Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: Recurrent Nephrolithiasis in Adults: A Comparative Effectiveness Review of Preventative Medical Strategies

Draft review available for public comment from October 21, 2011 to November 21, 2011.

Research Review Citation: Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, Brasure M, Kane RL, Monga M. Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies**.** Comparative Effectiveness Review No. 61. (Prepared by the University of Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.) AHRQ Publication No. 12-EHC049-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Assimos, Dean	Executive Summary	There is epidemiologic evidence that high fructose consumption is a risk factor for kidney stone formation. They might mention that this could have impacted the reduced soft drink dietary study. They should point out that the Borghi et al study (reference 45) included only those subjects with recurrent stones and hypercalciuria which is a different cohort than the other dietary studies.	We revised our Introduction in both the Executive Summary and main report to acknowledge the epidemiologic data supporting high fructose consumption as a risk factor for incident stone formation. In the section of the main report discussing the results of the soft drink dietary trial, we Regarding the soft drink study, the reviewer is correct that it is possible that reduction in high fructose corn syrup consumption that sweetens most U.S. soft drinks could have contributed to the reduction in recurrent stones in the group assigned to limit soft drink consumption versus usual care. Authors did not report baseline or followup high fructose corn syrup consumption or perform a subgroup analyses based on the estimated baseline high fructose corn syrup consumption. However, it was not clear whether the types of soft drinks participants consumed varied enough in fructose content to have facilitated such an analysis. We added discussion of this issue to the revised report (main report Results section and Discussion section of both Executive Summary and main report). The reviewer is correct that the Borghi 2002 study is the only diet trial in which 100% of participants had hypercalciuria. Regarding the frequency of past stone episodes among diet trials, four trials were limited to participants with only a single past stone episode, 2 were limited to participants with recurrent stones (Borghi 2002)(DiSilverio 2000), and 2 included both participants with a single past episode and those with recurrent stones.(Shuster 1992)(Dussol 2008) Consequently, we modified our statement in the Executive Summary that dietary trials enrolled "predominately participants…with a single calcium stone episode" to the following: "Half

Commentator & Affiliation	Section	Comment	Response
			of diet trials included only participants with a single calcium stone episode, and half included or were limited to those with recurrent stones." We also revised our Executive Summary Summary of Evidence table for diet trials to explicitly indicate which trials included participants with a single past stone episode, recurrent stone episodes, or either.
Assimos, Dean	Executive Summary	Cystine is miss-spelled throughout the document.	This error has been corrected.

Commentator & Affiliation	Section	Comment	Response
Assimos, Dean	Executive Summary	They should consider adding abnormalities of urine pH as a risk factor for stone formation on page 1, section on epidemiology. They should consider adding radiation exposure to the Final Clinical Health Outcomes box on the page 3 figure.	We agree with the reviewer and have revised the Executive Summary and Introduction to the main report by adding having either low or high urine pH to the list of biochemical abnormalities that may be associated with risk of kidney stone formation. With regard to the comment on radiation exposure, we agree that patients with kidney stones may be at risk for increased radiation exposure. They could be exposed during imaging performed to confirm a kidney stone when the patient presents with clinical symptoms suspicious for an acute stone recurrence (which would result in more radiation exposure if treatment is less effective) or if they are undergoing scheduled radiographic imaging to ascertain recurrence of asymptomatic stones (in which the amount of radiation exposure would be independent of treatment efficacy). It is unclear, then, whether reduced radiographic testing/radiation exposure should be considered a potential benefit or an adverse effect of treatment. However, the figure was the conceptual model we developed a priori to guide our study methods. Because we didn't formally look for this outcome during data extraction, we don't believe it would be appropriate to modify the figure in the manner suggested at this time. Nevertheless, we do recall that other than reporting their protocols for scheduled imaging, eligible trials did not report results for imaging of symptomatic stone events or cumulative radiation exposure. In the revised report, we added a future research recommendation that future RCTs consider reporting "the laboratory and radiographic testing participants undergo, including their cumulative radiation exposure."

