medical problems; having social, economic and logistical problems that would hinder compliance and/or follow up	N=210 Age (yr): 49 Gender (Male %): 100 Race/Ethnicity (%): NR Spinal cord injury: 100% Weight (mean, kg): AHA 79.1, placebo 72.6 Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): 1.0 Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Stone type: Struvite 100% Past stone episodes: single NR, multiple NR Residual stones/ fragments: 88% by excretory urogram. Urine analysis: Hypercalciuria NR; hypocitraturia NR ; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder NR Blood analysis: Hyperuricemia NR Diet characteristics: NR	1. Acetohydroxamic acid 0.5-1.0 gm/d (n=121) 2. Placebo (n=89) Follow up period: up to 24 mos Study stated that no attempt was made to control antibiotic use during the study. Study withdrawals (%): 103 (49) Study withdrawals (%): • AHA 62%, placebo 31% • due to adverse events AHA 20%, placebo 5% (severe reactions) • due to loss to follow-up NR Assessment of compliance and adherence to treatment: Pill count (at least 80% of pills at previous visit), 79-91% in AHA and 84-94% in placebo group Setting (e.g., medicine, urology): NR Follow up biochemical measures collected:	1. Allocation Concealment: adequate 2. Blinding: double and radiologist who reviewed radiographs. Results reviewed by independent monitoring body. 3. Intention to Treat Analysis: No 4. Withdrawals/Dropouts adequately described: Yes *Quality of harms reporting:* 1. Harms predefined: No 2. Harms specified as ALL events collected: No 3. Number of participants that withdrew/lost to follow up adequately described: Yes 4. Total number of participants affected by harms specified for each study group: NR 5. Number for each type of harm event specified for each study group: NR

Appendix C. Table 5. Evidence table: Acetohydroxamic acid (AHA) trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/Duration	Study Quality
				(y/n): Yes	
Williams, 1984[28] Location: USA Funding Source: Government and non industry	Inclusion Criteria: • Documented struvite nephrolithiasis concomitant with infection with a urea-splitting organism • > 18 years of age • serum creatinine <3mg/dL • hematocrit > 25% • patients on the phosphate depleting Shor regimen were continued on it Exclusion Criteria: • participants unable to understand the protocol • pregnancy • lactation • oral contraceptive use • history of varicose veins, phlebitis or pulmonary embolism.	N=39 Age (yr): AHA 52, placebo 44 Gender (Male %): 17.9 Race/Ethnicity (%): NR BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): NR History of renal transplant (%): NR Urinary tract anatomic abnormality (%): AHA 20% and placebo 15.7% had supra vesical dversions (17.9% overall); AHA 5% and placebo 10% had neurogenic bladders (7.7% overall) Pregnancy: 0% History of CAD: NR History of DM: NR History of HTN: NR	Stone type: Struvite 100% Past stone episodes: multiple 100% Residual stones/ fragments: NR for all but 7 placebo patients had stones that doubled in area versus 0 for AHA patients (determined by X-ray). Urine analysis: Hypercalciuria NR; hypocitraturia NR ; hyperuricosuria NR; hyperoxaluria NR; mixed NR; no metabolic disorder NR Blood analysis: Hyperuricemia NR Diet characteristics: NR	1. Acetohydroxamic acid 15 mg/kg/d (n= 20) 2. Placebo (n=19) Other: Both groups treated with suppressive antibiotics throughout study. Follow up period: overall mean 18 (up to 30 mos), mean AHA 15.8, mean placebo 19.6 Study withdrawals (%): • overall 6 (15.3) • due to adverse events AHA 2 (10) • due to loss to follow-up NR Assessment of compliance and adherence to treatment: Assessed by pill counts and urine AHA screening; participants determined by either measure to be taking <50% of medication were withdrawn from the study. 16% of AHA group and 5% of placebo group excluded from 7 to 10 months analysis for noncompliance, but compliance not reported over full study duration.	1. Allocation Concealment: adequate 2. Blinding: double and radiologist who reviewed radiographs 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Harms predefined: No 2. Harms specified as ALL events collected: No 3. Number of participants that withdrew/lost to follow up adequately described: Yes 4. Total number of participants affected by harms specified for each study group: Yes 5. Number for each type of harm event specified for each study group: Yes

Appendix C. Table 5. Evidence table: Acetohydroxamic acid (AHA) trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics / Biochemistry	Intervention/Duration	Study Quality
				Setting (e.g., medicine, urology): NR Follow up biochemical measures collected: (y/n): NR	

Appendix C. Table 6. Evidence table: Magnesium trials for recurrent nephrolithiasis

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
Ettinger, 1988[12] Location: US Funding Source: Industry and non-industry	Inclusion Criteria: • recurrent calculous disease; • calculous composition exceeding 79% calcium oxalate; • 2 or more calculi within the previous 5 years and at least 1 calculus within the previous 2 years. Exclusion Criteria: • secondary causes for nephrolithiasis.	N=124 Age (yr): 47 Gender (Male %): 88 Race/Ethnicity (%): white 94 BMI, weight, or percent with obesity: NR Previous bariatric surgery (%): NR Chronic kidney disease (%): NR Serum creatinine (mg/dL): Estimated GFR (ml/min/1.73m^2): NR Solitary kidney (%): History of renal transplant (%): NR Urinary tract anatomic abnormality (%): NR Pregnancy: NR History of CAD: NR History of DM: NR History of HTN: NR	Stone type: calcium oxalate 100% (stones could be all CaOx or mix of CaOx + CaP) Past stone episodes: single 0%, multiple 100% Residual stones/ fragments: 47% on X-ray Urine analysis: Hypercalciuria 36%; hypocitraturia %; NR hyperuricosuria 37%; hyperoxaluria NR; mixed 23%; no metabolic disorder 50% Blood analysis: NR Diet characteristics: none stated	1. Magnesium hydroxide 650 mg/d (n=30) 2. Magnesium hydroxide 1300 mg/d (n=21) 3. Chlorthalidone 25 mg/d (n=19) 4. Chlorthalidone 50 mg/d (n=23) 5. Placebo (n=31) All groups to drink fluid for urine output of 2L/day; restrict salt, animal protein, and high oxalate foods; increase cereal fiber; avoid vitamin C; consume ≤2 dairy servings/day. Followup period: 36 mos Study withdrawals (%): • overall: ~32* (possibly 26) • due to adverse events: unclear, range was 3.2% (placebo) to 22.6% (Chlorthalidone 25 mg). None reported for Magnesium hydroxide 650 mg • due to loss to follow-up: 0 Assessment of compliance and adherence to treatment: Pill counts, no results reported Setting (e.g., medicine, urology): NR	1. Allocation Concealment: adequate (identical appearing drugs)) 2. Blinding: double, outcomes assessor 3. Intention to Treat Analysis: no 4. Withdrawals/Dropouts adequately described: yes *Quality of harms reporting:* 1. Adverse events predefined: no 2. Adverse events reported for all participants: yes 3. Number of participants with adverse events reported for each study group: no 4. Number of participants with each type of adverse event reported for each study group: no 5. Number of participants that withdrew/lost to followup adequately described: yes

Appendix C. Table 6. Evidence table: Magnesium trials for recurrent nephrolithiasis (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Baseline Stone Characteristics/ Biochemistry	Intervention/Duration	Study Quality
				Follow up biochemical measures collected: (y/n): yes * Approximate estimate based on the percentages provided in the text by each treatment arm. Actual number of subjects not reported (and it was difficult to calculate the number of patients withdrawing due to the discrepancies between the reported percentages and the numbers in each arm that were reported).	

Abbreviation: NR = not reported

Appendix C. Table 7. Individual study quality for diet trials

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	Withdrawals Described	Study Rating
Dussol 2008[1]	adequate	outcomes assessor	no	yes	Fair
Sarica 2006[2]	unclear*	none stated	yes	no dropouts	Fair
Borghi 2002[3]	adequate	outcomes assessor	yes	yes	Good
Di Silverio 2000[4]	unclear*	none stated	no	no dropouts	Fair
Kocvara 1999[5]	unclear*	none stated	no	no	Poor
Borghi 1996[6]	unclear*	none stated	no	no	Poor
Hiatt 1996[7]	unclear*	outcomes assessor	yes	yes	Fair
Shuster 1992[8]	unclear*	controls and outcomes assessor	yes	yes	Fair

*Methods of concealment not described/reported

Appendix C. Table 8. Individual study quality for pharmocological trials

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	Withdrawals/ Described	Study Rating
Thiazide trials (n=7)					
Fernández-Rodriguez 2006[9]	unclear*	none stated	yes	no dropouts	Fair
Ahlstrand 1995[10]	unclear	open-label	yes	yes	Fair
Borghi 1993[11]	unclear	open-label	no	yes	Fair
Ettinger 1988[12]	unclear**	double, outcomes assessor	no	yes	Fair
Ala-Opas 1987[13]	unclear*	none stated	yes	no dropouts	Fair
Laerum 1984[14]	unclear*	double	yes	yes	Fair
Scholz 1982[15]	unclear*	double	no	yes	Fair
Citrate trials (n=7)					
Lojanapiwat, 2011[16]	unclear*	none stated	no	yes	Fair
Fernández-Rodriguez 2006[9]	unclear*	none stated	yes	no dropouts	Fair
Soygur 2002[17]	unclear*	outcomes assessor	no	yes	Fair
Premgamone, 2001[18]	unclear*	outcomes assessor	no	yes	Fair
Ettinger 1997[19]	adequate	double, outcomes assessor	yes	yes	Good
Hofbauer 1994[20]	unclear*	none stated	no	yes	Fair
Barcelo 1993[21]	unclear*	double	no	yes	Fair
Allopurinol trials (n=5)					
Borghi 1993[11]	unclear	open-label	no	yes	Fair
Ettinger 1986 [22]	adequate	double, outcomes assessor	no	yes	Fair
Miano 1985[23]	unclear*	double	no†	unclear†	Fair
Robertson, 1985[24]	unclear*	none stated	no†	unclear†	Fair
Smith 1977[25]	unclear**	double	no	yes	Fair
Acetohydroxamic Acid (AHA) trials (n=3)					
Griffith 1991[26]	unclear*	double, outcomes assessor	yes	yes	Fair
Griffith 1988 [27]	adequate	double, outcomes assessor	no	yes	Fair
Williams 1984[28]	adequate	double, outcomes assessor	no	yes	Fair
Magnesium trials (n=1)					
Ettinger 1988[12]	unclear**	double, outcomes assessor	no	yes	Fair

*Methods of concealment not described/reported;

** Trial had inadequate sequence generation (assigned according to medical record number) which could have revealed assignment to investigators, but assignment may have been concealed from participants (because of identical drug and placebo appearance);

†Both studies reported preliminary results such that it was unclear whether any of randomized participants not included in analyses were dropouts.

Appendix D. Primary Stone Recurrence Outcomes Tables

Appendix D. Table 1. Primary stone recurrence outcomes for the diet trials

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Diet	Control or Diet B	Diet	Control or Diet B	Diet	Control or Diet B
Dussol 2008[1]	Composite: a) symptomatic - passage of stone or stone confirmed radio-logically based on colic or hematuria *or* b) silent- appearance of a new stone or a >50% increase in size of a previously present stone on radiological or ultrasound exams.	NR	NR	NR	NR	Month 24 Low animal protein diet 34.2% (12/35) High fiber diet 40.5% (17/42) P=NS* (all groups) Month 48** Low animal protein diet 47.8% (11/23) High fiber diet 63.0% (17/27) P=NS (all groups)	Month 24 Usual diet 34.2% (12/35) Month 48 47.8% (11/23)
Sarica 2006[2]	Radiographic: Plain abdominal X-ray (including renal tomography), kidney sonography or excretory urogram at regular intervals (3, 6, and 12 months after stone disintegration)	NR	NR	Forced fluid 8.3% (1/12)† P<0.05	No intervention 55.6% (5/9)†	NR	NR
Borghi 2002[3]	Composite: Passage of stone or stone identified by annual ultrasound and abdominal flat-plate examinations	NR	NR	NR	NR	Low calcium diet 38.3% (23/60) P=0.03	Low protein/ low sodium diet 20.0% (12/60)
Di Silverio 2000[4]	Radiographic: X-ray and abdominal echographic studies upon recruitment and thereafter every 6 months until the onset of recurrence.	NR	NR	Oligomineral water, calcium 15 mg/l 16.7% (32/192) P=0.13	Tap water, calcium 55-130 mg/l 22.9% (44/192)	NR	NR

Appendix D. Table 1. Primary stone recurrence outcomes for the diet trials (continued)

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Diet	Control or Diet B	Diet	Control or Diet B	Diet	Control or Diet B
Kocvara 1999[5]	Composite: radiography and ultrasonography (but over half of the stones were "asymptomatic") so symptomatic passage also	NR	NR	NR	NR	Tailored diet with evaluation 6.2% (7/113) P<0.01	General diet recommendations 19.1% (18/94)
Borghi 1996[6]	Composite: Passage of stone, renal colic, annual x-ray and ultrasound screening	NR	NR	NR	NR	Achieve daily urine volume >2 liters 12.1% (12/99) P=0.008	No intervention 27.0% (27/100)
Hiatt 1996[7]	Composite: Passage of stone, surgical removal or annual radiological detection of previously unrecognized stone	NR	NR	NR	NR	Low animal protein and high fiber diet 24.0% (12/50) P=0.004	Standard advice 4.1% (2/49)
Shuster 1992[8]	Symptomatic: Self reported stone episode, possibly confirmed by physician	Decrease soft drink consumption 33.7% (170/504) "failed" P=0.023	No intervention 40.6% (205/505) "failed"	NR	NR	NR	NR

*P values versus control unless noted; ** of the 39 patients with stone recurrence, 5 patients had silent recurrence; †These results are limited to the subset of subjects who were stone free after SWL. NS = not statistically significant

