**Supplementary file 1**

## I. Criteria for considering studies for this review

### *Types of studies*

All randomised controlled trials (RCTs) and quasi-RCTs (e.g. allocation using alternation, case record numbers, date of birth or day of the week).

### *Types of participants*

- **Inclusion criteria:** Studies performed on adults or children with idiopathic hypercalciuria, defined as hypercalcuria in the absence of any evidence of secondary cause, undergoing pharmacological treatment to control the illness and its complications.
- **Exclusion criteria:**Patients with secondary hypercalciuria or suffering other illnesses that could cause osteopenia or urinary stones.

### *Types of interventions*

We investigated any pharmacological intervention for preventing complications in idiopathic hypercalciuria versus control/comparator. The comparators could be placebo, other pharmacological intervention or a different administration mode or dose of the same treatment. We assessed only those interventions that had a follow-up period of at least six months based on the slow rate of stone formation (1–3).

Concomitant interventions were allowed if they were the same in both the intervention and comparator groups. If a trial included multiple arms, we included any arm that met the inclusion criteria in the review.

### *Types of outcome measures*

Measurement of outcomes assessed was not used as an eligibility criterion. Thus, we did not exclude trials that did not report all of our primary or secondary outcome measures. If a trial was deemed eligible for inclusion but did not report any of our primary or secondary outcomes, we did not include it and briefly described its basic information in the Characteristics of excluded studies table (section IV of this supplementary file).

- **Primary outcomes:**
  - Stone free patients
  - Urinary symptoms
  - Severe adverse events
- **Secondary outcomes:**
  - Stone formation rate.
  - Changes in bone mass density.
  - Quality of life.
  - Calciuria.
  - Any adverse events

### *Method and timing of outcome measurement*

All outcomes were assessed at the end of treatment period.

- Stone-free patients: number or proportion of participants who had not formed stones during the study follow up. Stones were assessed by radiography, ultrasonography, pyelography or spontaneous passage.
- Urinary symptoms: number or proportion of participants who had suffered from haematuria, dysuria, enuresis or abdominal pain. Measured as prevalence of those symptoms.
- Severe adverse events: number or proportion of participants who had suffered from any adverse event that leads to the discontinuation of treatment.
- Urinary tract infection (UTI): number or proportion of participants with urinary symptoms and a positive urine culture.
- Stone formation rate: number of stones that were detected during the study follow up. Stones were assessed by radiography, ultrasonography, pyelography or spontaneous passage.
- Changes in bone mass: measured through dual-energy X-ray or absorptiometry.
- Quality of life: assessed by a validated scale or assessed as days in hospital, days off work or days off school.
- Calciuria: reported as 24-hour calciuria or urinary calcium/creatinine ratio.
- Any adverse events: number or proportion of participants who had suffered from any adverse regardless of severity.

## II. Search methods for identification of studies

### *Electronic searches*

The search update for the previous published version 2009 has been conducted in two stages:

On September 2014, searches were conducted following the Cochrane Renal Group search strategy recommendations. Those searches were performed in the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The period searched was 2008 to 30 September 2014. The Cochrane Renal Group’s Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. Weekly searches of MEDLINE OVID SP;
3. Hand searching of renal-related journals and the proceedings of major renal conferences;
4. Searching of the current year of EMBASE OVID SP;
5. Weekly current awareness alerts for selected renal journals;
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of hand-searched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Renal Group.

Afterwards, and subsequent to the transfer of this review from the Cochrane Renal Group to the Cochrane Urology Group, individual searches were run in MEDLINE, EMBASE (both accessed through Ovid), and CENTRAL (accessed through The Cochrane Library) up to April 17th 2018. We searched the International Clinical Trials Register (ICTRP)

Search Portal as well as Clinical trial.gov for on-going studies (up to April 17th 2018). Additionally, we searched grey literature in Open Grey (www.opengrey.eu) and Grey Literature Report (www.greylit.org/about) (up to April 17th 2018).

No restrictions based on language of publication were applied as eligibility criteria.

See **Appendix 1** for search terms used in strategies (both for Renal and for Urology Cochrane Groups) for this review update.

### *Searching resources*

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
3. Abstracts of the annuals meetings of the Urological and Nephrological societies (European and American) from 2013-2017 (See **Appendix 2**).

## III. Data collection and analysis

### *Selection of studies*

We used reference management software (EndNote) to identify and remove potential duplicate records. Four authors working in pairs (JE, EP, AB and AF) independently assessed the titles, abstract, or both, of records identified in the search against the predefined inclusion criteria to determine which studies should be assessed further. Four review authors working in pairs (JE, EP, AB and AF) investigated all potentially-relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the Cochrane Handbook for Systematic Reviews of Interventions (4). We resolved any discrepancies through discussion or arbitration by a third review author (JE or JF). If resolution of a disagreement was not possible, we designated the study as 'awaiting classification' and contacted study authors for clarification. We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We presented an adapted PRISMA flow diagram showing the process of study selection (5).