Commentator & Affiliation	Section	Comment	Response
Public Reviewer # 1 AUA	Executive Summary	On page 28, or ES-8, it was noted that 2 participants died during the trial comparing reduced soft drink consumption versus no treatment. Although there were 1009 subjects enrolled in the trial, the mortality rate (0.2%) is surprising in a diet trial. What were the circumstances and should it affect the usefulness of the trial?	This 3 year trial enrolled 1009 participants, including 504 in the soft drink avoidance group and 505 in the control group. (Shuster 1989) There were 2 deaths in each treatment group, for a total of 4 deaths. These were rare events without sufficient evidence to suggest that risk of death was associated with treatment assignment. It seems unlikely, however, that reduction of soft drink consumption would increase risk of mortality. The study did not report any information regarding the circumstances of the deaths, which we revised the report to note.
Public Reviewer # 1 AUA	Executive Summary	On page ES-6, in the incomplete bullet point at the top of the page, the authors state "This suggests low dietary calcium may increase stone risk". Elsewhere (i.e., page 58 in Discussion) the authors are careful to state that the effects of individual dietary measures comprising a multi-component diet have not been independently evaluated and that results have been conflicting regarding the role of dietary measures. Indeed, in the trial comparing stone recurrence rates on a normal calcium, low animal protein, low sodium diet versus those on a low calcium diet, there was no control group in which subjects received no treatment. In fact, stone recurrence rates were reduced in *both* groups compared with no treatment or placebo arms of other randomized trials. Consequently, there is no evidence that a low calcium diet *increases* stone risk, but only that it may not be as effective in reducing stone recurrence rates compared to a normal calcium, low sodium, low animal protein diet. Furthermore, the instructions for other dietary components (i.e., oxalate) were more strictly outlined to the latter group of subjects (multi-component diet) compared with the former group of subjects (low calcium diet), further confounding the picture. We suggest stating the conclusions about this trial in this section as carefully as it was in other sections of the document.	The reviewers are correct that in the bullet in the Executive Summary we used language that may have been insufficiently cautious in describing what could be inferred about the independent effect of dietary calcium levels on risk of recurrent stones from the Borghi 2002 trial. We have modified our language here. That said, we would caution this reviewer regarding comparing the event rate in the low calcium group in the Borghi 2002 trial with the event rate in the control group in different studies. It is difficult if not impossible to know how much if at all to attribute any difference in recurrence rates to a benefit from a low calcium diet. Epidemiological data suggest that low calcium diets increase risk of kidney stones, and differences in rates between the trials described above may be attributable to differences in populations or other factors.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	The introduction summarizes the issues adequately. Given that available interventional studies all focus on altering urine chemistries, the emphasis on this aspect of stone pathogenesis makes sense. However, it is likely that there are other important biologic processes involved in the initiation and growth of stones. These pathways might be potential targets of treatments in the future, once better understood. It would be good to include a paragraph that addresses this aspect of stone pathogenesis	While the interventions evaluated in eligible trials in this systematic review may alter urine chemistries, recurrent stones and not alteration in urine chemistry measures was our main endpoint of interest. Other biological processes besides urine chemistries may contribute to risk of recurrent stones. We revised our introduction to state that genetic and anatomical factors also contribute to increased risk of kidney stones. That said, better understanding of these processes from future research may guide development of novel treatments for reduction in risk of recurrent kidney stones. We added this point in the Future Research Recommendations section of the revised report.
Peer Reviewer #1	Introduction	On page 10, might include malabsorption as an important secondary cause of stones.	We added mention of malabsorption as a potential risk factor for kidney stones to the revised Executive Summary and main report.
Peer Reviewer #2	Introduction	The introduction is informative and appropriate to the topic. It provides a sufficient amount of background information and clearly delineates what the review is going to address	Thank you.
Peer Reviewer #3	Introduction	Introduction is clear and covers pertinent areas in the field. However the authors do state that small stones usually pass without symptoms, this is not true (Page 1). 2 to 3 mm stones often cause significant symptoms, though most pass spontaneously.	We agree with the reviewer. We modified the introduction because we could not find good data regarding the proportion of passed stones of different sizes that cause symptoms. We clarified that even very small stones may cause symptoms.: "While even stones as small as 1 mm in diameter may cause symptoms,(Coll DM, Am J Roentgenol 2002:178:101) 90 percent of stones smaller than 5 mm pass through the urinary system without ~~symptoms~~ requiring intervention to aid expulsion. By comparison, ~~large stones are more likely to cause symptoms and~~ approximately 50 percent of stones 5 to 10 mm in diameter require intervention to aid expulsion.[61]

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Peer Reviewer #4	Introduction	Page 1: There is no mention of inherited or anatomic factors related to etiology. These factors should be noted, albeit briefly, to confirm that diet and environment, which can be manipulated, may not be the only relevant factors in an individual.	The Executive Summary and Introduction of the main report both were revised to address the role of inherited and anatomic factors in contributing to increased kidney stone risk. Of note, we identified no trials limited to patients with these kidney stone risk factors or that reported results stratified for a subgroup with such factors. Most trials excluded patients with conditions that increased their kidney stone risk, so that the generalizability of results reported to these populations is unknown.
Peer Reviewer #6	Introduction	Addresses lapses in available literature and RCT's on this topic	Thank you.
Nakada, Stephen	Introduction	Not all urologists believe all stone formers should undergo urine chemistries. True for blood chemistries.	We agree. We stated in our introduction: "Current practice varies in the use of both initial and follow-up biochemical testing, particularly in patients who present as first-time stone formers.
Public Reviewer # 1 AUA	Introduction	The introduction is informative and appropriate to the topic. It provides a sufficient amount of background information and clearly delineates what the review is going to address	Thank you.
Peer Reviewer #1	Methods	All relevant studies have been captured and appropriate methods used to analyze them in composite.	Thank you.
Peer Reviewer #2	Methods	The inclusion and exclusion criteria are justifiable. The authors only included randomized controlled trials. This provides the highest level of evidence available. Unfortunately, there are very few level one studies performed investigating the benefits of medical stone management. The search strategy the authors employ is exhaustive and thorough. The definitions and diagnostic outcome measures are explicitly stated. The authors chose clinical outcomes as the most important when evaluating efficacy of treatments. This decision makes sense as clinical outcomes should be the most relevant to providers and patients. The authors did evaluate secondary or intermediate outcomes such as stone recurrence. There is no clearly agreed upon end point for evaluating the efficacy of stone prevention; however the authors' choice of outcomes to evaluate is appropriate and reasonable. The statistical methods used are appropriate.	Thank you.
Peer Reviewer #3	Methods	Criteria are clear and justifiable. All methods seem appropriate.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	Inclusion/ exclusion criteria are justified. Search strategies are understandable and logical. Definitions for outcome measures appear appropriate. Statistical methods used appear appropriate.	Thank you.
Peer Reviewer #6	Methods	The inclusion and exclusion criteria are appropriate , statistical methods are appropriate	Thank you.
Assimos, Dean	Methods	On page 6 under the Population(s) section it was stated that the subjects must no longer be symptomatic. Was this clearly stated in all of the studies that were analyzed?	Our intent, with this eligibility criterion, was to exclude studies in which patients could still have been undergoing treatment for an ongoing acute stone event (e.g. pain control, aid in expulsion). We looked for any language that indicated that their most recent stone event was past. We recognize that stating that subjects must no longer have been symptomatic was not clear. Also, the reviewer is correct in surmising that no studies specifically stated that patients were no longer symptomatic. In our attempt to clarify the revised report, we modified the Executive Summary and main report text as follows: "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 ~~(no longer symptomatic)~~ kidney stone episodes. We excluded studies of children, and those that addressed acute pain management and treatment to promote expulsion of ureteral stones."
Assimos, Dean	Methods	On page 7 in the Timing section it was mentioned that follow-up of at least 12 months was required. Many would consider that the optimal interval should be at least 3 years to account for the "stone clinic effect".	We also thought that follow-up longer than 1 year might be needed to detect a difference in risk of stone recurrence between treatment and control groups. Therefore, we decided in advance to perform stratified analyses to evaluate whether the effect of treatment versus control differed between shorter and longer-term trials. We reported these results for interventions that had sufficient data, i.e., thiazide and citrate treatment trials.