Abbreviation: NR = not reported

Appendix D. Table 2. Primary stone recurrence outcomes for thiazide trials

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)
Fernández-Rodriguez, 2006[9]	Composite: Passage or removal of any stone; radiologically detected new stone (plain x-ray every 6 months for 3 years).	NR	NR	NR	NR	HCTZ monotherapy 32% (16/50) P=0.02 vs. no treatment*,**; HCTZ + citrate 30% (15/50) P=0.83 vs. HCTZ monotherapy**	no treatment 56% (28/50)
Ahlstrand, 1995[10]	Composite: x-ray examinations annually and "at clinical events"	NR	NR	NR	NR	53% (9/17) P=0.04;	86% (19/22)
Borghi, 1993[11]	Composite: Passage or removal of any stone; radiologically detected new stone (x-ray abdominal flat plate with renal tomograms at 6 & 12 months, then annually through 3 years).	NR	NR	NR	NR	Indapamide *monotherapy* 15.8% (3/19)* P=0.09 vs. control Indapamide+ *allopurinol* 12.5% (3/24)* P=0.04 vs. control P=0.01 for combined Indapamide groups	42.8% (9/21)*

Appendix D. Table 2. Primary stone recurrence outcomes for thiazide trials (continued)

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)
Ettinger, 1988[12]	Composite: Passage of previously unrecognized stone >3 months after baseline; or radiologically detected new stone or enlargement in residual fragment (annual x-ray	NR	NR	NR	NR	chlorthalidone 25 mg/d 15.8% (3/19) P=0.06 vs. placebo P=0.39 vs. $MgOH_2$ 650 mg P=0.22 vs. $MgOH_2$ 1300 mg chlorthalidone 50 mg/d 13.0% (3/23); P=0.03 mg vs. placebo P=0.25 vs. $MgOH_2$ 650 mg P=0.13 vs. $MgOH_2$ 1300 mg P=0.007 for combined chlorthalidone groups vs. placebo	1. placebo 45.2% (14/31) 2. $MgOH_2$ 650 mg/d 26.7% (8/30) 3. $MgOH_2$ 1300 mg/d 33.3% (7/21)

Appendix D. Table 2. Primary stone recurrence outcomes for thiazide trials (continued)

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)
Ala-Opas, 1987[13]	Composite: Passage or removal of stone; or radiologically detected new stone (x-ray every 6 months).	NR	NR	NR	NR	HCTZ normocalciuric patients 28.6% (4/14) P=0.71†; hypercalciuric patients 14.3% (2/14) P=0.41† all patients 21.4% (6/28) P=0.62†	Control normocalciuric patients 22.2% (6/27) hypercalciuric patients 33.3% (6/18) all patients 26.7% (12/45)
Laerum, 1984[14]	Composite: Passage of new stone; or radiologically detected new stone (annual plain abdominal x-ray plus pyelography and tomography in ambiguous cases).	NR	NR	NR	NR	HCTZ + KCl 21.7% (5/23)** P=0.05	Placebo 48.0% (12/25)
Scholz, 1982[15]	Symptomatic: Passage of new stone.	HCTZ 24.0% (6/25) P=1.0†	Placebo 23.1% (6/26)	NR	NR	NR	NR

***** n and/or N were calculated from data presented in the manuscript; **P values versus control unless noted; †P-value calculated from data presented in the manuscript
Abbreviations: HCTZ = hydrochlorothiazide; HCL = hydrochloride; K = potassium; $MgOH_2$ = magnesium hydroxide; Na phos = sodium phosphate; NR = not reported; NS = not significant

Appendix D. Table 3. Primary stone recurrence outcomes for citrate trials

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Citrate	Control(s)	Citrate	Control(s)	Citrate	Control(s)
Lojanapiwat, 2011[16]	Composite: Spontaneous stone passage and/or radiologically detected new stone (KUB x-ray at 12 months).	NR	NR	NR	NR	stone free group 8% (1/13); P=0.08	stone free group 42% (11/26)
Fernández-Rodriguez, 2006[9]	Composite: Passage or removal of any stone; radiologically detected new stone (x-ray every 6 months for 3 years).	NR	NR	NR	NR	Citrate + HCTZ 30% (15/50) P= 0.01 vs. no treatment*; P= 0.83 vs. HCTZ**	1. no treatment 56% (28/50) 2. HCTZ 32% (16/50)
Soygur, 2002[17]	Composite: Passage of previously unrecognized stone; or any radiologically detected new stone or >2mm increase in residual fragment (ultrasound + plain abdominal x-ray at 1 year post-baseline).	NR	NR	NR	NR	stone free group 0% (0/28); P=0.004	stone free group 28.6% (8/28)
Premgamone, 2001[18]	Radiologic: Percentage reduction in stone diameter per year (ultrasound every 5-7 weeks).	NR	NR	NR	NR	NR	NR
Ettinger, 1997[19]	Composite: Passage of previously unrecognized stone >1m after baseline; or radio-logically detected new stone or enlargement in residual fragment (annual x-ray).	NR	NR	NR	NR	12.9% (4/31)†† P=0.001	63.6% (21/33)††

Appendix D. Table 3. Primary stone recurrence outcomes for citrate trials (continued)

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Citrate	Control(s)	Citrate	Control(s)	Citrate	Control(s)
Hofbauer, 1994[20]	Radiologic: Detection by ultrasound + x-ray every 6 months for 3 years.	NR	NR	68.8% (11/16)	72.7% (16/22)	NR	NR
Barcelo, 1993[21]	Composite: Passage of previously unrecognized stone; new stone requiring SWL or surgery; or radiologically detected new stone (every 6 months, x-ray for 3 years).	NR	NR	NR	NR	27.8% (5/18) P=0.003	80% (16/20)

*P values versus control unless noted; ** P-value calculated from data presented in the manuscript**;** † Recurrence for subjects with residual stones was 55.6% (10/18) and 87.5% (14/16) for the citrate and control groups, respectively (P=0.06); †† n and/or N were calculated from data presented in the manuscript
Abbreviations: HCTZ = hydrochlorothiazide; K = potassium; Na = sodium; NR = not reported

Appendix D. Table 4. Primary stone recurrence outcomes for allopurinol trials

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Allopurinol	Control(s)	Allopurinol	Control(s)	Allopurinol	Control(s)
Borghi, 1993[11]	Composite: Passage or removal of any stone; radiologically detected new stone (x-ray at 6 & 12 months, then annually through 3 years).	NR	NR	NR	NR	+ *indapamide* 12.5% (3/24)* P<0.02 vs. control**; P=0.76 vs. indapamide	1. control 42.8% (9/21)* 2. indapamide 15.8% (3/19)*
Ettinger, 1986[22]	Composite (Beginning 6 months post-baseline): Passage of new stone; or radiologically detected new stone or enlargement of pre-existing stone (annual x-ray).	10.3% (3/29)	29.0% (9/31)	6.9% (2/29)	6.5% (2/31)	17.2% (5/29)†	35.5% (11/31)†
Miano, 1985[23]	Symptomatic: Passage of new stone.	NR	NR	NR	NR	NR	NR
Robertson, 1985[24]	Symptomatic: Passage or removal of any stone.	NR	NR	NR	NR	NR	NR
Smith, 1977[25]	Composite: Passage of new stone; or radiologically detected new stone (study did not report type or frequency of imaging modality utilized).	NR	NR	NR	NR	42.9% (21/49) P=0.01†	69.8% (30/43)

***** n and/or N were calculated from data presented in the manuscript;
**P values versus control unless noted;
†Results indicated here for composite of new symptomatic stones or radiographically detected stones, excluding events reported in the manuscript for stone growth.
Abbreviations: HCTZ = hydrochlorothiazide; K = potassium; Mg = magnesium; Na phos. = sodium phosphate; NR = not reported; NS = not significant

Appendix D. Table 5. Primary stone recurrence outcomes for the acetohydroxamic acid (AHA) trials

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		AHA	Control(s)	AHA	Control(s)	AHA	Control(s)
Griffith, 1991[26]	Radiologic: X-ray. Stone growth (>25% increase in area) or new stone formation detected by x-ray at 3 and 12m, then annually)	NR	NR	0 (0/3) who were stone free at baseline p= NS*	28 (2/7) who were stone free at baseline	NR	NR
Griffith, 1988[27]	Radiologic: X-ray. Definite (>50% increase in area) or possible (10-50% increase in area) stone growth or new stone formation detected by x-ray every 3 months	NR	NR	16.6 (2/12) who were stone free at baseline p= NS*	15.3 (2/13) who were stone free at baseline	NR	NR
Williams, 1984[28]	Composite: Radiologically detected new stone or stone growth (>100% increase in area) on x-ray every 3 months or surgical intervention for stone obstruction or infection	NR	NR	0.0 (0/18) among all patients; no separate results reported by baseline residual stone status	NR	NR	NR

* NS = not significant

Appendix D. Table 6. Primary stone recurrence outcomes for magnesium trials

Study	Definition of Stone Recurrence	Symptomatic Stone Recurrence % (n/N)		Radiographically Detected Stone Recurrence % (n/N)		Composite Stone Recurrence % (n/N)	
		Magnesium	Control(s)	Magnesium	Control(s)	Magnesium	Control(s)
Ettinger, 1988[12]	Composite: Passage of previously unrecognized stone >3 months after baseline; or radiologically detected new stone or enlargement in residual fragment (annual x-ray)	NR	NR	NR	NR	650 mg/d 26.7% (8/30) P=0.15 vs. placebo; P=0.39 vs. chlorthalidone 25 mg; P=0.25 vs. chlorthalidone 50 mg 1300 mg/d 33.3% (7/21) P=0.41 vs. placebo; P=0.22 chlorthalidone 25 mg; P=0.13 vs. chlorthalidone 50 mg P=0.14 for combined groups vs. placebo	1. placebo 45.2% (14/31) 2. chlorthalidone 25 mg 15.8% (3/19) 3. chlorthalidone 50 mg 13.0% (3/23);

Abbreviation: NR = not reported

Appendix E. Secondary Stone Recurrence Outcomes Tables

Appendix E. Table 1a. Secondary stone recurrence outcomes for diet trials

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Residual or Stone Fragment Clearance	
		Diet	Control or Diet B	Diet	Control or Diet B	Diet	Control or Diet B
Dussol 2008[1]	Composite: a) symptomatic - passage of stone or stone confirmed radio-logically based on colic or hematuria *or* b) silent- appearance of a new stone or a >50% increase in size of a previously present stone on radiological or ultrasound exams.	NR	NR	3 patients had an increase of >50% (silent recurrence) but the authors did not report to which study arms the patients were randomized.		NR	NR
Sarica 2006[2]	Radiographic: Plain abdominal X-ray (including renal tomography), kidney sonography or excretory urogram at regular intervals (3, 6, and 12 months after stone disintegration)	NR	NR	NR	NR		
Borghi 2002[3]	Composite: Passage of stone or stone identified by annual ultrasound and abdominal flat-plate examinations	NR	NR	NR	NR	NR	NR
Di Silverio 2000[4]	Radiographic: X-ray and abdominal echographic studies upon recruitment and thereafter every 6 months until the onset of recurrence.	NR	NR	NR	NR	NR	NR
Kocvara 1999[5]	Composite: radiography and ultrasonography (but over half of the stones were "asymptomatic") so symptomatic passage also	NR	NR	NR	NR	NR	NR
Borghi 1996[6]	Composite: Passage of stone, renal colic, annual x-ray and ultrasound screening	Mean time to 1st recurrence (months) 38.7 (SD 13.2) P=0.016	Mean time to 1st recurrence (months) 25.1 (SD 16.4)	NR	NR	NR	NR
Hiatt 1996[7]	Composite: Passage of stone, surgical removal or annual radiological detection of previously unrecognized stone	7.1 per 100 person-years P=0.006	1.2 per 100 person-years	NR	NR	NR	NR
Shuster 1992[8]	Symptomatic: Self reported stone episode, possibly confirmed by physician	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 1b. Health outcomes for diet trials

Study	Pain % (n/N)		Urinary Tract Obstruction with Acute Renal Failure % (n/N)		Infection % (n/N)		Procedure-Related Morbidity % (n/N)	
	Diet	Control or Diet B	Diet	Control or Diet B	Diet	Control or Diet B	Diet	Control or Diet B
Dussol 2008[1]	NR	NR	NR	NR	NR	NR	NR	NR
Sarica 2006[2]	NR	NR	NR	NR	NR	NR	NR	NR
Borghi 2002[3]	NR	NR	NR	NR	NR	NR	NR	NR
Di Silverio 2000[4]	NR	NR	NR	NR	NR	NR	NR	NR
Kocvara 1999[5]	NR	NR	NR	NR	NR	NR	NR	NR
Borghi 1996[6]	NR	NR	NR	NR	NR	NR	NR	NR
Hiatt 1996[7]	NR	NR	NR	NR	NR	NR	NR	NR
Shuster 1992[8]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 1c. Health outcomes for diet trials

Study	Emergency Room Treatment Related to Stone Recurrence (e.g., renal colic) % (n/N)		Hospitalizations Related to Stone Recurrence (e.g., renal colic) % (n/N)		Quality of Life	
	Diet	Control or Diet B	Diet	Control or Diet B	Diet	Control or Diet B
Dussol 2008[1]	NR	NR	NR	NR	NR	NR
Sarica 2006[2]	NR	NR	NR	NR	NR	NR
Borghi 2002[3]	NR	NR	NR	NR	NR	NR
Di Silverio 2000[4]	NR	NR	NR	NR	NR	NR
Kocvara 1999[5]	NR	NR	NR	NR	NR	NR
Borghi 1996[6]	NR	NR	NR	NR	NR	NR
Hiatt 1996[7]	NR	NR	NR	NR	NR	NR
Shuster 1992[8]	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 2a. Secondary stone recurrence outcomes for thiazide trials

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)
Fernández-Rodriguez, 2006[9]	Composite: Passage or removal of any stone; radiologically detected new stone (plain x-ray every 6 months for 3 years).	NR	NR	NR	NR	NR	NR
Ahlstrand, 1995[10]	Composite: x-ray examinations annually and "at clinical events"	NR	NR	NR	NR	NR	NR
Borghi, 1993[11]	Composite: Passage or removal of any stone; radiologically detected new stone (x-ray abdominal falte plate with renal tomograms at 6 & 12 months, then annually through 3 years).	NR	NR	NR	NR	NR	NR
Ettinger, 1988[12]	Composite: Passage of previously unrecognized stone >3 months after baseline; or radiologically detected new stone or enlargement in residual fragment (annual x-ray)	NR	NR	NR	NR	NR	NR