Commentator & Affiliation	Section	Comment	Response
Assimos, Dean	Methods	Is it appropriate to use unpublished RCTs as they may not be subjected to the scrutiny of peer review? If so, should such results be adjusted for or weighted?	The reviewer is correct that the two RCTs included in our review that were published only as conference proceedings may not have been subjected to the same rigorous evaluation as those published in a peer-reviewed journal. These two trials were one that compared thiazide vs. control (Ahlstrand, Urolithiasis Proceedings 1995) and one that compared allopurinol vs. placebo (Miano L, Urolithiasis 1985). We do not believe there would be an acceptable method to adjust or weigh results to account for this factor. Therefore, in the revised report we performed additional sensitivity analyses excluding the two RCTs that were not published as peer-reviewed articles. Results for thiazide vs. placebo/control for composite stone recurrence were similar when including (RR, 0.53 [CI, 0.41 to 0.68], n=6 trials) and not including Ahlstrand (RR, 0.50 [CI, 0.38 to 0.67], n=5 trials). The Miano trial reported only stone recurrence rates, so excluding it in a sensitivity analysis had no effect on estimated risk of stone recurrence for allopurinol vs. placebo.

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Assimos, Dean	Methods	They should comment on the definitions of hypercalciuria, Hyperuricosuria and Hypocitraturia used in the various studies.	Of 17 trials that reported prevalence of hypercalciuria, 11 defined it. They used fairly consistent thresholds, including >300 mg/day (2 trials), >276 mg/day (1 trial), >=300 mg/day in men and >=250 mg/day in women (3 trials), >=300 mg/day in men and >=250 mg/day in women or >4 mg/kg in either gender (2 trials), >=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 (1 trial), > 6 mmol/day (1 trial), and >0.1 mmol/kg/day (1 trial). Of 10 trials that reported prevalence of hyperuricosuria, 6 defined it. One defined it as >763 mg/day, two defined it as >600 mg/day, one defined it as >3.5 mmol/day, and two defined it as >800 mg/day in men or >750 mg/day in women. Of 8 trials that reported prevalence of hyperoxaluria, 3 defined it. One defined it as >46 mg/day, one as > 40 mg/day, and one as >500 micromol/day. Of 7 trials that reported prevalence of hypocitraturia, 4 defined it. Of these, 2 defined it as <320 mg/day, 1 defined it as <273 mg/day, and 1 defined it as <3.4 mmol/day. We have included the above data in the revised report and have commented throughout on the inconsistent reporting of baseline biochemistry data, and on the inconsistent definitions of biochemical abnormalities in studies that report prevalence of biochemical abnormalities. We also have recommended that these issues be addressed in future research studies.

Commentator & Affiliation	Section	Comment	Response
Nakada, Stephen	Methods	Could consider Scandinavian publications in the survey--specifically check Tiselius.	We appreciate this suggestion. We are familiar with the work of Dr. Tiselius and other investigators/collaborators. We reviewed titles/abstracts of all publications by Tiselius HG that included any of several MESH terms or text words related to urolithiasis, and found no RCTs not already included in our pool of eligible studies.
Public Reviewer # 1 AUA	Methods	The inclusion and exclusion criteria are justifiable. The authors only included randomized controlled trials. This provides the highest level of evidence available. Unfortunately, there are very few level one studies performed investigating the benefits of medical stone management. The search strategy the authors employ is exhaustive and thorough. The definitions and diagnostic outcome measures are explicitly stated. The authors chose clinical outcomes as the most important when evaluating efficacy of treatments. This decision makes sense as clinical outcomes should be the most relevant to providers and patients. The authors did evaluate secondary or intermediate outcomes such as stone recurrence. There is no clearly agreed upon end point for evaluating the efficacy of stone prevention; however the authors'choice of outcomes to evaluate is appropriate and reasonable. The statistical methods used are appropriate.	Thank you.
Peer Reviewer #1	Results	All relevant studies are included and adequately summarized.	Thank you.
Peer Reviewer #2	Results	The amount of detail is appropriate. The studies are clearly described and the appendices provide additional detail. The key messages are clearly spelled out and are applicable to the key questions the authors set forth to answer. The authors search was exhaustive and there were no studies that were excluded. Based on the authors stated goals and based on the studies available, all of the studies included were appropriate and applicable. There is clearly a significant need for more Level One investigations in this field.	Thank you.
Peer Reviewer #3	Results	The authors need to define the term "metabolic abnormality" (Page ES-9, ES16 and elsewhere). The authors seem to be using metabolic abnormality to mean systemic disease such as RTA or hyperparathyroidism, whereas some people would include hypercalciuria or hypocitraturia etc to be a metabolic abnormality. This point needs to be clarified in the text.	In the revised report, we have clarified the text by replacing the phrase "metabolic abnormality" with "biochemical abnormality." This latter phrase has been used to refer a biochemical laboratory abnormality, which is distinct from a systemic disease such as RTA that could predispose patients to nephrolithiasis.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Drugs that are not FDA approved are not to be included in this review. The pharmacologic dose of K-Mg citrate used in the single study was 63 meq per day (6 tablets). That formulation is not FDA approved. Though it is true there is an over the counter K-Mg citrate, it is a dose of 2.1 meq/pill, thus requiring 30 pills per day to reproduce the study dose. This is impractical and for all intents and purposes, this drug is not available in the US.	The correct statement is that drugs that are not FDA approved or available over the counter in the U.S. are not included in this review. While it clearly is impractical to take 30 pills per day of 2.1 meq/pill K-Mg citrate to reproduce the dose used in the trial, it is still available and will remain in the revised review. However, we also acknowledged as a research gap the uncertainty regarding whether the formulation available in the U.S. has comparable effectiveness as that studied in the trial.
Peer Reviewer #3	Results	References 24 and 41 appear to be incorrect. I did not check all other references.	The reviewer is correct that references 24 and 41 were incorrect. Inadvertently, we inserted the incorrect references. After reviewing all references, we discovered that the incorrect Miano reference also was inserted as reference 34, and that the incorrect Ettinger reference had been referenced in the section on Magnesium monotherapy versus placebo or active treatment. All these errors were corrected in the revised report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	The authors seem to take the Borghi trial (2002) results as indicating that low calcium diets increase stone formation (Pages ES-14). This trial does not allow this supposition, only that low Ca diets are inferior to the multi-component diet in the trial. In fact, no study has ever been done assessing the effectiveness of low Ca diets using a stone formation outcome. Considering how long low Ca diets were standard therapy, this is an amazing weakness in our field.	In the first draft of this report, in the Key Findings section of the Executive Summary we stated in referring to the Borghi 2002 trial that its findings suggested "low dietary calcium may increase stone risk." While this comes in the context of epidemiological studies supporting this association, we agree with this reviewer that strictly interpreted this Borghi trial only showed that a low calcium diet was less effective than the multi-component diet that included normal to high calcium. Therefore, we deleted the above sentence. However, we believe that the language on page ES-14 is appropriately cautious and does not need revision (beyond the changes we made to enhance readability): "…one multi-component 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,[45] However, results from other trials do not ~~provide consistent evidence for~~ clarify whether high dietary calcium, low animal protein, and low sodium individually are protective and/or whether low dietary calcium ~~independently~~ increases stone recurrence risk. No other trials assigned participants to different dietary calcium or sodium intakes as isolated interventions or within multi-component diets."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	The authors comment on lack of data supporting baseline classification of patients by risk factors such as hypercalciuria and hypocitraturia. The authors should recognize that kidney stone risks are continuous and that such categorization is often based on arbitrary cut-points. This is particularly germane in relation to diet and thiazide studies in Ca stone formers; though not all studies of Ca stone formers were restricted to those with hypercalciuria the mean urine Ca in almost all those studies was significantly above the mean of a normal population, such that treatment based on lowering urine Ca was directed at patients who had excess urine Ca as a stone risk, even if not formally meeting the definition of hypercalciuria.	We agree with the reviewer's comments that there are no established biochemical thresholds above or below which risk of kidney stones begins. Further, the risk conferred by biochemical abnormalities, where present, appears to be continuous (Curhan GC, Kidney Int 2001;59:2290) That said, the decision to treat with diet or medication is a categorical yes-no decision. A clinician using baseline biochemistry information to guide a treatment decision will ultimately need to decide whether the individual patient's biochemistry level(s) are at a level (i.e. threshold) that he/she thinks support treatment. Current data are insufficient to clarify the relative effectiveness of different treatments across a range of biochemistry levels (e.g. within several categories across a range of 24 hour urine calcium levels). We added this suggestion to the revised report as a worthwhile area for future research, by adding the following as a research gap: "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." We added the corresponding future research recommendation: "Additional RCTs, not just in patients with biochemical abnormalities defined by a specific threshold (which should be standardized across trials and consistently reported), but also reporting results stratified by different standardized levels of specific biochemistry measures." We also addressed this issue in the Discussion section.

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Peer Reviewer #3	Results	On page ES-9 the authors state they found low strength evidence that AHA does not reduce risk of radiographic recurrence of struvite stones. Though this statement is true, they do not give enough weight to the endpoint of stone growth that happen to be quite important in struvite stones that can grow silently and damage kidneys. The data in Appendix E, table 5a suggest that AHA is effective in reducing stone growth, an important endpoint in struvite stones.	A priori, we judged stone growth to be a secondary efficacy outcome measure, and one that deserves to be given less weight than ones that directly cause patient symptoms, such as symptomatic stone recurrence. While it is possible that asymptomatic stone growth could lead to kidney damage, then the more direct patient-centered outcome is clinically meaningful kidney damage (e.g. incident end stage renal disease, progression to stage 4 CKD or worse, developing of acute renal failure requiring hospitalization, etc.) We believe that we thoroughly reported the effects of AHA treatment on stone growth outcomes, which incidentally were reported using a different threshold in every study. It does not appear that any threshold for clinically meaningful stone growth has been established. Please note that on revision, for the comparison of AHA vs. placebo for the outcome of radiographic recurrence of struvite stones, we changed our strength of evidence rating from low to insufficient.
Peer Reviewer #4	Results	Page 12: Literature flow diagram is clear and useful. Study characteristics are clearly described. Key messages are explicit. Tables (1 and 2) are easy to read; nicely formatted.	Thank you.
Peer Reviewer #6	Results	Results are described in appropriate detail, tables and flow-sheet are descriptive	Thank you.
Assimos, Dean	Results	On page 15, Pharmacological Therapy Trials Section, paragraph 2, they should clarify if the symptomatic stone recurrence results are significant or not.	We revised the report by inserting the numerical results for the referenced study (RR, 1.04 [CI, 0.39 to 2.80]) to clarify that the difference in risk of symptomatic stone recurrence was not statistically significant.

Commentator & Affiliation	Section	Comment	Response
Assimos, Dean	Results	On page 17,Overview section, they should mention the Borghi study (reference 45).	We added information to this section regarding the results of both the Borghi 2002 trial and the Hiatt 1996 trial: "We found low strength of evidence that a multi-component diet including normal to high calcium, low protein, and low sodium reduced risk of recurrent stones compared to 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."
Assimos, Dean	Results	Page 33, first paragraph, last sentence, do they need to change it to "but not among controls"?	We are unclear which sentence the reviewer is describing, but do not believe that either the paragraph that begins on page 32 and ends on page 33 nor the first paragraph that starts on page 33 needs the suggested change. However, we made an unrelated change to clarify the final sentence of the first paragraph beginning on page 33 as follows: "Five trials based urine biochemistry measures on 24-hour urine collections, and two did not specify how urine was collected."

Commentator & Affiliation	Section	Comment	Response
Assimos, Dean	Results	Page 55, The argument that changes in urine calcium excretion is most likely a poor predictor of clinical response is not compelling.	We have presented the evidence from RCTs associating followup measures or changes in urine calcium with subsequent stone recurrence. As we stated in the report, all 3 diet trials that reported followup urine calcium (low protein vs. high fiber vs. control, and 2 multifactorial diet vs. control studies) reported that there was no change in urine calcium with treatment. To be more precise, we have revised our statement in the report regarding the usefulness of urine calcium for predicting stone recurrence with diet treatments to focus only on these particular trials and to not be generalized to all diet trials (underlines do not appear in the text): "Collectively, these trials suggest that <u>for these diet interventions</u> followup urine calcium is unlikely to be a useful predictor of stone recurrence." With regard to pharmacological therapy, we found the most data in the thiazide trials. Reduction in hypercalciuria happened in both the thiazide treatment groups and in the control group in more than one thiazide trial. This means that improvement in this measure may commonly occur with or without thiazide treatment, which is the reason we stated that reduction in urine calcium with thiazide treatment may be a nonspecific marker and could represent regression to the mean. In the Discussion section of the ES and main report, when addressing the potential utility of followup urine calcium measures for predicting stone outcomes with treatment considered more broadly, we modified our language in the report as follows: "Data from both diet and pharmacological RCTs suggest that followup urine calcium ~~is unlikely to be~~ <u>may have limitations as a</u> ~~useful~~ predictor of stone recurrence."