Appendix E. Table 2a. Secondary stone recurrence outcomes for thiazide trials (continued)

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)
Ala-Opas, 1987[13]	Composite: Passage or removal of stone; or radiologically detected new stone (x-ray every 6 months).	*Normocalciuric patients* 0.18 stones per patient year; reduction from pretreatment of 0.41 stones per patient year P<0.0005 versus pretreatment *Hypercalciuric patients* 0.21 stones per patient year; reduction from pretreatment of 0.30 stones per patient year P<0.10 versus pretreatment	*Normocalciuric patients* 0.17 stones per patient year; reduction from pretreatment of 0.30 stones per patient year P<0.0005 versus pretreatment *Hypercalciuric patients* 0.25 stones per patient year; reduction from pretreatment of 0.54 stones per patient year P<0.05 versus pretreatment	NR	NR	NR	NR
Laerum, 1984[14]	Composite: Passage of new stone; or radiologically detected new stone (annual plain abdominal x-ray plus pyelography and tomography in ambiguous cases).	NR	NR	NR	NR	NR	NR
Scholz, 1982[15]	Symptomatic: Passage of new stone.	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 2b. Health outcomes for thiazide trials

Study	Pain % (n/N)		Urinary Tract Obstruction with Acute Renal Failure % (n/N)		Infection % (n/N)		Procedure-related Morbidity % (n/N)	
	Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)
Fernández-Rodriguez, 2006[9]	NR	NR	NR	NR	NR	NR	NR	NR
Ahlstrand, 1995[10]	NR	NR	NR	NR	NR	NR	NR	NR
Borghi, 1993[11]	NR	NR	NR	NR	NR	NR	NR	NR
Ettinger, 1988[12]	NR	NR	NR	NR	NR	NR	NR	NR
Ala-Opas, 1987[13]	NR	NR	NR	NR	NR	NR	NR	NR
Laerum, 1984[14]	NR	NR	NR	NR	NR	NR	NR	NR
Scholz, 1982[15]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 2c. Health outcomes for thiazide trials

Study	Emergency Room Treatment Related to Stone Recurrence (e.g., renal colic) % (n/N)		Hospitalizations Related to Stone Recurrence (e.g., renal colic) % (n/N)		Quality of Life	
	Thiazide	Control(s)	Thiazide	Control(s)	Thiazide	Control(s)
Fernández-Rodriguez, 2006[9]	NR	NR	NR	NR	NR	NR
Borghi, 1993[11]	NR	NR	NR	NR	NR	NR
Ettinger, 1988[12]	NR	NR	NR	NR	NR	NR
Ala-Opas, 1987[13]	NR	NR	NR	NR	NR	NR
Laerum, 1984[14]	NR	NR	NR	NR	NR	NR
Scholz, 1982[15]	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 3a. Secondary stone recurrence outcomes for citrate trials

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		Citrate	Control(s)	Citrate	Control(s)	Citrate	Control(s)
Lojanapiwat, 2011[16]	Composite: Spontaneous stone passage and/or radiologically detected new stone (KUB x-ray at 12 months).	NR	NR	NR	NR	NR	NR
Fernández-Rodriguez, 2006[9]	Composite: Passage or removal of any stone; radiologically detected new stone (x-ray every 6 months for 3 years).	NR	NR	NR	NR	NR	NR
Soygur, 2002[17]	Composite: Passage of previously unrecognized stone; or any radiologically detected new stone or >2mm increase in residual fragment (ultrasound + plain abdominal x-ray at 1 year post-baseline).	NR	NR	NR	NR	NR	NR
Premgamone, 2001[18]	Radiologic: Percentage reduction in stone diameter per year (ultrasound every 5-7 weeks).	NR	NR	38.5% diameter reduction per year at 18 months P*=NS	40.9% diameter reduction per year at 18 months	NR	NR
Ettinger, 1997[19]	Composite: Passage of previously unrecognized stone >1m after baseline; or radio-logically detected new stone or enlargement in residual fragment (annual x-ray).	NR	NR	NR	NR	NR	NR

Appendix E. Table 3a. Secondary stone recurrence outcomes for citrate trials (continued)

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		Citrate	Control(s)	Citrate	Control(s)	Citrate	Control(s)
Hofbauer, 1994[20]	Radiologic: Detection by ultrasound + x-ray every 6 months for 3 years.	0.7 stones per patient year P=0.65*	0.9 stones per patient year	NR	NR	NR	NR
Barcelo, 1993[21]	Composite: Passage of previously unrecognized stone; new stone requiring SWL or surgery; or radiologically detected new stone (every 6 months, x-ray for 3 years).	0.1 stones per patient year (p<0.001)	1.1 stones per patient year	NR	NR	NR	NR

*P versus control

Abbreviations: HCTZ = hydrochlorothiazide; NR = not reported; NS = not significant

Appendix E. Table 3b. Health outcomes for the citrate trials

Study	Pain % (n/N)		Urinary Tract Infection with Acute Renal Failure % (n/N)		Infection % (n/N)		Procedure-related Morbidity % (n/N)	
	Citrate	Control(s)	Citrate	Control(s)	Citrate	Control(s)	Citrate	Control(s)
Lojanapiwat, 2011 [16]	NR	NR	NR	NR	NR	NR	NR	NR
Fernández-Rodriguez, 2006[9]	NR	NR	NR	NR	NR	NR	NR	NR
Soygur, 2002[17]	NR	NR	NR	NR	NR	NR	NR	NR
Premgamone, 2001[18]	NR	NR	NR	NR	NR	NR	NR	NR
Ettinger, 1997[19]	NR	NR	NR	NR	NR	NR	NR	NR
Hofbauer, 1994[20]	9 of 16 (56%) subjects reported spontaneous stone elimination to be painless P=0.001*	1 of 22 (4%) subjects reported spontaneous stone elimination to be painless	NR	NR	NR	NR	NR	NR
Barcelo, 1993[21]	NR	NR	NR	NR	NR	NR	NR	NR

*versus control

Abbreviation: NR = not reported

Appendix E. Table 3c. Health outcomes for citrate trials

Study	Emergency Treatment Related to Stone Recurrence (e.g., renal colic) % (n/N)		Hospitalizations Related to Stone Recurrence (e.g., renal colic) % (n/N)		Quality of Life	
	Citrate	Control(s)	Citrate	Control(s)	Citrate	Control(s)
Lojanapiwat, 2011[16]	NR	NR	NR	NR	NR	NR
Fernández-Rodriguez, 2006[9]	NR	NR	NR	NR	NR	NR
Soygur, 2002[17]	NR	NR	NR	NR	NR	NR
Premgamone, 2001[18]	NR	NR	NR	NR	NR	NR
Ettinger, 1997[19]	NR	NR	NR	NR	NR	NR
Hofbauer, 1994[20]	NR	NR	NR	NR	NR	NR
Barcelo, 1993[21]	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 4a. Secondary Stone recurrence outcomes for allopurinol trials

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		Allopurinol	Control(s)	Allopurinol	Control(s)	Allopurinol	Control(s)
Borghi, 1993[11]	Composite: Passage or removal of any stone; radiologically detected new stone (x-ray at 6 & 12 months, then annually through 3 years).	NR	NR	NR	NR	NR	NR
Ettinger, 1986[22]	Composite (Beginning 6 months post-baseline): Passage of new stone; or radiologically detected new stone or enlargement of pre-existing stone (annual x-ray).	*0.12 stones per patient year; *Mean time to first recurrence 33.3 months p not reported for stones per patient year; p for time to recurrence <0.05 vs. control	*0.26 stones per patient year; *Mean time to first recurrence 27.4 months	13.8% (4/29)	22.6% (7/31)	NR	NR
Miano, 1985[23]	Symptomatic: Passage of new stone.	0.96 stones per patient year; Mean percent reduction in passed stones 72.2% compared to before treatment p not reported for stones per patient year; p =NS for percent reduction in passed stones vs. placebo	0.66 stones per patient year; Mean percent reduction in passed stones 63.2%	NR	NR	NR	NR

Appendix E. Table 4a. Secondary Stone recurrence outcomes for allopurinol trials (continued)

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		Allopurinol	Control(s)	Allopurinol	Control(s)	Allopurinol	Control(s)
Robertson, 1985[24]	Symptomatic: Passage or removal of any stone.	0.54 stones per patient year no p values provided	0.58 stones per patient year	NR	NR	NR	NR
Smith, 1977[25]	Composite: Passage of new stone; or radiologically detected new stone (study did not report type or frequency of imaging modality utilized	NR	NR	NR	NR	NR	NR

*Rate reported only for composite stone recurrence outcome that includes symptomatic and radiographic recurrences as well as incidences of stone growth.
Abbreviations: HCTZ = hydrochlorothiazide; NR = not reported; NS = not significant

Appendix E. Table 4b. Health outcomes for the allopurinol trials

Study	Pain % (n/N)		Urinary Tract Obstruction with Acute Renal Failure % (n/N)		Infection % (n/N)		Procedure-related Morbidity % (n/N)	
	Allopurinol	Control(s)	Allopurinol	Control(s)	Allopurinol	Control(s)	Allopurinol	Control(s)
Borghi, 1993[11]	NR	NR	NR	NR	NR	NR	NR	NR
Ettinger, 1986[22]	NR	NR	NR	NR	NR	NR	NR	NR
Miano, 1985[23]	NR	NR	NR	NR	NR	NR	NR	NR
Robertson, 1985[24]	NR	NR	NR	NR	NR	NR	NR	NR
Smith, 1977[25]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 4c. Health outcomes for allopurinol trials

Study	Emergency Room Treatment Related to Stone Recurrence (e.g., renal colic) % (n/N)		Hospitalizations Related to Stone Recurrence (e.g., renal colic) % (n/N)		Quality of Life		Other? % (n/N)	
	Allopurinol	Control(s)	Allopurinol	Control(s)	Allopurinol	Control(s)	Allopurinol	Control(s)
Borghi, 1993[11]	NR	NR	NR	NR	NR	NR	NR	NR
Ettinger, 1986[22]	NR	NR	NR	NR	NR	NR	NR	NR
Miano, 1985[23]	NR	NR	NR	NR	NR	NR	NR	NR
Robertson, 1985[24]	NR	NR	NR	NR	NR	NR	NR	NR
Smith, 1977[25]	NR	NR	NR	2.9 (2/67)	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 5a. Secondary stone recurrence outcomes for the acetohydroxamic acid trials

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		AHA	Control(s)	AHA	Control(s)	AHA	Control(s)
Griffith, 1991[26]	Radiologic: X-ray. Stone growth (>25% increase in area) or new stone formation detected by abdominal radiographs at 3 and 12m, then annually)	NR	NR	19.0% (8/42) stone growth* P < 0.05	50.0% (21/42) stone growth*	NR	NR
Griffith, 1988[27]	Radiologic: X-ray. Definite (>50% increase in area) or possible (10-50% increase in area) stone growth or new stone formation detected by abdominal radiographs every 3 months	NR	NR	33.3% (14/42) definite or possible stone growth at 1 yr* p=0.017 41.7% (10/24) definite or possible stone growth at 2 yrs* p=0.26	60.5% (26/43) definite or possible stone growth at 1 yr* 60.0% (21/35) definite or possible stone growth at 2 yrs*	2.7 (3/109) at 1yr 3.7 (4/106) at 2yrs P=NS at both time intervals	3.9 (3/76) at 1yr 1.7 (1/75) at 2yrs
Williams, 1984[28]	Composite: Radiologically detected new stone or stone growth (>100% increase in area by planimetry) on x-ray every 3 months or surgical intervention for stone obstruction or infection	NR	NR	0% (0/18) stone area doubling† P=0.008	39% (7/19) stone area doubling†	NR	NR

*Study reported these results for subset of participants with residual stones at baseline
†Study reported results for all participants, without providing separate results for participants with residual stones at baseline.
Abbreviations: NR = not reported; NS = not significant

Appendix E. Table 5b. Health outcomes for acetohydroxamic acid trials

Study	Pain % (n/N)		Urinary Tract Obstruction with Acute Renal Failure % (n/N)		Infection % (n/N)		Procedure-related Morbidity % (n/N)	
	AHA	Control	AHA	Control	AHA	Control	AHA	Control
Griffith, 1991[26]	NR	NR	NR	NR	NR	NR	NR	NR
Griffith, 1988[27]	NR	NR	NR	NR	NR	NR	NR	NR
Williams, 1984[28]	NR	NR	NR*	NR*	All patients had UTI at start of the study	All patients had UTI at start of the study	NR	NR

*Two patients in placebo group and none in the AHA group were stated to have undergone surgery for obstruction or infection.
Abbreviations: NR = not reported; UTI = urinary tract infection

Appendix E. Table 5c. Health outcomes for the acetohydroxamic acid trials

Study	Emergency Room Treatment Related to Stone Recurrence (e.g., renal colic) % (n/N)		Hospitalizations Related to Stone Recurrence (e.g., renal colic) % (n/N)		Quality of Life		Other? % (n/N)	
	AHA	Control	AHA	Control	AHA	Control	AHA	Control
Griffith, 1991[26]	NR	NR	NR	NR	NR	NR	NR	NR
Griffith, 1988[27]	NR	NR	NR	NR	NR	NR	NR	NR
Williams, 1984[28]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 6a. Secondary stone recurrence outcomes for the magnesium trials

Study	Definition of Stone Recurrence	Stone Recurrence Rate		Change in Stone Size		Stone Fragment Clearance	
		Magnesium	Control(s)	Magnesium	Control(s)	Magnesium	Control(s)
Ettinger, 1988[12]	Composite: Passage of previously unrecognized stone >3 months after baseline; or radiologically detected new stone or enlargement in residual fragment (annual x-ray)	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 6b. Health outcomes for the magnesium trials

Study	Pain % (n/N)		Urinary Tract Obstruction with Acute Renal Failure % (n/N)		Infection % (n/N)		Procedure-related Morbidity % (n/N)	
	Magnesium	Control(s)	Magnesium	Control(s)	Magnesium	Control(s)	Magnesium	Control(s)
Ettinger, 1988[12]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix E. Table 6c. Health outcomes for the magnesium trials

Study	Emergency Room Treatment Related to Stone Recurrence (e.g., renal colic) % (n/N)		Hospitalizations Related to Stone Recurrence (e.g., renal colic) % (n/N)		Quality of Life		Other? % (n/N)	
	Magnesium	Control(s)	Magnesium	Control(s)	Magnesium	Control(s)	Magnesium	Control(s)
Ettinger, 1988[12]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviation: NR = not reported

Appendix F. Baseline Characteristics Summary Tables

Appendix F. Table 1. Summary of study baseline characteristics for diet studies

Characteristic	Mean (range) *Unless Otherwise Noted*	Number of Trials Reporting
Total number of patients evaluated	2270 (45 to 1009)	8
Study withdrawals, % of patients	12 (0 to 58)	8
Age of subjects, years	42 (32 to 45)	7 [a,b,c,d,f,g,h]
Gender, male, % of patients	80 (46 to 100)	8
Race/ethnicity, white, % of patients	77	1 [g]
Weight, pounds	157.3 (152 to 171)	3 [a,c,f]
Body mass index, kg/m2	24.5 (24 to 25.5)	2 [a,g]
Creatinine, mg/dL	1.0 (1.0 to 1.1)	2 [a,c]
Creatinine clearance	88 ml/min/1.73m^2 to 126 ml/min	2 [a,c]
Stone type, calcium oxalate stones, % of patients (n/N)	20 (460/2270)	4 [b,c,f,g]*
Stone type, "mixed calcium or other stones," % of patients (n/N)	80 (1810/2270)	4 [a,d,e,h]
Multiple past stones, % of patients (n/N)	54 (1140/2095)	3 [c,d,h]**
Single past stone, % of patients (n/N)	46 (955/2095)	5 [b,e,f,g,h] †
Residual stones at baseline, % of patients	21 [e], 4 trials with 0 [c,d,f,g]	
Hypercalciuria at baseline, % of patients	18 [g], 38 [a], 100 [c], 1 trial with 0 [b], 1 trial with 67 reported only for intervention group [e]	
Hypocitraturia at baseline, % of patients	1 trial with 19 reported only for intervention group [e]	
Hyperuricosuria at baseline, % of patients	1 trial with 27 reported only for intervention group [e], 1 trial with 0 [b]	
Hyperoxaluria at baseline, % of patients	18 [c], 1 trial with 18 reported only for intervention group [e], 2 trials with 0 [a,b]	
Hypomagnesuria at baseline, % of patients	9	1 trial reported only intervention group [e]
Mixed at baseline, % of patients	2 trials with 0 [c,d]	
No metabolic disorder at baseline (% of patients)	100 [b], 4 trials with 0 [a,c,e,g]	
Randomized to low animal protein diet, % of patients (n/N)	2 (55/2235††)	1 [a]
Randomized to high fiber diet, % of patients (n/N)	3 (60/2235)	1 [a]
Randomized to low animal protein/high fiber diet, % of patients (n/N)	2 (50/2235)	1 [g]
Randomized to low protein/low sodium diet, % of patients (n/N)	3 (60/2235)	1 [c]
Randomized to low calcium diet, % of patients (n/N)	3 (60/2235)	1 [c]
Randomized to "tailored" diet, % of patients (n/N)	5 (113/2235)	1 [e]
Randomized to increased fluid or urine output, % of patients (n/N)	23 (506/2235)	3 [b,d,f]
Randomized to decreased soft drink consumption, % of patients (n/N)	22 (504/2235)	1 [h]
Randomized to no treatment/usual care, % of patients (n/N)	37 (827/2235)	6 [a,b,e,f,g,h]
Studies conducted in the US, % of patients (n/N)	49 (1108/2270)	2 [g,h]
Studies conducted in Europe, % of patients (n/N)	51 (1162/2270)	6 [a,b,c,d,e,f]
Mean study duration (months)	39 (19 to 60)	7 [a,c,d,e,f,g,h]

* All trials 100%; ** 2 trials 100% (Borghi 2002,[3] Di Silverio 2000[4]); † 4 trials 100% (Sarica 2006,[2] Kocvara 1999,[5] Borghi 1996,[6] Hiatt 1996[7]). †† The denominator for diet allocation includes completers only from Kocvara 1999,[5] number randomized to each arm at baseline not reported. Therefore, there are 207 subjects versus 242 randomized.

[a]Dussol 2008;[1] [b]Sarica 2006;[2] [c] Borghi 2002;[3] [d] Di Silverio 2000;[4] [e] Kocvara 1999;[5] [f] Borghi 1996;[6] [g] Hiatt 1996;[7] [h] Shuster 1992[8]

Appendix F. Table 2. Summary of baseline characteristics for thiazide studies

Characteristic	Mean (range)‡ *Unless Otherwise Noted*	Trials Reporting
Total number of patients evaluated	564 (41 to 150)	7
Study withdrawals, % of patients	12* (0 to 46)	7
Study withdrawals due to adverse events, % of patients	2** (0 to 12)	7
Age of subjects, years	45 (35 to 48)	6 [b,c,d,e,f,g]
Gender, male, % of patients	80 (61 to 88)	6 [b,c,d,e,f,g]
Race/ethnicity, white, % of patients	94	1 [d]
Stone type, calcium oxalate stones, % of patients (n/N)	69† (390/564)	4 [a,b,c,d,]
Stone type, "calcium stones," % of patients (n/N)	31 (174/564)	3 [e,f,g]
Multiple past stones, % of patients (n/N)	100 (564/564)	6
Single past stone, % of patients (n/N)	0 (0/564)	-
Residual stones at baseline, % of patients	0% [c], 47% [d]	2
Hypercalciuria at baseline, % of patients	47 (12 to 100)	7
Hypocitraturia at baseline, % of patients	7 (0 to 15)	4 [a,b,c,e]
Hyperuricosuria at baseline, % of patients	12 (0 to 37)	6 [a,b,c,d,e,f]
Hyperoxaluria at baseline, % of patients	11 (0 to 100)	6 [a,b,c,d,e,g]
Hypomagnesuria at baseline, % of patients	10	1 [b]
Mixed at baseline, % of patients	11 (0 to 23)	5 [a,b,c,d,e]
No metabolic disorder at baseline (% of patients)	29 (0 to 56)	6 [a,b,c,d,e,g]
Studies evaluating HCTZ, % of patients (n/N)	65 (365/564)	5 [a,b,e,f,g]
Studies evaluating chlorthalidone, % of patients (n/N)	22 (124/564)	1 [d]
Studies evaluating indapamide, % of patients (n/N)	13 (75/564)	1 [c]
Studies conducted in the US, % of patients (n/N)	22 (124/564)	1 [d]
Studies conducted in Europe, % of patients (n/N)	78 (440/564)	6 [a,b,c,e,f,g]
Mean study duration (months)	34 (12 to 48)	7

*Unclear in the Ettinger 1988[12] trial, possibly 26% overall. **overall due to adverse events for all study groups unclear in the Ettinger 1988[12] trial, the range was 3.2% for placebo up to 22.6% for chlorthalidone 25 mg. None reported for magnesium hydroxide 650 mg. †Two trials (Barcelo[21]) reported either calcium oxalate or a mixture of calcium oxalate and calcium phosphate stones. ‡Data reported in this table is from trials comparing thiazide vs. placebo/control as well as trials comparing thiazide + second active therapy vs. control.

HCTZ = hydrochlorthiazide [a]Fernandez-Rodriguez 2006;[9] [b]Ahlstrand 1995;[10] [c] Borghi 1993;[11] [d] Ettinger 1988;[12e] Ala-Opas 1987;[13] [f] Laerum 1984;[14g] Scholz 1982[15]

Appendix F. Table 3. Summary of baseline characteristics for citrate studies

Characteristic	Mean (range) *Unless Otherwise Noted***	Trials Reporting
Total number of patients evaluated	559 (48 to 150)	7
Study withdrawals, % of patients	15 (0 to 36)	7
Study withdrawals due to adverse events, % of patients	4 (0 to 10)	7
Age of subjects, years	47 (42 to 55)	5[b,d,e,f,g]
Gender, male, % of patients	63 (44 to 78)	6[b,c,d,e,f,g]
Race/ethnicity, white, % of patients	NR	-
Stone type, calcium oxalate stones, % of patients (n/N)	100* (431/431)	5 [a,b,d,e,f]of 5 report stone type
Multiple past stones, % of patients (n/N)	74 (321/431)	4[a,d,e,f]of 5 report stone history
Single past stone, % of patients (n/N)	26 (110/431)	1[b]of 5 report stone history
Residual stones at baseline, % of patients	61 (38 to 100)	3[b,c,d]
Hypercalciuria at baseline, % of patients	24 (0 to 44)	5[a,b,e,f,g]
Hypocitraturia at baseline, % of patients	22 (0 to 69)	5[a,b,e,f,g]
Hyperuricosuria at baseline, % of patients	7 (0 to 18)	4[a,b,f,g]
Hyperoxaluria at baseline, % of patients	6 (0 to 18)	3[a,f,g]
Mixed at baseline, % of patients	12 (0 to 16)	2[a,f]
No metabolic disorder at baseline, % of patients	49 (29 to 100)	2[a,f]
Studies evaluating potassium (K) citrate, % of patients (n/N)	57 (317/559)	3[a,b,f]
Studies evaluating sodium/K citrate, % of patients (n/N)	32 (178/559)	2[c,e]
Studies evaluating magnesium/K citrate, % of patients (n/N)	11 (64/559)	1[d]
Studies conducted in the US, % of patients (n/N)	11 (64/559)	1[d]
Studies conducted in Europe, % of patients (n/N)	66 (367/559)	4 [a,b,e,f]
Studies conducted in Other, % of patients (n/N)	23 (128/559)	2[c,g]
Mean study duration (months)	26 (12 to 37)	7

*One trial (Barcelo[21]) reported either calcium oxalate or a mixture of calcium oxalate and calcium phosphate stones

**Data reported in this table is from trials comparing citrate vs. placebo/control as well as trials comparing citrate + second active therapy vs. control.

Abbreviation: NR = not reported

[a]Fernandez-Rodriguez 2006;[9] [b]Soygur 2002;[17] [c] Premgamone 2001;[18] [d] Ettinger 1997;[19] [e] Hofbauer 1994;[20] [f] Barcelo 1993[21]; [g]Lojanapiwat, 2011[16]

Appendix F. Table 4. Summary of baseline characteristics for allopurinol studies

Characteristic	Mean (range) *Unless Otherwise Noted***	Trials Reporting
Total number of patients evaluated	339* (15 to 132)	5
Study withdrawals, % of patients	*23 (15 to 30)	3 [a,b,e]
Study withdrawals due to adverse events, % of patients	0*	3 [a,b,e]
Age of subjects, years	46 (45 to 48)	2 [a,b]
Gender, male, % of patients	87 (79 to 100)	2 [a,d]
Race/ethnicity, white, % of patients	NR	-
Stone type, calcium oxalate stones, % of patients	100% in 3 studies	3 [c,d,e]
Stone type, mixed calcium oxalate stones and calcium phosphate or other, % of patients	2 studies with ≥80% calcium oxalate only	2 [a,b]
Multiple past stones, % of patients (n/N)	100% in all studies	5
Single past stone, % of patients (n/N)	0% in all studies	5
Residual stones at baseline, % of patients (n/N)	(0 to 47)	2 [a,b]
Hypercalciuria at baseline, % of patients	100	1 [a]
Hypocitraturia at baseline, % of patients	NR	
Hyperuricosuria at baseline, % of patients	100	1 [b]
Hypeoxaluria at baseline, % of patients	NR	
Hyperuricemia at baseline, % of patients	100	1 [e]
Mixed at baseline, % of patients	NR	
No metabolic disorder at baseline, % of patients	0	3 [a,b,e]
Studies conducted in the US, % of patients (n/N)	60 (204/339)	2 [b,e]
Studies conducted in Europe, % of patients (n/N)	40 (135/339)	4 [a,c,d]
Mean study duration (months)	46 (24 to 60)	5

*Two trials, Miano 1985[23] and Robertson 1985[24], reported only preliminary data on 15 patients (of 30 randomized) and 45 (of 120 randomized), respectively. No further data on either of these two studies were identified.

**Data reported in this table is from trials comparing allopurinol vs. placebo/control as well as trials comparing allopurinol + second active therapy vs. control.

Abbreviation: NR = not reported

[a]Borghi 1996;[6] [b]Ettinger 1986;[22] [c] Miano 1985;[23] [d] Robertson1985;[24] [e] Smith 1977[25]

Appendix F. Table 5. Summary of study baseline characteristics for acetohydroxamic acid trials

Characteristic	Mean (range) *Unless Otherwise Noted*	Trials Reporting
Total number of patients evaluated	343 (39 to 210)	3
Study withdrawals, % of patients	49 (15 to 69)	3
Study withdrawals due to adverse events, % of patients	13 (5 to 16)	3
Age of subjects, years	49 (48 to 49)	2 [b,c]
Gender, male, % of patients	77 (18 to 100)	3
Race/ethnicity, white, % of patients	NR	
Stone type, struvite stones, % of patients	100% for all trials	
Multiple past stones, % of patients (n/N)	100% for 2 trials	2 [a,c]
Single past stone, % of patients (n/N)	0% for 2 studies	2 [a,c]
Residual stones at baseline, % of patients (n/N)	88* (269/304)	2 [a,b]
Hypercalciuria at baseline, % of patients	NR	
Hypocitraturia at baseline, % of patients	NR	
Hyperuricosuria at baseline, % of patients	NR	
Hyperoxaluria at baseline, % of patients	NR	
Mixed at baseline, % of patients	NR	
No metabolic disorder at baseline, % of patients	NR	
Spinal cord injury, % of patients (n/N)	85** (257/304)	2 [a,b]
Studies conducted in the US	All trials	
Mean study duration (months)	18 months for Williams1984. Only range for follow-up period reported for Griffith 1991 (6-32 mos) and Griffith 1988 reported up to 24 months.	

* For Williams1984,[28] residual stones at baseline were not reported for all subjects except for 7 placebo patients who had stones that doubled in area versus 0 for AHA patients (determined by X-ray). **10% of subjects in Williams1984[28] study had neurogenic bladders.