Commentator & Affiliation	Section	Comment	Response
Nakada, Stephen	Results	I largely agree there are knowledge gaps, particularly as they relate to specifically RCTs. The issue of fluid intake may be related to lower target urine volumes in the studies reviewed. Review of medications, dietary therapy, and adverse effects seem appropriate to me.	Thank you.
Public Reviewer # 1 AUA	Results	The amount of detail is appropriate. The studies are clearly described and the appendices provide additional detail. The key messages are clearly spelled out and are applicable to the key questions the authors set forth to answer. The authors search was exhaustive and there were no studies that were excluded. Based on the authors stated goals and based on the studies available, all of the studies included were appropriate and applicable. There is clearly a significant need for more Level One investigations in this field.	Thank you.
Peer Reviewer #1	Discussion	All conclusions appear justified by the data available and presented.	Thank you.
Peer Reviewer #1	Discussion	In Table 3, point 1, page 90 the last research gap appears to have been truncated accidentally "In patients with hypercalciuria,"	We have corrected this accidental truncation by replacing this text with the following research gap: “It is uncertain whether thiazide treatment is more effective in preventing stone recurrence in patients with hypercalciuria than in those without or unselected for hypercalciuria.” We then added the corresponding future research recommendation: “RCTs of thiazides versus control treatments in patients with hypercalciuria or reporting results stratified by baseline hypercalciuria status.”
Peer Reviewer #1	Discussion	I believe the case for what areas might benefit from more controlled studies is clearly and objectively presented.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion	One might want to point out that more knowledge is needed to identify key pathogenic steps that might be amenable to novel treatment strategies.	We agree with the reviewer that novel treatment strategies may be valuable. In the revised report, we updated our Future Research Recommendations section in the Executive Summary and main report to add the following research gap: "No eligible trial has evaluated a new pharmacological monotherapy since 1988. No eligible trial has evaluated a new combination pharmacological therapy since 2006." We then added the following recommendation for future research: "RCTs of novel treatment strategies to prevent stone recurrence are needed. Better understanding is needed regarding kidney stone pathogenesis to help identify potential new preventive treatments."
Peer Reviewer #2	Discussion	The implications of the major findings are clearly stated. The major limitation of the review is the lack of data to sufficiently answer the questions asked. The reviewers discuss this limitation and propose future research projects to address this issue. There is a particular lack of data in regards to treatment for non-calcium stones. There is also a lack of data on the adverse effects of the treatments that are currently used. The future research section is clear and easily translated.	Thank you.
Peer Reviewer #2	Discussion	There is a clear and obvious need for well done randomized controlled trials comparing treatments versus control. The authors propose that the primary endpoint should be symptomatic stone event. This is very reasonable since ultimately the goal of these treatments is to prevent patients from having symptomatic stones. However I believe it is just as important to track stone growth and interventions for stones in these patients.	In defining symptomatic stone recurrence, trials considered incidence of either spontaneous stone passage or intervention to assist in stone expulsion. Almost no trials reported interventions as a separate outcome, but where this was done we collected and reported it as an important clinical outcome. (e.g., Fernandez-Rodriguez 2006). Though we do not agree that stone growth is as important an outcome as symptomatic recurrent stones, we agree that it is sufficiently important that we collected and reported it in all studies that reported recurrent stones.
Peer Reviewer #2	Discussion	In some patients, particularly those with larger stones, symptoms may not be what determines the need for surgical intervention. Patients with asymptomatic stones may opt for surgery if their stones show evidence of growth or if they have an increase number of stones. It is important in any future	In this example, patients with asymptomatic stone growth determined to "need" surgery likely would be responding to their belief that doing something for asymptomatic stone growth is good or the recommendation from

Commentator & Affiliation	Section	Comment	Response
		studies also evaluate for stone growth radiographically as well as the number of interventions required in each arm. One other addition to the future research section would be studies to evaluate the cost-effectiveness of using these medications/dietary modifications to prevent stone recurrence. Included in the cost analysis should the utility and cost of following patients with repeat imaging and repeat serum and urine chemistries. Ultimately cost will play a role in any official policy and therefore this is something that must be evaluated along with efficacy.	their doctor that surgery is warranted. Stone growth in the absence of clinical outcomes is at best a surrogate outcome and at worst a radiographic finding leading to unnecessary and potentially harmful interventions. This argument doesn't prove that these patients would have clinically worse outcomes than patients with similar evidence of growth or increased number of stones. Though we systematically collected stone growth outcomes, we a priori judged stone growth to be a less important efficacy outcome than outcomes that directly cause patient symptoms, such as symptomatic stone recurrence. While it is possible that asymptomatic stone growth could lead to kidney damage, in this case the more direct patient-centered outcome still wouldn't' be stone growth but rather some clinically meaningful measure of kidney damage (e.g. incident end stage renal disease, progression to stage 4 CKD or worse, developing of acute renal failure requiring hospitalization, etc.) It does not appear that any threshold for clinically meaningful stone growth has been established. So, future research could study the clinical benefits/harms including the number of interventions and associated complications required in patients with asymptomatic stone growth above some absolute stone size or growth rate threshold(s), comparing intervention versus observation/watchful waiting. Alternatively, prospective observational studies could identify patients with asymptomatic stone growth and then follow them without assigning treatment for several years for symptomatic stone recurrence. We added these recommendations to the Future Research Recommendations in the revised report. Finally, we agree with the reviewer that cost-effectiveness analyses as described are a