Abbreviation: NR = not reported

[a] Griffith 1991;26 [b] Griffith 1988;27 [c] Williams198428

Appendix G. Withdrawals and Adverse Events Tables

Appendix G. Table 1. Withdrawals and adverse events for diet trials

Study	Any Study Withdrawals n/N (%)		Any or Serious Adverse Events Leading to Study Withdrawal n/N (%)		Subjects with at Least One Adverse Event n/N (%)		Adverse Event: (*describe*) n/N (%)		Adverse Event: (*describe*) n/N (%)	
	Diet	**Control**	**Diet**	**Control**	**Diet**	**Control**	**Diet**	**Control**	**Diet**	**Control**
Dussol 2008[1]	Month 48 Low animal protein diet 32/55 (58.2%) High fiber diet 33/60 (55.0%)	Month 48 37/60 (61.7%)	NR	NR	NR	NR	NR	NR		
Sarica 2006[2]	0/12	0/9	0/12	0/9	NR	NR	NR	NR		
Borghi 2002[3]	Low protein/ Na diet 8/60 (13.3)	Low calcium diet 9/60 (15.0)	Low protein/ Na diet 3/60 (5.0)	Low calcium diet 7/60 (11.7)	NR	NR	HTN† 1/60 (1.7)	HTN† 7/60 (11.7)	Stroke† 1/60 (1.7) Gout† 1/60 (1.7)	Death (accidental) 2/60 (3.3)
Di Silverio 2000[4]	Mineral H_20 calcium 15 mg/l 0/192	Tap H_20 calcium 55-130 mg/l 0/192	Mineral H_20 calcium 15 mg/l 0/192	Tap H_20 calcium 55-130 mg/l 0/192	NR	NR	NR	NR		
Kocvara 1999[5]	Not stated per arm, 35 patients (14%) not assessed at year 3		NR	NR	NR	NR	NR	NR		
Borghi 1996[6]	11/99 (11.1)	10/100 (10.0)	NR	NR	NR	NR	NR	NR		
Hiatt 1996[7]	9/51 (17.6)	15/51 (29.4)	NR	NR	NR	NR	NR	NR		
Shuster 1992[8]	44/504 (8.7)	28/505 (5.5)	2/504 (0.4)	2/505 (0.4)	NR	NR	Death 2/504 (0.4)	Death 2/505 (0.4)		

Abbreviations: HTN= hypertension; Na = sodium; NR = not reported

†These results refer only to the number of participants who withdrew for these specific reasons. No data were reported on specific adverse effects that did not lead to study withdrawal.

Appendix G. Table 2. Withdrawals and adverse events for thiazide trials

Study	Any Study Withdrawals n/N (%)		Any or Serious Adverse Events Leading to Study Withdrawal n/N (%)		Subjects with at Least One Adverse Event n/N (%)		Adverse Event: (*describe*) n/N (%)		Adverse Event: (*describe*) n/N (%)	
	Thiazide	Control	Thiazide	Control	Thiazide	Control	Thiazide	Control	Thiazide	Control
Fernández-Rodriguez, 2006[9]	0/50	0/50	0/50	0/50	NR	NR	NR	NR		
Ahlstrand, 1995[10]	10/17 (58.8)	9/24 (37.5)	5/17 (29.4)	0/24	NR	NR	*Composite A**5/17 (29.4)	NR		
Borghi, 1993[11]	6/25 (24.0)	Control 4/25 (16.0) Allopurinol 1/25 (4.0)	2/25 (8.0)	Control 0/25 Allopurinol 0/25	NR	NR	*Hypotension* 1**/25 (4.0)	NR	*Severe hypokalemia* 1**/25 (4.0)	NR
Ettinger, 1988[12]	17.7% due to loss of interest (not reported separately for each dose) and 22.6% and 18.9% due to AE for 25 and 50 mg dose groups, respectively	Placebo 16.7% $MgOH_2$ 17.7% due to loss of interest (not reported separately for each dose) and 13.3% due to AE (1330 mg dose group only)	25 mg 22.6% 50 mg 18.9%	Placebo 3.2% $MgOH_2$1300 mg 13.3%	NR	NR	*Composite B** 25 mg 22.6% 50 mg 18.9%	*GI upset* Placebo 3.2% *Diarrhea* $MgOH_2$1300 mg 13.3%		
Ala-Opas, 1987[13]	0/28	0/45	0/28	0/45	NR, "Side effects uncommon"	NR	NR	NR		

Appendix G. Table 2. Withdrawals and adverse events for thiazide trials (continued)

Study	Any Study Withdrawals n/N (%)		Any or Serious Adverse Events Leading to Study Withdrawal n/N (%)		Subjects with at Least One Adverse Event n/N (%)		Adverse Event: (*describe*) n/N (%)		Adverse Event: (*describe*) n/N (%)	
	Thiazide	Control	Thiazide	Control	Thiazide	Control	Thiazide	Control	Thiazide	Control
Laerum, 1984[14]	2/25 (8.0)	0/25	0/25	0/25	6/25 (24.0)	2/25 (8.0)	*Composite* C* 3/25 (12.0)	*Composite* C* 2/25 (8.0)	*Gout* 1/25 (4.0) *Hypokalemia* 1/25 (4.0) Impotence 1/25 (4.0)	NR
Scholz, 1982[15]	2/25 (8.0)	1/26 (3.8)	2/25 (8.0)	1/26 (3.8)	13/25 (52.0)	6/26 (23.1)	*Composite* D* 11/25 (44.0)	*Composite* D* 5/26 (19.2)		

* Composite A = orthostatic reactions, dizziness, GI symptoms, muscle cramp, gout, and erectile dysfunction; Composite B = lassitude, fatigue, impotence, lightheadedness, or muscular symptoms; Composite C = minor adverse events such as slight fatigue and dyspepsia; Composite D = weariness, nausea, symptoms of hypotension. **Patient removed from study.

Abbreviations: GI = gastrointestinal; $MgOH_2$ = magnesium hydroxide; NR = not reported

Appendix G. Table 3. Withdrawals and adverse events for citrate trials

Study	Any Study Withdrawals n/N (%)		Any or Serious Adverse Events Leading to Study Withdrawal n/N (%)		Subjects with at Least One Adverse Event n/N (%)		Adverse Event: Gastrointestinal Complaints n/N (%)		Adverse Event: (*describe*) n/N (%)	
	Citrate	Control	Citrate	Control	Citrate	Control	Citrate	Control	Citrate	Control
Lojanapiwat, 2011 [16]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fernández-Rodriguez, 2006[9]	0/50	0/50	0/50	0/50	NR	NR	NR	NR	NR	NR
Soygur, 2002[17]†	20 of 110 subjects randomized were excluded but number excluded from each study group was not reported		6 subjects withdrew due to epigastric discomfort but number withdrawing from each study group was not reported		NR	NR	6 subjects overall		NR	NR
Premgamone, 2001[18]	5/24 (20.8)	2/24 (8.3)	5/24 (20.8)	0/24	8/24 (33.3)	0/24	NR	NR	*Fatigue or loss of appetite* 8/24 (33.3)	0/24
Ettinger, 1997[19]	15/31 (48.4)	8/33 (24.2)	5/31 (16.1)	1/33 (3.0)	NR	NR	13/31 (41.9); 8/31 (25.8%) had more than slight symptoms	13/33 (39.4); 5/33 (15.2%) had more than slight symptoms	*Diarrhea* (11.5)*	*Diarrhea* 0/33 (0)
Hofbauer, 1994[20]	9/25 (36.0)	3/25 (12.0)	4/25 (16.0)	0/25 (0.0)	4/25 (16.0)	0/25 (0.0)	4/25 (16.0)	0/25 (0.0)	NR	NR
Barcelo, 1993[21]	10/28 (35.7)	9/29 (31.0)	2/28 (7.1)	1/29 (3.4)	NR	NR	5/28 (17.9)	1/29 (3.4)	NR	NR

Abbreviations: fu = followup; NR = not reported

* number of subjects unclear/ indeterminable

† Study did not report withdrawal and adverse event data separately for subjects who were stone free at baseline from those who had residual stones at baseline.

Appendix G. Table 4. Withdrawals and adverse events for allopurinol trials

Study	Any Study Withdrawals n/N (%)		Any or Serious Adverse Events Leading to Study Withdrawal n/N (%)		Subjects with at leastOne Adverse Event n/N (%)		Adverse Event: *(describe)* n/N (%)		Adverse Event: *(describe)* n/N (%)	
	Allopurinol	**Control**	**Allopurinol**	**Control**	**Allopurinol**	**Control**	**Allopurinol**	**Control**	**Allopurinol**	**Control**
Borghi, 1993[11]	Allopurinol + Indapamide 1/25 (4.0)	Control 4/25 (16.0) Indapamide 6/25 (24.0)	Allopurinol + Indapamide 0/25	Control 0/25 Indapamide 2/25 (8.0)	NR	NR	NR	Control NR; Indapamide *Hypotension* 1/25 (4.0)	NR	Control NR; Indapamide *Severe hypokalemia* 1/25 (4.0)
Ettinger, 1986[22]	7/36 (19.4)	5/36 (13.8)	2/36 (5.5)	2/36 (5.5)	NR	NR	*Gastrointestinal discomfort, rash, or fatigue* 2*/36 (5.6)	*Gastrointestinal discomfor, rash, or fatigue* 2*/36 (5.6)	1/36 (2.8) maculopapular rash; 2/36 (5.6) intercurrent illness	
Miano, 1985[23]	NR**	NR**	NR	NR	NR	NR	NR	NR		
Robertson, 1985[24]	NR**	NR**	NR	NR	NR	NR	NR	NR		
Fellstrom, 1985[29]	2/33 (6)	NR	2/33 (6)	NR	NR	NR	*Rash* 2/33 (6)	NR		
Smith, 1977[25]	Before 6 months 16/65 (24.6); Total 24/65 (36.9)	Before 6 months 24/67 (35.8); Total 38/67 (56.7)	"Drug sickness" 2/65 (3.1)	"Drug sickness" 6/67 (9.0)	NR	NR	*Skin rash* 1/65 (1.5)	*Skin rash* 1/67 (1.5)	*Acute gout* 3/65 (4.6) *Leukopenia* 1/65 (1.5)	NR

* Patients removed from study; ** Study provided only preliminary data on a portion of randomized participants and was unclear regarding whether any of participants not included in analyses had withdrawn.

Abbreviation: NR = not reported

Appendix G. Table 5. Withdrawals and adverse events for acetohydroxamic acid trials

Study	Any Study Withdrawals n/N (%)		Any or Serious Adverse Events Leading to Study Withdrawal n/N (%)		Subjects with at Least One Adverse Event n/N (%)		Adverse Event: *(describe)* n/N (%)		Adverse Event: *(describe)* n/N (%)	
	AHA	Control	AHA	Control	AHA	Control	AHA	Control	AHA	Control
Griffith, 1991[26]	29/45 (64.4) Deaths 0/45 (0)	36/49 (73.5) Deaths 1/49 (2.0)	12/45 (26.6)	3/49 (6.1)	35/45 (77.7)	24/49 (48.9)	*Anemia* 1/45 (2.2) *Phlebitis* 1/45 (2.2)	*Anemia* 0/45 (0) *Phlebitis* 1/49 (2.0)	*Alopecia* 4/45 (8.9) *Headache* 4/45 (8.9)	*Alopecia* 1/49 (2.0) *Headache* 2/49 (4.1)
Griffith, 1988[27]	75/121 (62.0)*	28/89 (31.5)*	20%†	5%†	75/121 (61.9)	26/89 (29.2)	*Anemia* 25/99 (25)	*Anemia* 10/85 (11.7)		
Williams, 1984[28]	Overall 6/20 (30), of which 2/20 (10) within 3 months	NR	2/20 (10)	NR	9/20 (45.0)	1/19 (5.3)	*Tremulousness* 5/20 (25) *Myocardiopathy* NR	*Tremulousness* NR *Myocardiopathy* 1/19 (5%)	*Deep vein thrombosis* 3/19 (15.7) *Intolerable headache* 1/20 (5)	NR

* numbers calculated from percentages reported; †Actual numbers not provided by and not possible to determine from original study.
Abbreviation: NR = not reported

Appendix G. Table 6. Withdrawals and adverse events for magnesium trials

Study	Any Study Withdrawals n/N (%)		Any or Serious Adverse Events Leading to study Withdrawal n/N (%)		Subjects with at Least One Adverse Event n/N (%)		Adverse Event: *(describe)* n/N (%)		Adverse Event: *(describe)* n/N (%)	
	Magnesium	**Control**	**Magnesium**	**Control**	**Magnesium**	**Control**	**Magnesium**	**Control**	**Magnesium**	**Control**
Ettinger, 1988[12]	†9/51 17.7% due to loss of interest (suspect 3/30 in 650mg group & 6/21 in 1300mg group); 0/27 of remaining 650 mg group and 2/15 (13.3%) remaining 1300 mg group due to GI upset	†Placebo 5/31 (16.7%) Thiazide 17.7% due to loss of interest (not reported separately for each dose) and 22.6% and 18.9% due to AE for 650 and 50 mg dose groups, respectively	1300 mg 13.3%	Placebo 3.2% Thiazide 25 mg 22.6% 50 mg 18.9%	NR	NR	*Diarrhea* 1300 mg 13.3% stated as "not a problem" for the 650 mg dose group	*GI upset* Placebo 3.2% *Composite** Thiazide 25 mg 22.6% 50 mg 18.9%		

* lassitude, fatigue, impotence, lightheadedness, or muscular symptoms.
†Raw numbers estimated from percentages provided in publication.
Abbreviations: GI = gastrointestinal; NR = not reported