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			worthwhile area of future research. We also have added this to the Future Research Recommendations in the revised report.
Peer Reviewer #3	Discussion	In the section "Future Research Recommendations"General Issues: The authors feel that radiographic stone recurrence is a lesser "nonclinical" outcome. I disagree with this approach. The formation of kidney stones is often offset in time (perhaps by years) before becoming symptomatic; in treating patients I do use radiology in concert with stone passage to judge treatment success. Focusing on stone passage as an outcome will make RCTs difficult to perform as the number of subjects and duration will likely be impractical. In fact, many in the field are hoping the use of CT scan to provide a more sensitive and reproducible marker of stone formation/growth will allow RCTs of shorter duration and thus more likely to be performed. I agree that reporting both radiologic and symptomatic stone outcomes in RCTs is desirable.	Stone growth, radiographic stone recurrence, and even asymptomatic stone passage in the absence of clinical outcomes may be surrogate outcomes at best and radiographic findings at worst, and may lead to unnecessary and potentially harmful interventions. We agree that use of stone growth and radiographic stone recurrence (using standardized and ideally sensitive detection methods) as outcomes in future RCTs would allow trials of shorter duration that may be more feasible to complete. However, this may lead investigators to draw inappropriate conclusions about the efficacy of treatments on clinical outcomes. Future research should investigate if and under what circumstances stone growth and radiographic stone recurrence are appropriate surrogates for symptomatic stone recurrence. We addressed this issue in the revised report.
Peer Reviewer #3	Discussion	Using acute renal failure or end stage renal disease as outcomes is impractical as both are very rare in stone disease.	We agree that these may be rare outcomes in stone disease and would therefore be impractical to designate as the primary outcomes of an RCT. However, they could be a consequence of stone disease and would be clinically relevant if they occurred. Therefore, we decided a priori to record incidence of these outcomes if they were reported.
Peer Reviewer #3	Discussion	Key Question #1. It would be worthwhile to have an RCT for the treatment of calcium phosphate stones. This would be particularly important for treatment with citrate, since alkali will raise urine pH which can promote calcium phosphate crystallization.	We appreciate this suggestion. In the Future Research Recommendations section of the Executive Summary and main report, we noted the absence of such studies as a research gap and recommended that future studies examine this question.
Peer Reviewer #3	Discussion	Key Question #4 It would make more sense to have magnesium therapy studied in patients with hypomagnesuria than hypomagnesemia.	We changed the report to state hypomagnesuria rather than hypomagnesemia.

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Peer Reviewer #3	Discussion	Key Question #6 The authors should consider an additional use of follow up serum and urine chemistries: to allow adjustment of dosing for pharmacologic interventions and feedback of dietary compliance in diet studies.	We noted in the Introduction that clinicians may use followup blood and urine biochemical measures to We raised this issue in the Introduction of the main report as follows: "Clinicians may use laboratory evaluations to guide initial treatment selection or to assess treatment adherence or effectiveness." Based on this reviewer's feedback, we modified our statement slightly: Clinicians may use laboratory evaluations to guide initial treatment selection, ~~or~~ to assess treatment adherence or effectiveness, and to adjust pharmacological treatment dosing." However, what we think is the important question is whether performing any of these measures reduces risk of stone recurrence.
Peer Reviewer #4	Discussion	Implications and limitations are clear. Limitations of individual studies are described adequately. The future research section is especially clear. I like that there is "general issues" as well as research recommendations for each key question.	Thank you.
Peer Reviewer #6	Discussion	Implications of major findings are clear. Future research section is relevant	Thank you.

Commentator & Affiliation	Section	Comment	Response
Assimos, Dean	Discussion	Future studies to consider are the utilization of pro-biotic preparations or pyridoxine in those with hyperoxaluria. The impact of therapy on associated co-morbidity should be assessed I future studies. RCTs on the treatment of cystinuria are needed. A search for molecular markers that will help tailor therapy is needed.	We agree that future research should investigate novel therapies to prevent recurrence of calcium oxalate stones. We have revised the report by recommending the following future research: "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." We agree that future research should investigate both dietary and pharmacological interventions to prevent recurrent cystine stones. We have revised the report by recommending the following future research: "RCTs for prevention of recurrent cystine stones involving dietary (e.g., increased fluid, low sodium) and pharmacological interventions (e.g., penicillamine, captopril, tiopronin, others)." We also agree that future RCTs should assess the impact of therapy on comorbidities. Therefore, we modified the future research needs section as follows: "RCTs should collect and completely report withdrawals, withdrawals due to adverse events, and predefined adverse events including effects on comorbid conditions in all randomized participants ~~(e.g. any, serious, specific, causing withdrawal)~~."