Appendix H. Baseline and Followup Urine Biochemical Measures Tables

Appendix H. Table 1. Followup urine biochemical measures for diet trials

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
Dussol, 2008[1]	A. Low animal protein diet, decrease intake of animal protein by limiting consumption of meat and fish to 3 servings per week and to not exceed 100 g/day of milk products. The target was to obtain a daily contribution of protein to energy of <13% (n=55). B. High fiber diet, increase intake of fruits and vegetables and to substitute their usual cereals with whole grain dietary products in order to limit the increase in energy. The target was to obtain a 25-g/day increase in fiber intake. Subjects were not instructed to exclude fruits and vegetables particularly rich in oxalate (n=60). C. Controls (usual diet) (n=60) 24 hour collection	CALCIUM Baseline Mean mmol (SD): A (n=55) 6.8 (3.1) B (n=60) 6.8 (3.1) C (n=60) 6.8 (3.1) % hyperCa: NR F/u Time 1: 12 mo. Mean mmol (SD): A (n=41) 6.0 (2.4) B (n=45) 6.9 (3.0) C (n=37) 5.8 (3.0) % hyperCa: NR OXALATE Baseline Mean mmol (SD): A (n=55) 0.30 (0.1) B (n=60) 0.31 (0.2) C (n=60) 0.32 (0.1) % hyperOx: NR F/u Time 1: 12 mo. Mean mmol (SD): A (n=41) 0.25 (0.1) B (n=45) 0.29 (0.1) C (n=37) 0.27 (0.1) % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo.	URIC ACID Baseline N Mean (SD): NR % hyperUA: NR F/u Time 1: mo. N Mean (SD): NR % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean mmol (SD): A (n=55) 2.9 (1.9) B (n=60) 3.3 (3.2) C (n=60) 3.2 (2.5) % hypoCit: NR F/u Time 1: 12 mo. Mean mmol (SD): A (n=41) 2.8 (1.1) B (n=45) (2.3 (1.2) C (n=37) 2.6 (1.2) % hypoCit: NR SODIUM Baseline Mean mmol (SD): A (n=55) 149 (44) B (n=60) 163 (58) C (n=60) 164 (56) % hyperNa: NR F/u Time 1: 12 mo. Mean mmol (SD): A (n=41) 167 (46) B (n=45) 144 (70) C (n=37) 146 (64) % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean L (SD): A (n=55) 1.9 (0.8) B (n=60) 2.0 (0.7) C (n=60) 1.8 (0.7) F/u Time 1: 12 mo. Mean L (SD): A (n=41) 2.0 (0.9) B (n=45) 2.0 (0.7) C (n=37) 1.8 (0.6) pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 1. Followup urine biochemical measures for diet trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
	Study reported any data on participant compliance/adherence: No	N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR			F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	
Borghi, 2002[3]	A. Low calcium diet (<10 mmol) (n= 60) B. Low protein (<93 g) and low sodium (50 mmol) diet (n=60) 24 hour collection Study reported any data on participant compliance/adherence: Yes (urine specimen obtained one week after randomization was analyzed to check compliance with the dietary regimen, but no data was reported)	CALCIUM Baseline Mean mmol (SD): A (n=60) 11.0 (2.5) B (n=60) 11.5 (2.5) % hyperCa: NR F/u Time 1: 12 mo. Mean mmol (SD): A (n=51) 7.6 (2.9) B (n=53) 7.3 (2.5) % hyperCa: NR OXALATE Baseline Mean µmol (SD): A (n=60) 367 (136) B (n=60) 411 (132) % hyperOx: NR F/u Time 1:12 mo. Mean µmol (SD): A (n=51) 422 (144) B (n=53) 344 (92) [p<0.001] % hyperOx: NR CA-OX PRODUCT	URIC ACID Baseline N Mean (SD): NR % hyperUA: NR F/u Time 1: mo. N Mean (SD): NR % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline Mean mmol (SD): A (n=60) 227 (59) B (n=60) 241 (67) % hyperNa: NR F/u Time 1: 12 mo. Mean mmol (SD): A (n=51) 210 (55) B (n=53) 130 (85) [p<0.001] % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean mL (SD): A (n=60) 1755 (844) B (n=60) 1852 (643) F/u Time 1: 12 mo. Mean mL (SD): A (n=51) 1905 (713) B (n=53) 2095 (623) pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 1. Followup urine biochemical measures for diet trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		Baseline Mean molX10-6/L (SD): A (n=60) 2.07 (2.11) B (n=60) 1.82 (1.26) Time 1: 12 mo. Mean molX10-6/L (SD): A (n=51) 1.25 (1.17) B (n=53) 0.70 (0.48) [p<0.01] CA-OX SUPERSAT Baseline Mean (SD): A (n=60) 10.1 (5.5) B (n=60) 9.6 (4.2) Time 1: 12 mo. Mean (SD): A (n=51) 7.3 (4.3) B (n=53) 5.1 (2.5) [p<0.01]			% hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	
Di Silverio, 2000[4]	A. "Fiuggi water'" oligo-mineral water with a calcium content of 15 mg/l, 2 liters within a 24-hour period (n=192) B. tap water with a calcium content between 55 and 130 mg/l, 2 liters within a 24-hour period (n=192) 24 hour collection	CALCIUM Baseline Mean mg (SD): A (n=192) 270.67 B (n=192) 283.09 % hyperCa: NR F/u Time 1: mo. N Mean (SD): NR % hyperCa: NR OXALATE	URIC ACID Baseline Mean mg (SD): A (n=192) 554.95 B (n=192) 577.45 % hyperUA: NR F/u Time 1: mo. N Mean (SD): NR % hyperUA: NR URIC-A SUPERSAT	PHOSPHATE Baseline Mean mg (SD): A (n=192) 768.92 B (n=192) 841.08 % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline Mean mmol (SD):	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline N Mean (SD): NR

Appendix H. Table 1. Followup urine biochemical measures for diet trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
	Study reported any data on participant compliance/adherence: No	Baseline N Mean (SD): NR % hyperOx: NR F/u Time 1: mo. N Mean (SD): NR % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR	Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	A (n=192) 186.3 B (n=192) 181.1 % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline Mean mg (SD): A (n=192) 107.4 B (n=192) 105.8 % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	F/u Time 1: mo. N Mean (SD): NR pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR
Kočvara, 1999[5]	A. Tailored diet (n=113) B. General diet (n=94) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean mmol (SD): A (n=113) 5.09 (2.36) B (n=94) NR % hyperCa: NR F/u Time 1: 6 mo. Mean mmol (SD): A (n=113) 5.77 (2.30) [p<0.01] B (n=94) NR % hyperCa: NR	URIC ACID Baseline Mean mmol (SD): A (n=113) 3.74 (1.18) B (n=94) NR % hyperUA: NR F/u Time 1: 6 mo. Mean mmol (SD): A (n=113) 3.62 (1.34) B (n=94) NR % hyperUA: NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N	CITRATE Baseline Mean mmol (SD): A (n=113) 3.08 (1.54) B (n=94) NR % hypoCit: NR F/u Time 1: 6 mo. Mean mmol (SD): A (n=113) 2.99 (1.43) B (n=94) NR % hypoCit: NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean mL (SD): A (n=113) 2354 (645)

Appendix H. Table 1. Followup urine biochemical measures for diet trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		OXALATE Baseline Mean µmol (SD): A (n=88) 351 (156) B (n=94) NR % hyperOx: NR F/u Time 1:6 mo. Mean µmol (SD): A (n=88) 334 (138) B (n=94) NR % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR	URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	Mean (SD): NR	SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline Mean mmol (SD): A (n=113) 4.13 (1.44) B (n=94) NR % hypoMg: NR F/u Time 1: 6 mo. Mean mmol (SD): A (n=113) 4.78 (1.94) [p<0.01] B (n=94) NR % hypoMg: NR	B (n=94) NR F/u Time 1: 6 mo. Mean mL (SD): A (n=113) 2342 (693) B (n=94) NR pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR
Borghi, 1996[6]	A. Achieve urine volume >2 liters/day. Urine volume to be measured every 2 months to ensure high volume (n=110) B. No treatment (n=110) 24 hour collection	CALCIUM Baseline Mean mg (SD): A (n=110) 244 (109) B (n=110) 266 (112) % hyperCa: NR F/u Time 1: mo. N Mean (SD): NR	URIC ACID Baseline Mean mg (SD): A (n=110) 588 (183) B (n=110) 572 (211) % hyperUA: NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean mg (SD): NR A (n=110) 707 (250) B (n=110) 670 (255) % hyperP: NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean mg (SD): A (n=110) 512 (207) B (n=110) 530 (259) % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR	POTASSIUM Baseline Mean mmol (SD): A (n=110) 47 (14) B (n=110) 47 (15) % hypoK: NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 1. Followup urine biochemical measures for diet trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
	Study reported any data on participant compliance/adherence: No	% hyperCa: NR OXALATE Baseline Mean mg (SD): A (n=110) 28.7 (9.5) B (n=110) 28.6 (10.5) % hyperOx: NR F/u Time 1: mo. N Mean (SD): NR % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline Mean (SD): A (n=110) 10.1 (4.9) B (n=110) 11.2 (5.3) Time 1: 12 mo. Mean (SD): A (n=110) 5.2 (3.2) [p<0.0001] B (n=110) 8.1 (5.2)	% hyperUA: NR URIC-A SUPERSAT Baseline Mean (SD): A (n=110) 3.48 (2.95) B (n=110) 3.64 (3.08) F/u Time 1: 12 mo. Mean (SD): A (n=110) 1.72 (1.49) [p<0.001] B (n=110) 2.66 (2.3)	% hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	% hypoCit: NR SODIUM Baseline Mean mmol (SD): A (n=110) 158 (52) B (n=110) 162 (55) % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline Mean mg (SD): A (n=110) 85 (31) B (n=110) 88 (33) % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	% hypoK: NR VOLUME Baseline Mean mL (SD): A (n=110) 1068 (240) B (n=110) 1008 (231) F/u Time 1: mo. Mean mL (SD): A (n=110) 2127 (546) [p<0.0001] B (n=110) 1258 (292) pH Baseline N Mean (SD): A (n=110) 5.91 (0.49) B (n=110) 5.90 (0.5) F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 1. Followup urine biochemical measures for diet trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
Hiatt, 1996[f]	A. Low animal protein and high fiber diet: Decrease intake of animal protein (56 to 64 gm/day) and of purine containing foods (75 mg/day); increase fruits,vegetables, and whole grains; and add 1/4 cup bran/day (n= 51, 50 included in study, 1 excluded post randomization) B. Standard advice instructed on fluid intake and adequate calcium intake (n=51, 49 included in study 2 excluded post randomization) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean mmol (SD): A (n=42) 5.21 (0.36) B (n=37) 5.24 (0.49) % hyperCa: NR F/u Time 1: 6 mo. Mean mmol (SD): A (n=31) 5.5 B (n=28) 5.9 % hyperCa: NR OXALATE Baseline Mean mmol (SD): A (n=41) 445 (32) B (n=35) 474 (43) % hyperOx: NR F/u Time 1: 6 mo. Mean mmol (SD): A (n=32) 470 B (n=28) 620 % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR	URIC ACID Baseline Mean mmol (SD): A (n=43) 4.36 (0.22) B (n=37) 4.40 (0.29) % hyperUA: NR F/u Time 1: 6 mo. Mean mmol (SD): A (n=32) 3.8 B (n=28) 4.2 % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean mL (SD): A (n=43) 1510 (111) B (n=37) 1459 (105) F/u Time 1: 6 mo. Mean mL (SD): A (n=29) 1800 B (n=32) 1950 pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 1. Followup urine biochemical measures for diet trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		Time 1: mo. N Mean (SD): NR				

Abbreviation: NR = not reported

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
Fernandez-Rodriguez, 2006[9]	A. Hydrochlorothiazide 50 mg/d (n=50) B. Potassium citrate 20 mEq/d + hydrochlorothiazide 50 mg/d + (n=50) C. No treatment (n= 50) Urine collection method not specified Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean (SD): NR % hyperCa: A – 42% B – 28% C – 34% F/u Time 1: 12 mo. Mean (SD): NR % hyperCa: A – 16% B – 4% C – 26% OXALATE Baseline Mean (SD): NR % hyperOx: A – NR B – 2% C – 2%	URIC ACID Baseline Mean (SD): NR % hyperUA: A – 2% B – 6% C – 4% F/u Time 1: 12 mo. Mean (SD): NR % hyperUA: A – NR B – 16% C – 2% URIC-A SUPERSAT Baseline Mean (SD): NR F/u Time 1: mo. Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: F/u Time 1: mo. N Mean (SD): NR % hyperP: CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean (SD): NR % hypoCit: A – 14% B – 16% C – 14% F/u Time 1: 12 mo. Mean (SD): NR % hypoCit: A – 22% B – 16% C – 14% SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		F/u Time 1:12 mo. Mean (SD): NR % hyperOx: A – NR B – 2% C – 4% CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR			Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	
Borghi, 1993[11]	A. Indapamide 2.5 mg/d (n=25). B. Allopurinol 300 mg/d + Indapamide 2.5 mg/d (n=25). C. Control (diet/increased fluid treatment) (n=25) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean mg/24 hr(SD): A (n=19) 387 (121); B (n=24) 410 (154); C (n=21) 381 (156) % hyperCa: NR F/u Time 1: 6 mo. Mean mg/24 hr(SD): A (n=19) 237 (96) [p<0.001]; B (n=24) 231 (115) [p<0.001];	URIC ACID Baseline Mean mg/24 hr(SD): A (n=19) 642 (191); B (n=24) 811 (351); C (n=21) 788 (210) % hyperUA: NR F/u Time 1: 6 mo. Mean mg/24 hr(SD): A (n=19) 692 (319); B (n=24) 535 (255)	PHOSPHORUS Baseline Mean mg/24 hr(SD): A (n=19) 812 (189); B (n=24) 936 (314); C (n=21) 884 (262) % hyperP: NR F/u Time 1: 6 mo. Mean mg/24 hr(SD): A (n=19) 776 (265); B (n=24) 911 (263);	CITRATE Baseline Mean mg/24 hr(SD): A (n=19) 484 (172); B (n=24) 535 (271); C (n=21) 637 (391) % hypoCit: NR F/u Time 1: 6 mo. Mean mg/24	POTASSIUM Baseline Mean mM/24 hr(SD): A (n=19) 54 (15); B (n=24) 54 (15); C (n=21) 50 (13) % hypoK: NR F/u Time 1: 6 mo. Mean mM/24 hr(SD): A (n=19) 51 (22); B (n=24) 58 (25);

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		C (n=21) 284 (99) [p<0.01] % hyperCa: NR OXALATE Baseline Mean mg/24 hr(SD): A (n=19) 29 (13); B (n=24) 33 (15); C (n=21) 25 (8) % hyperOx: NR F/u Time 1: 6 mo. Mean mg/24 hr(SD): A (n=19) 27 (14); B (n=24) 28 (11); C (n=21) 24 (13) % hyperOx: NR CA-OX PRODUCT Baseline Mean (SD): NR Time 1: mo. Mean (SD): NR CA-OX SUPERSAT Baseline Mean (SD): NR Time 1: mo. Mean (SD): NR	[p<0.001]; C (n=21) 613 (193) [p<0.01] % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	C (n=21) 772 (237) [p<0.05] % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	hr(SD): A (n=19) 491 (214); B (n=24) 484 (234); C (n=21) 557 (247) % hypoCit: NR SODIUM Baseline Mean mM/24 hr(SD): A (n=19) 210 (61); B (n=24) 218 (80); C (n=21) 201 (64) % hyperNa: NR F/u Time 1: 6 mo. Mean mM/24 hr(SD): A (n=19) 208 (80); B (n=24) 190 (76); C (n=21) 159 (51) [p<0.05] % hyperNa: NR MAGNESIUM Baseline Mean mg/24 hr(SD):	C (n=21) 51 (15) % hypoK: NR VOLUME Baseline Mean mL/24 hr(SD): A (n=19) 1813 (480); B (n=24) 1995 (772); C (n=21) 1541 (774) F/u Time 1: 6 mo. Mean mL/24 hr(SD): A (n=19) 2045 (807); B (n=24) 2193 (897); C (n=21) 1509 (646) pH Baseline Mean 24 hr(SD): A (n=19) 5.83 (0.43); B (n=24) 5.75 (0.46); C (n=21) 5.86 (0.51) F/u Time 1: 6 mo. Mean 24 hr(SD): A (n=19) 5.95

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
					A (n=19) 106 (37); B (n=24) 116 (36); C (n=21) 108 (33) % hypoMg: NR F/u Time 1: 6 mo. Mean mg/24 hr(SD): A (n=19) 94 (38); B (n=24) 104 (44); C (n=21) 81 (28) [p<0.001] % hypoMg: NR	(0.49); B (n=24) 6.06 (0.59) [p<0.005]; C (n=21) 5.90 (0.53)
Ettinger, 1988[12]	A. Chlorthalidone 25 mg/d (n=19) B. Chlorthalidone 50 mg/d (n=23) C. Magnesium hydroxide 650 mg/d (n=30) D. Magnesium hydroxide 1300 mg/d (n=21) E. Placebo (n=31) 24 hour collection Study reported any data on participant compliance/adherence: Yes (medication compliance confirmed by tablet count – no results reported)	CALCIUM Baseline Mean mg/24 hr(SD): A (n=19) 271 (125) B (n=23) 299 (138) C (n=30) 275 (127) D (n=21) 247 (136) E (n=31) 232 (117) % hyperCa: A (n=19) 15.8 B (n=23) 13.0 C (n=30) 13.3 D (n=21) 14.3 E (n=31) 9.7 F/u Time 1: 24 mo. Mean (SD): A (n=19) 196 [p<0.01] B (n=23) 233 [p<0.01]	URIC ACID Baseline Mean mg/24 hr(SD): A (n=19) 768 (207) B (n=23) 826 (206) C (n=30) 837 (257) D (n=21) 734 (181) E (n=31) 699 (210) % hyperUA: A (n=19) 21.1 B (n=23) 26.1 C (n=30) 6.7 D (n=21) 9.5 E (n=31) 9.7 F/u Time 1: mo. Mean mg/24 hr(SD):	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean mL/24 hr(SD): A (n=19) 1744 (720) B (n=23) 1671 (690) C (n=30) 1894 (814)

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		C (n=30) no signif change D (n=21) no signif change E (n=31) no signif change % hyperCa: NR OXALATE Baseline Mean mg/24 hr(SD): A (n=19) 21 (16) B (n=23) 19 (12) C (n=30) 29 (19) D (n=21) 28 (19) E (n=31) 23 (15) % hyperOx: NR F/u Time 1: 24 mo. Mean mg/24 hr(SD): A (n=19) 8 [p<0.05] B (n=23) 14 [not signif] C (n=30) no signif change D (n=21) no signif change E (n=31) no signif change % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N	All groups- no signif change % hyperUA: NR URIC-A SUPERSAT Baseline Mean (SD): NR F/u Time 1: mo. Mean (SD): NR		Mean mg/24 hr(SD): A (n=19) 93 (33) B (n=23) 97 (38) C (n=30) 91 (27) D (n=21) 97 (27) E (n=31) 95 (45) % hypoMg: NR F/u Time 1: 24 mo. Mean mg/24 hr(SD): A (n=19) no signif change B (n=23) no signif change C (n=30) 137 [p<0.001] D (n=21) 148 [p<0.001] E (n=31) no signif change % hypoMg: NR	D (n=21) 1579 (675) E (n=31) 1482 (671) F/u Time 1: 24 mo. Mean mL/24 hr(SD): All groups- no signif change pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		Mean (SD): NR Time 1: mo. N Mean (SD): NR				
Ala-Opas, 1987[13]	A. Hydrochlorothiazide 100mg/day for first 5 months (+ bran) (n=28) [hypercalciuric [HU] = 14, normocalciuric [NU] = 14] B. Control (bran) (n=45) [hypercalciuric [HU] = 18, normocalciuric [NU] = 27] 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM/CREATININE Baseline Mean mmol/mmol (SD): A[HU] (n=14) 0.64 (0.17) B[HU] (n=18) 0.57 (0.12) A[NU] (n=14) 0.36 (0.14) B[NU] (n=27) 0.37 (0.08) % hyperCa: 41.0 F/u Time 1: 6 mo. Mean mmol/mmol (SD): A[HU] (n=14) 0.34 (0.15) [p<0.05] B[HU] (n=18) 0.37 (0.13) [p<0.05] A[NU] (n=14) 0.19 (0.08) B[NU] (n=27) 0.29 (0.16) % hyperCa: OXALATE Baseline Mean µmol (SD): A[HU] (n=14) 256 (101) B[HU] (n=18) 276 (153) A[NU] (n=14) 167 (71) B[NU] (n=27) 219 (111) % hyperOx: NR F/u Time 1: 6 mo. Mean µmol (SD): A[HU] (n=14) 194 (70) B[HU] (n=18) 281 (189) A[NU] (n=14) 279 (136) B[NU] (n=27) 334 (86)	URIC ACID Baseline Mean (SD): NR % hyperUA: NR F/u Time 1: mo. Mean (SD): NR % hyperUA: NR URIC-A SUPERSAT Baseline Mean (SD): NR F/u Time 1: mo. Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean (SD): NR % hypoCit: NR F/u Time 1: mo. Mean (SD): NR % hypoCit: NR SODIUM Baseline Mean mmol (SD): A[HU] (n=14) 156 (88) B[HU] (n=18) 158 (62) A[NU] (n=14) 113 (33) B[NU] (n=27) 135 (53) % hyperNa: NR F/u Time 1: 6 mo. Mean µmol (SD): A[HU] (n=14) 149 (71) B[HU] (n=18) 144 (53) A[NU] (n=14) 130 (52) B[NU] (n=27) 138 (70) % hyperNa: NR MAGNESIUM Baseline	POTASSIUM Baseline Mean (SD): NR % hypoK: NR F/u Time 1: mo. Mean (SD): NR % hypoK: NR VOLUME Baseline Mean (SD): NR F/u Time 1: mo. Mean (SD): NR pH Baseline Mean (SD): NR F/u Time 1: mo. Mean (SD): NR

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		% hyperOx: NR CA-OX PRODUCT Baseline Mean (SD): NR Time 1: mo. Mean (SD): NR CA-OX SUPERSAT Baseline Mean (SD): NR Time 1: mo. Mean (SD): NR			Mean mmol (SD): A[HU] (n=14) 4.1 (2.1) B[HU] (n=18) 3.0 (1.4) A[NU] (n=14) 3.7 (1.6) B[NU] (n=27) 4.0 (1.6) % hypoMg: NR F/u Time 1: 6 mo. Mean µmol (SD): A[HU] (n=14) 3.4 (1.4) B[HU] (n=18) 3.6 (1.4) A[NU] (n=14) 3.5 (1.4) B[NU] (n=27) 3.7 (1.4) % hypoMg: NR	
Laerum, 1984[14]	A. Hydrochlorothiazide 50 mg/d + potassium chloride 1.2 gm/d (n=23) B. Placebo (n=25) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean mmol (SD): A (n=23) 4.3 (0.55) B (n=25) 4.92 (0.42) % hyperCa: 27.1 F/u Time 1: 10 mo. Mean mmol (SD): A (n=17) 3.79 (0.46) B (n=21) 5.0 (0.44) [p<0.05 A vs B] % hyperCa: NR	URIC ACID Baseline Mean mmol (SD): A (n=23) 3.2 (0.25) B (n=25) 3.1 (0.21) % hyperUA: 25.0 F/u Time 1: 10 mo. Mean mmol (SD): A (n=17) 3.3 (0.28) B (n=21) 3.5 (0.19) % hyperUA: NR URIC-A	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean mL (SD): A (n=23) 1522 (114) B (n=25) 1374 (108)

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		OXALATE Baseline Mean (SD): NR % hyperOx: NR F/u Time 1: mo. N Mean (SD): NR % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR	SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR		Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline Mean mmol (SD): A (n=23) 3.79 (0.26) B (n=25) 4.20 (0.22) % hypoMg: NR F/u Time 1: 10 mo. Mean mmol (SD): A (n=17) 4.28 (0.26) B (n=21) 4.40 (0.22) % hypoMg: NR	F/u Time 1: 10 mo. Mean mL (SD): A (n=17) 1492 (95) B (n=21) 1638 (96) pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR
Scholz, 1982[15]	A. Hydrochlorothiazide 50 mg/d (n=25) B. Placebo (n=26) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean mg (SD): A (n=25) 249 (20) B (n=20) 272 (32) % hyperCa: NR F/u Time 1: 12 mo. Mean mg (SD): A (n=25) 153 (22) [p<0.001] B (n=20) 235 (26) % hyperCa: NR OXALATE Baseline	URIC ACID Baseline Mean mg (SD): A (n=25) 641 (45) B (n=19) 699 (37) % hyperUA: NR F/u Time 1: 12 mo. Mean mg (SD): A (n=25) 593 (50) B (n=19) 551 (33) % hyperUA: NR URIC-A SUPERSAT Baseline	PHOSPHATE Baseline Mean mg (SD): A (n=25) 784 (70) B (n=19) 824 (75) % hyperP: NR F/u Time 1: 12 mo. Mean mg (SD): A (n=25) 737 (46) B (n=19) 759 (44) % hyperP: NR CA-P SUPERSAT Baseline N	CITRATE Baseline Mean mg (SD): A (n=16) 345 (74) B (n=16) 350 (46) % hypoCit: NR F/u Time 1: 12 mo. Mean mg (SD): A (n=16) 332 (70) B (n=16) 309 (41) % hypoCit: NR SODIUM Baseline	POTASSIUM Baseline Mean mEq (SD): A (n=25) 61 (5) B (n=19) 64 (7) % hypoK: NR F/u Time 1: 12 mo. Mean mEq (SD): A (n=25) 60 (5) B (n=19) 50 (4) % hypoK: NR VOLUME Baseline

Appendix H. Table 2. Followup urine biochemical measures for thiazide trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		Mean mg (SD): A (n=16) 42 (6) B (n=13) 47 (6) % hyperOx: NR F/u Time 1:12 mo. Mean mg (SD): A (n=16) 35 (6) B (n=13) 22 (6) [p<0.05] % hyperOx: NR CA-OX PRODUCT Baseline Mean (SD): A (n=16) 0.96 (0.07) B (n=13) 0.98 (0.06) Time 1: 12 mo. Mean (SD): A (n=16) 0.71 (0.08) [p<0.05] B (n=13) 0.71 (0.08) [p<0.05] CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR	N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	Mean mEq (SD): A (n=25) 197 (15) B (n=19) 184 (13) % hyperNa: NR F/u Time 1: 12 mo. Mean mEq (SD): A (n=25) 173 (14) B (n=19) 142 (11) [p<0.05] % hyperNa: NR MAGNESIUM Baseline Mean mg (SD): A (n=25) 103 (9) B (n=20) 102 (9) % hypoMg: NR F/u Time 1: 12 mo. Mean mg (SD): A (n=25) 89 (9) B (n=20) 85 (5) [p<0.05] % hypoMg: NR	Mean mL (SD): A (n=25) 1820 (136) B (n=20) 1891 (116) F/u Time 1: 12 mo. Mean mL (SD): A (n=25) 1820 (166) B (n=20) 1658 (142) pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Abbreviation: NR = not reported

Appendix H. Table 3. Followup urine biochemical measures for citrate trials

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
Lojanapiwat, 2011[16]	A. Sodium- potassium citrate 81 mEq/d (n=13 *stone-free only, 39 total*) B. No treatment (n=26 *stone-free only, 37 total*) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean (SD): NR % hyperCa: A – 10.3% (4/39) B – 18.9% (7/37) F/u Time 1: 12 mo. Mean (SD): NR % hyperCa: A – 20.5% (8/39) B – 18.9% (7/37) OXALATE Baseline Mean (SD): NR % hyperOx: A – 20.5% (8/39) B – 16.2% (6/37) F/u Time 1: 12 mo. Mean (SD): NR % hyperOx: A – 20.5% (8/39) B – 27.0% (10/37)	URIC ACID Baseline Mean (SD): NR % hyperUA: A – 2.6% (1/39) B – 0% (0/37) F/u Time 1: 12 mo. Mean (SD): NR % hyperUA: A – 2.6% (1/39) B – 8.1% (3/37) URIC-A SUPERSAT Baseline Mean (SD): NR F/u Time 1: mo. Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: F/u Time 1: mo. N Mean (SD): NR % hyperP: CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean (SD): NR % hypoCit: A – 51.3% (20/39) B – 40.5% (15/37) F/u Time 1: 12 mo. Mean (SD): NR % hypoCit: A – 7.69% (3/39) B – 37.83% (14/37) SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Total volume < 1500 mL/day: A – 43.6% (17/39) B – 37.8% (14/37) F/u Time 1: 12 mo. Total volume < 1500 mL/day: A – 38.5% (15/39) B – 54.1% (20/37) pH Baseline Mean (SD): A (n=39) 5.8 (0.77) B (n=37) 5.7 (0.66) F/u Time 1: 12 mo. Mean (SD): A (n=39) 6.6 (0.97) B (n=37) 5.9 (0.70)