Commentator & Affiliation	Section	Comment	Response
Nakada, Stephen	Discussion	Research recommendations are largely appropriate. The report included only adults, and primarily calcium stones, and is thus less translatable to other stone types, and those without baseline biochemistries. Another major issue largely understated in the report is the longterm nature of the data requested; specifically, many years and stringent follow up are needed for high level efficacy measurements of these strategies on stone recurrence. As such, although clearly compelling, these data are difficult to collect to say the least. The data will take time to mature, even with urgent study and emphasis.	We appreciate this reviewer's comments and agree that some future research we recommended will be difficult conduct. We disagree with the reviewer's comment that the results have limited relevance to patients without baseline biochemistries. Most trials reported some baseline biochemical data. However, most trials did not restrict study entry to participants with biochemical abnormalities, and there was very limited evidence that baseline biochemistry abnormalities usefully predicted response to treatment.
Public Reviewer #1 AUA	Discussion	The implications of the major findings are clearly stated. The major limitation of the review is the lack of data to sufficiently answer the questions asked. The reviewers discuss this limitation and propose future research projects to address this issue. There is a particular lack of data in regards to treatment for noncalcium stones. There is also a lack of data on the adverse effects of the treatments that are currently used. The future research section is clear and easily translated. There is a clear and obvious need for well done randomized controlled trials comparing treatments versus control.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 AUA	Discussion	The authors propose that the primary endpoint should be symptomatic stone event. This is very reasonable since ultimately the goal of these treatments is to prevent patients from having symptomatic stones. However we believe it is just as important to track stone growth and interventions for stones in these patients. In some patients, particularly those with larger stones, symptoms may not be what determine the need for surgical intervention. Patients with asymptomatic stones may opt for surgery if their stones show evidence of growth or if they have an increase number of stones. It is important in any future studies also evaluate for stone growth radiographically as well as the number of interventions required in each arm.	As above, in this example, patients with asymptomatic stone growth determined to "need" surgery likely would be responding to a recommendation from their doctor that surgery is "needed." This argument doesn't prove that these patients would have clinically worse outcomes than patients with similar evidence of growth or increased number of stones. Though we systematically collected stone growth outcomes, we a priori judged stone growth to be a less important efficacy outcome than outcomes that directly cause patient symptoms, such as symptomatic stone recurrence. While it is possible that asymptomatic stone growth could lead to kidney damage, in this case the more direct patient-centered outcome still wouldn't' be stone growth but rather some clinically meaningful measure of kidney damage (see above). It is also possible that use of stone growth as a clinical outcome to guide treatment could lead to use of unnecessary and/or ineffective therapies in asymptomatic patients that may result in treatment related harms and costs. It does not appear that any threshold for clinically meaningful stone growth has been established. So, future long-term observational studies could investigate if and under what circumstances asymptomatic stone growth predicts symptomatic stone recurrence and therefore may be an appropriate surrogate for symptomatic stone recurrence. They could randomize patients with stone growth above some absolute stone size or growth rate threshold(s) to intervention vs. observation/watchful waiting to study the clinical benefits/harms including the number of interventions and associated complications required. We addressed these issues in the Discussion and added these recommendations to the Future Research Recommendations in the revised report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 AUA	Discussion	One other addition to the future research section would be studies to evaluate the cost-effectiveness of using these medications/dietary modifications to prevent stone recurrence. Included in the cost analysis should the utility and cost of following patients with repeat imaging and repeat serum and urine chemistries. Ultimately cost will play a role in any official policy and therefore this is something that must be evaluated along with efficacy.	We agree with this reviewer. However, AHRQ policy mandates that cost-effectiveness not be considered in any of their evidence reports. With that ~~restraint~~ constraint, we've recommended modeling studies evaluating the effectiveness and harms of different kidney stone evaluation, treatment and followup strategies versus a control strategy.
Public Reviewer #1 AUA	Discussion	We have a few specific comments on the future research commendations below: In Table C, under future research recommendations, it is recommended to use symptomatic stone episodes as the primary outcome parameter, or to at least separate symptomatic from radiographic stone recurrences. We have concerns about using symptomatic stones as the sole outcome parameter. We do not know what causes stones to become detached and/or to pass and most non-obstructing renal calculi are not symptomatic. Some patients never pass stones but only experience growth of existing stones or formation of new stones. By counting only symptomatic episodes as "recurrences", a significant number of episodes of true stone progression/recurrence will be missed. Although one could argue that symptomatic stone events comprise a more reproducible, easily countable outcome measure, there is still concern that 1) some "symptomatic" episodes, if not documented radiographically, may not actually reflect a stone event at all, 2) multiple stone events may be a result of the same stone (if the stone is not recovered) and 3) some stones may pass spontaneously asymptomatically. Although the issue is complicated, for future carefully designed trials, we tend to favor a strict definition of stone recurrence that includes radiographic evidence of new stones or stone growth, or treatment or passage of a previously unaccounted for stone. Ideally the imaging study of choice is CT, but concerns about excessive radiation exposure have led some to discourage its routine use in stone follow-up. With low dose CT providing fairly sensitive identification of stones without excessive radiation exposure (exposure on par with or minimally higher than KUB), this modality should be able to be safely applied in a properly designed trial.	The reviewer raises several valid concerns regarding our recommendation to use symptomatic stone episodes as the primary outcome parameter in future RCTs of treatments to prevent recurrent kidney stones. We have addressed them in several responses above and also have addressed them in our revised report in the both the Discussion and Future Research Recommendations sections.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 AUA	Discussion	Under Future Research Recommendations, Key Question 1, we recommend adding an RCT comparing empiric therapy without regard to metabolic background versus selective medical and/or dietary therapy based on urinary stone risk factors.	We agree with this recommendation for future research and have added it to the revised report.
Peer Reviewer #4	Figures	I found the figures (3 through 12) a bit difficult to read. Could there be vertical lines separating the columns?	We agree that these figures are not as easy to read as the surrounding text. These are generated from RevMan and unfortunately there is nothing we can do to improve their appearance.
Assimos, Dean	Appendix	Very thorough.	Thank you.
Peer Reviewer #1	General	This is a well done report that captures the state of the art regarding interventions to prevent kidney stone recurrence.	Thank you.
Peer Reviewer #2	General	The authors report on a meta-analysis of randomized controlled trials examining different medications and dietary modifications used for the prevention of recurrent nephrolithiasis. This is a clinically meaningful document. The prevalence of stones is increasing as is the cost of treatment. These factors make prevention of recurrent stones all the more important. The target population and audience are clearly defined. The target population is patients with kidney stones. The target audience is both providers (i.e. urologists and nephrologists) and patients. The key questions presented by the authors are appropriate to the topic. Patients with nephrolithiasis often undergo baseline metabolic work-up with 24 hour urine collections which guide further treatment. The question of whether these baseline studies predict treatment outcomes is very appropriate to this population. The authors also ask about the comparative effectiveness of medications and dietary changes in stone prevention. The authors also address potential adverse effects from these treatments which is important because many of these patients will be on stone-prevention regimens for life. Finally, the authors ask about whether follow up urine and serum chemistries predict outcomes.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	The report is well structured and the main points are clearly presented. The conclusions can be used to inform policy and practice decisions. However, the main conclusion to be drawn from this report is that future well-performed, randomized prospective trials are needed. Currently, there is limited evidence to support practice decisions. This is not a limitation of this report but rather a limitation on the available data	Thank you.