Appendix H. Table 3. Followup urine biochemical measures for citrate trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR				
Fernandez-Rodriguez, 2006[9]	A. Hydrochlorothiazide 50 mg/d (n=50) B. Potassium citrate 20 mEq/d + hydrochlorothiazide 50 mg/d + (n=50) C. No treatment (n= 50) Urine collection method not specified Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean (SD): NR % hyperCa: A – 42% B – 28% C – 34% F/u Time 1: 12 mo. Mean (SD): NR % hyperCa: A – 16% B – 4% C – 26% OXALATE Baseline Mean (SD): NR	URIC ACID Baseline Mean (SD): NR % hyperUA: A – 2% B – 6% C – 4% F/u Time 1: 12 mo. Mean (SD): NR % hyperUA: A – NR B – 16% C – 2% URIC-A SUPERSAT Baseline	PHOSPHATE Baseline N Mean (SD): NR % hyperP: F/u Time 1: mo. N Mean (SD): NR % hyperP: CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean (SD): NR % hypoCit: A – 14% B – 16% C – 14% F/u Time 1: 12 mo. Mean (SD): NR % hypoCit: A – 22% B – 16% C – 14% SODIUM Baseline N Mean (SD): NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 3. Followup urine biochemical measures for citrate trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		% hyperOx: A – NR B – 2% C – 2% F/u Time 1:12 mo. Mean (SD): NR % hyperOx: A – NR B – 2% C – 4% CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR	Mean (SD): NR F/u Time 1: mo. Mean (SD): NR		% hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	
Ettinger, 1997[19]	A. Potassium (42 mEq/d)-magnesium (21 mEq/d) citrate (63 mEq/d) (n=31) B. Placebo (n=33) 24 hour collection Study reported any data on participant	CALCIUM Baseline Mean mg (SD): A (n=31) 237 (120) B (n=33) 275 (131) % hyperCa: NR F/u Time 1: 36 mo. Mean mg (SD):	URIC ACID Baseline Mean mg (SD): A (n=31) 722 (239) B (n=33) 695 (227) % hyperUA: NR F/u Time 1: 36 mo. Mean mg (SD):	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR	CITRATE Baseline Mean mg (SD): A (n=31) 587 (37.4) B (n=33) 549 (280) % hypoCit: NR F/u Time 1: 36 mo. Mean mg (SD):	POTASSIUM Baseline Mean mEq (SD): A (n=31) 56 (25) B (n=33) 58 (20) % hypoK: NR F/u Time 1: 36 mo. Mean mEq (SD):

Appendix H. Table 3. Followup urine biochemical measures for citrate trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
	compliance/adherence: Yes (counting tablets)	A (n=16) 225 (92) B (n=25) 261 (123) % hyperCa: NR OXALATE Baseline Mean mg (SD): A (n=31) 37 (13) B (n=33) 36 (12) % hyperOx: NR F/u Time 1: 36 mo. A (n=16) 44 (21) [p<0.05] B (n=25) 39 (10) % hyperOx: NR CA-OX PRODUCT Baseline Mean m2 X 10-8 (SD): A (n=31) 1.40 (0.76) B (n=33) 1.77 (0.87) Time 1: 36 mo. Mean m2 X 10-8 (SD): A (n=16) 1.48 (0.75) B (n=25) 1.72 (0.53) CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR	A (n=16) 726 (210) B (n=25) 694 (194) % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	A (n=16) 769 (289) [p<0.05] B (n=25) 548 (265) % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline Mean mg (SD): A (n=31) 116 (44) B (n=33) 121 (47) % hypoMg: NR F/u Time 1: 36 mo. Mean mg (SD): A (n=16) 142 (42) [p<0.05] B (n=25) 105 (32) % hypoMg: NR	A (n=16) 89 (27) [p<0.001] B (n=25) 58 (17) % hypoK: NR VOLUME Baseline Mean L (SD): A (n=31) 1.98 (1.15) B (n=33) 1.74 (0.70) F/u Time 1: 36 mo. Mean L (SD): A (n=16) 2.01 (1.00) B (n=25) 1.79 (0.84) pH Baseline Mean (SD): A (n=31) 6.01 (0.46) B (n=33) 5.96 (0.41) F/u Time 1: 36 mo. Mean (SD): A (n=16) 6.29 (0.58) B (n=25) 6.02 (0.32)

Appendix H. Table 3. Followup urine biochemical measures for citrate trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
Hofbauer, 1994[20]	A. Sodium-potassium citrate 30 gm/d initially, then adjusted to keep urine pH 7.0-7.2 (n=25) B. Control (n=25) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline N Mean (SD): NR % hyperCa: A (n=25) 48% B (n=25) 40% F/u Time 1: 36 mo. N Mean (SD): NR % hyperCa: A (n=16) 25% B (n=22) 45% OXALATE Baseline N Mean (SD): NR % hyperOx: NR F/u Time 1: mo. N Mean (SD): NR % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N	URIC ACID Baseline N Mean (SD): NR % hyperUA: NR F/u Time 1: mo. N Mean (SD): NR % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean mmol/L (SD): A (n=25) 1.3 (0.8) B (n=25) 1.27 (0.9) % hypoCit: A (n=25) 72% B (n=25) 65% F/u Time 1: 36 mo. Mean mmol/L (SD): A (n=16) 2.28 (0.8) B (n=22) 1.47 (0.9) % hypoCit: A (n=16) 25% B (n=22) 55% SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 3. Followup urine biochemical measures for citrate trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		Mean (SD): NR				
Barcelo, 1993[21]	A. Potassium citrate 30-60 mEq/d (n=28) B. Placebo (n=29) 24 hour collection Study reported any data on participant compliance/adherence: Yes (interview and pill count)	CALCIUM Baseline N Mean (SD): NR % hyperCa: NR F/u Time 1: mo. N Mean (SD): NR % hyperCa: NR OXALATE Baseline N Mean (SD): NR % hyperOx: NR F/u Time 1: mo. N Mean (SD): NR % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR	URIC ACID Baseline N Mean (SD): NR % hyperUA: NR F/u Time 1: mo. N Mean (SD): NR % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline Mean nmol/day(SD): A (n=28) 1.9 (0.5) B (n=29) NR % hypoCit: NR F/u Time 1: 36 mo. Mean nmol/day(SD): A (n=18) 3.3 (0.5) [p<0.01] B (n=20) NR % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	POTASSIUM Baseline Mean mEq/day(SD): A (n=28) 61 (17) B (n=29) NR % hypoK: NR F/u Time 1: 36 mo. Mean mEq/day(SD): A (n=18) 105 (41) [p<0.01] B (n=20) NR % hypoK: NR VOLUME Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR pH Baseline Mean (SD): A (n=28) 5.4 (0.5) B (n=29) NR F/u Time 1: 36 mo. Mean (SD): A (n=18) 6.4 (0.3) [p<0.01] B (n=20) NR

Abbreviation: NR = not reported

Appendix H. Table 4. Followup urine biochemical measures for allopurinol trials

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
Ettinger, 1986[22]	A. Allopurinol 300 mg/d (n=36) B. Placebo (n=36) 24 hour collection Study reported any data on participant compliance/adherence: Yes (tablet counts)	CALCIUM Baseline Mean mg (SD): A (n=29) 238 (74) B (n=31) 211 (83) % hyperCa: NR F/u Time 1: 6 mo. Mean mg (SD): A (n=29) no signif change B (n=31) no signif change % hyperCa: NR OXALATE Baseline N Mean (SD): NR % hyperOx: NR F/u Time 1: mo. N Mean (SD): NR % hyperOx: NR CA-OX PRODUCT Baseline N	URIC ACID Baseline Mean mg (SD): A (n=29) 1017 (214) B (n=31) 935 (134) % hyperUA: NR F/u Time 1: 6 mo. Mean mg (SD): A (n=29) 660 (55) B (n=31) 885 (50) % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR % hypoMg: NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Appendix H. Table 4. Followup urine biochemical measures for allopurinol trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR				
Miano, 1985[23]	A. Allopurinol 300 mg/d (n=8) B. Placebo (n=7) 24 hour collection Study reported any data on participant compliance/adherence: No	CALCIUM Baseline Mean mg (SD): A (n=8) 203 (34) B (n=7) 218 (14) % hyperCa: NR F/u Time 1: 36 mo. Mean mg (SD): A (n=8) 210 (44) B (n=7) 218 (31) % hyperCa: NR OXALATE Baseline N Mean (SD): NR % hyperOx: NR F/u Time 1: mo. N Mean (SD): NR % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR	URIC ACID Baseline Mean mg (SD): A (n=8) 513 (136) B (n=7) 421 (55) % hyperUA: NR F/u Time 1: 36 mo. Mean mg (SD): A (n=8) 444 (103) B (n=7) 482 (67) % hyperUA: NR URIC-A SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline N Mean (SD): NR % hypoMg: NR F/u Time 1: mo. N Mean (SD): NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean mL (SD): A (n=8) 1314 (497) B (n=7) 1439 (368) F/u Time 1: 36 mo. Mean mL (SD): A (n=8) 1389 (312) B (n=7) 1653 (413) pH Baseline N Mean (SD): NR F/u Time 1: mo.

Appendix H. Table 4. Followup urine biochemical measures for allopurinol trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR			% hypoMg: NR	N Mean (SD): NR

Abbreviation: NR = not reported

Appendix H. Table 5. Followup urine biochemical measures for magnesium trials

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
Ettinger, 1988[12]	A. Chlorthalidone 25 mg/d (n=19) B. Chlorthalidone 50 mg/d (n=23) C. Magnesium hydroxide 650 mg/d (n=30) D. Magnesium hydroxide 1300 mg/d (n=21) E. Placebo (n=31) 24 hour collection Study reported any data on participant compliance/adherence: Yes (medication compliance confirmed by tablet count – no results reported)	CALCIUM Baseline Mean mg/24 hr(SD): A (n=19) 271 (125) B (n=23) 299 (138) C (n=30) 275 (127) D (n=21) 247 (136) E (n=31) 232 (117) % hyperCa: A (n=19) 15.8 B (n=23) 13.0 C (n=30) 13.3 D (n=21) 14.3 E (n=31) 9.7 F/u Time 1: 24 mo. Mean (SD): A (n=19) 196 [p<0.01] B (n=23) 233 [p<0.01] C (n=30) no signif change D (n=21) no signif change E (n=31) no signif change % hyperCa: NR	URIC ACID Baseline Mean mg/24 hr(SD): A (n=19) 768 (207) B (n=23) 826 (206) C (n=30) 837 (257) D (n=21) 734 (181) E (n=31) 699 (210) % hyperUA: A (n=19) 21.1 B (n=23) 26.1 C (n=30) 6.7 D (n=21) 9.5 E (n=31) 9.7 F/u Time 1: mo. Mean mg/24 hr(SD): All groups- no signif change % hyperUA: NR URIC-A SUPERSAT Baseline Mean (SD): NR F/u Time 1: mo. Mean (SD): NR	PHOSPHATE Baseline N Mean (SD): NR % hyperP: NR F/u Time 1: mo. N Mean (SD): NR % hyperP: NR CA-P SUPERSAT Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR	CITRATE Baseline N Mean (SD): NR % hypoCit: NR F/u Time 1: mo. N Mean (SD): NR % hypoCit: NR SODIUM Baseline N Mean (SD): NR % hyperNa: NR F/u Time 1: mo. N Mean (SD): NR % hyperNa: NR MAGNESIUM Baseline Mean mg/24 hr(SD): A (n=19) 93 (33) B (n=23) 97 (38) C (n=30) 91 (27) D (n=21) 97 (27) E (n=31) 95 (45) % hypoMg: NR	POTASSIUM Baseline N Mean (SD): NR % hypoK: NR F/u Time 1: mo. N Mean (SD): NR % hypoK: NR VOLUME Baseline Mean mL/24 hr(SD): A (n=19) 1744 (720) B (n=23) 1671 (690) C (n=30) 1894 (814) D (n=21) 1579 (675) E (n=31) 1482 (671) F/u Time 1: 24 mo. Mean mL/24 hr(SD): All groups- no signif change pH Baseline N Mean (SD): NR

Appendix H. Table 5. Followup urine biochemical measures for magnesium trials (continued)

Study	Treatment Groups, Urine Collection Method	Calcium, Oxalate, Ca-Ox Product, Ca-Ox Supersaturation	Uric Acid, Uric-A Supersaturation	Phosphate, Ca-P Supersaturation	Citrate, Sodium, Magnesium	Potassium (K), Volume, pH
		OXALATE Baseline Mean mg/24 hr(SD): A (n=19) 21 (16) B (n=23) 19 (12) C (n=30) 29 (19) D (n=21) 28 (19) E (n=31) 23 (15) % hyperOx: NR F/u Time 1: 24 mo. Mean mg/24 hr(SD): A (n=19) 8 [p<0.05] B (n=23) 14 [not signif] C (n=30) no signif change D (n=21) no signif change E (n=31) no signif change % hyperOx: NR CA-OX PRODUCT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR CA-OX SUPERSAT Baseline N Mean (SD): NR Time 1: mo. N Mean (SD): NR			F/u Time 1: 24 mo. Mean mg/24 hr(SD): A (n=19) no signif change B (n=23) no signif change C (n=30) 137 [p<0.001] D (n=21) 148 [p<0.001] E (n=31) no signif change % hypoMg: NR	pH Baseline N Mean (SD): NR F/u Time 1: mo. N Mean (SD): NR

Abbreviation: NR = not reported

Appendix I. References

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