Peer Reviewer #3	General	The report does a good job of summarizing all the relevant studies. Particularly useful are the tables in the appendices. The key questions are appropriate and clear.	Thank you.
Peer Reviewer #3	General	The report is well structured and clear	Thank you.
Peer Reviewer #4	General	The report is clinically meaningful. The target population and audience are defined. Key questions are explicity stated.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	Throughout the manuscript, the term "citrate" is used to refer to pharmacologic therapy with either potassium or sodium citrate. I find it confusing in 3 respects: (1.) in the review of pharmacologic trials, I would like to know the form of citrate used; and (2.) some could perhaps be under the impression that calcium citrate could fall under the rubric of "citrate;" and (3.) some might understand "citrate" therapy to include dietary strategies to enhance urinary citrate excretion.	To address this reviewer concern, we revised the Executive Summary as follows: "Previous systematic reviews of randomized controlled trials (RCTs) of dietary and pharmacological therapies have reported that increased fluid intake,[17] thiazide diuretics,[18-20] and citrate pharmacotherapy[20,21] reduce stone recurrence,…" We made similar modifications at other locations in the Executive Summary and in the main report to clarify that these studies evaluated citrate pharmacotherapy and not citrate diet therapy. The main report already detailed all the specific citrate agents evaluated, but we added a sentence at the end to state explicitly that calcium citrate was not evaluated: "Among the trials that compared citrate versus placebo or control, two utilized fixed potassium citrate doses of 60 mEq/day.[37,39] Two other trials used sodium-potassium citrate, at 5-10 gm/day in one study,[57] and, in a second study, at 30 gm/day initially followed by adjustments to keep urine pH between 7.0 and 7.2.[53] Last, one trial used magnesium-potassium citrate (42 mEq/day potassium, 21 mEq/day magnesium, and 63 mEq citrate).[38] No trials assessed calcium citrate."
Peer Reviewer #4	General	Report is well-organized. Main points are clearly presented. Executive summary is useful. Conclusions will be useful for clinical management and, thankfully, may be particularly useful in designing future research studies.	Thank you.
Peer Reviewer #6	General	Clinically meaningful; questions addressed appropriately. Key questions answered ina succinct fashion	Thank you.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 AUA	General	The aim of the comparative effectiveness review of preventative medical strategies was to determine the efficacy and adverse effects of dietary and pharmacologic therapies for the prevention of recurrent nephrolithiasis and to assess if urinary biochemical background or follow-up urinary parameters were predictive of treatment success. This is a clinically meaningful document. The prevalence of stones is increasing as is the cost of treatment. These factors make prevention of recurrent stones all the more important. The target population and audience are clearly defined. The target population is patients with kidney stones. The target audience is both providers (i.e. urologists and nephrologists) and patients. The key questions presented by the authors are appropriate to the topic. Patients with nephrolithiasis often undergo baseline metabolic work-up with 24 hour urine collections which guide further treatment. The question of whether these baseline studies predict treatment outcomes is very appropriate to this population. The authors also ask about the comparative effectiveness of medications and dietary changes in stone prevention. The authors also address potential adverse effects from these treatments which is important because many of these patients will be on stone-prevention regimens for life. Finally, the authors ask about whether follow up urine and serum chemistries predict outcomes. This is a very carefully done, comprehensive analysis of currently available literature on stone metaphylaxis.	Thank you.
Public Reviewer #1 AUA	Discussion	The report is well structured and the main points are clearly presented. The conclusions can be used to inform policy and practice decisions. However, the main conclusion to be drawn from this report is that future well-performed, randomized prospective trials are needed. Currently, there is limited evidence to support practice decisions. This is not a limitation of this report but rather a limitation on the available data.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer American College of Physicians	Results	Quality ratings need to be supported with specific elements or deficiencies that lead you to conclude that there is low or insufficient evidence.	For the assessment of individual study quality, following criteria developed by the Cochrane Collaboration, we used four domains (i.e. allocation concealment, blinding, intention to treat analysis, and description of withdrawals). We rated those trials that had a favorable rating for all four domains as "good" quality, those with unfavorable ratings for all four of these domains as "poor" quality, and all other trials as "fair" quality. We re-reviewed our assessments for individual study quality. As a result, changed Borghi 2002 from "fair" to "good"; and Kocvara and Borghi from "fair" to "poor".
Public Reviewer American College of Physicians	Methods	Strength of evidence need to be supported with specific elements or deficiencies that lead you to conclude that there is low or insufficient evidence.	We rated the body of evidence for each treatment comparison and outcome based on four domains (risk of bias, directness, precision, and consistency). We rated the evidence for all treatment comparisons as direct. We rated 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. We rated the SOE as moderate when the pooled estimated risk of effect of a treatment comparison was bounded by a narrow 95% confidence interval and was consistent between trials. Treatment comparisons with a single trial with a wide 95% confidence interval that was compatible with both a clinically significant benefit and harm were rated as insufficient SOE. Treatment comparisons with evidence from 1 to 2 trials, with narrower 95% confidence intervals and higher rates of stone recurrence were rated as low SOE. We revised the text and tables throughout to reflect these changes.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer American College of Physicians	Results	Some of the overall quality ratings also appear a bit out of line with the reported deficiencies. In particular, it is difficult to attach anything other than "poor" to the Kocvara (1999) and Borghi (1996) trials based on the unclear allocation concealment, not stated blinding, no intent-to-treat, and no reporting of withdrawals. Review your quality assessments and revise the tables and the text accordingly.	Thank you for your comment. We re-reviewed the quality ratings for each study. As a result we decided to change the quality rating for 3 trials. We agree with the reviewer that both Kocvara 1999 and Borghi 1996 are more appropriately rated "poor" quality, rather than "fair." We also believe that Borghi 2002 is more appropriately rated as "good" quality, rather than "fair." We made these changes in the report and tables.
Public Reviewer American College of Physicians	Results	Reconsider your strength of evidence statements. Inconclusive is the more likely assessment of the available evidence reported in this study.	We re-reviewed the strength of evidence ratings throughout the report. As a result we changed the SOE from low to insufficient for ~~several~~ five treatment comparisons for which both the lower bound of the 95% confidence interval was less than 0.5 and the upper bound was greater than 2.0 (i.e., increased fluid intake vs. control radiographic recurrence, thiazides vs. placebo symptomatic recurrence, allopurinol vs. placebo radiographic recurrence, AHA vs. placebo radiographic recurrence, and thiazide + allopurinol vs. thiazide composite recurrence). Consistent with the AHRQ Methods Guide, data that is highly imprecise may be graded as insufficient if the confidence intervals include within their bounds estimates that indicate that one treatment is both clinically better and worse than the other. For ~~two~~ one additional treatment comparison~~s~~ ~~(radiographic recurrence outcome for increased fluid vs. control, and~~ symptomatic recurrence outcome for allopurinol vs. placebo), the 95% confidence intervals excluded a clinically significant increase in risk of recurrence, so we stand by our initial assessment of low SOE.