### *Data extraction and management*

We developed a dedicated data abstraction form that we pilot tested ahead of time. For studies that fulfilled inclusion criteria, four authors working in pairs (JE, EP, NF, and AB) independently abstracted the following information, which we provided in the 'Characteristics of included studies' table:

- Study design
- Study dates (if dates are not available then this was reported as such)
- Study settings and country
- Participant inclusion and exclusion criteria
- Participant details, baseline demographics
- The number of participants by study and by study arm
- Details of relevant experimental and comparator interventions such as dose, route, frequency, and duration

- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups
- Study funding sources
- Declarations of interest by primary investigators

We extracted outcomes data relevant to this Cochrane review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals for population of a two by two table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we attempted to obtain means and standard deviations or data necessary to calculate this information. We resolved any disagreements by discussion, or, if required, by consultation with a third review author (JF or JE).

We provided information, including trial identifier, about potentially relevant ongoing studies in the table 'Characteristics of ongoing studies'

We attempted to contact authors of included studies to obtain key missing data as needed.

***Dealing with duplicate and companion publications***

In the event of duplicate publications, companion documents or multiple reports of a primary study, we maximized yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes. We presented the characteristics of included studies in two additional summary tables.

***Assessment of risk of bias in included studies***

The risk of bias of studies included was assessed independently by five authors (JE, EP, NF, AB, and AF), without blinding to authorship or journal. Studies were assessed using the risk of bias assessment tool (4). Focusing on the risk of selection bias through assessment of allocation concealment and random sequence generation, performance bias through assessment of blinding of participants and personnel, detection bias through assessment of blinding of outcome assessment, attrition bias through assessment of incomplete outcome data, and reporting bias through assessment of selective reporting of information. Discrepancies were resolved by discussion with a sixth author (MR).

Risk of detection bias was evaluated separately for objective and subjective outcomes.

We defined as objective outcomes:

- changes in bone mineral density;
- changes in calciuria.

We defined as subjective outcomes:

- stone formation;
- reduction in urinary symptoms;
- improvement in quality of life;
- adverse events.

Results of the assessment of risk of bias were presented in a 'Risk of bias' graph and a 'Risk of bias' summary figure.

***Measures of treatment effect***

We analysed the data using RevMan 5 software (Review Manager). We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MDs) with 95% CIs unless different studies use different measures to assess the same outcome, in which case we expressed data as standardized mean differences (SMDs) with 95% CIs.

### *Unit of analysis issues*

We identified, among those studies included in the analysis, the presence of crossover trials, cluster-randomised trials or trials with more than two intervention groups for inclusion in the review. If any such study were identified, we would handle them following the Cochrane Handbook for Systematic Reviews of Interventions.

### *Dealing with missing data*

Where data were missing or unclear, we contacted the original authors of studies to request additional data. We performed intention-to-treat (ITT) analyses if data were available; we otherwise performed available case analyses. We did not impute missing data. We investigated attrition rates, e.g. dropouts, losses to follow-up and withdrawals, and critically appraised issues of missing data.

### *Assessment of heterogeneity*

We assessed the heterogeneity (inconsistency) of included studies using the $Chi^2$ test, and we considered a P value of less than 0.10 as statistically significant heterogeneity. Furthermore, we measured the quantity of inconsistency using the $I^2$ statistic (6). We interpreted the $I^2$ statistic as follows:

- 0% to 40%, may not be important;
- 30% to 60%, represents moderate heterogeneity;
- 50% to 90%, represents substantial heterogeneity;
- 75% to 100%, represents considerable heterogeneity.

When we found heterogeneity, we attempted to determine possible reasons for it by examining individual study and subgroup characteristics.

### *Assessment of reporting biases*

We attempted to obtain study protocols to assess for selective outcome reporting.

Publication bias and small study effects were planned to be investigated drawing funnel plots if 10 or more studies were available for a single outcome. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. If any funnel plot was generated, we therefore interpreted results carefully.

### *Data synthesis*

We planned to undertake a meta-analysis only if participants, interventions, comparisons and outcomes were judged to be sufficiently similar to ensure the clinical meaningful. For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we used the inverse variance method; and for time-to-event outcomes, we used the generic inverse variance method. We used the Review Manager software to perform analysis (Review Manager).

### *Summary of findings table*

We presented the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (JVAF, JE) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT: GRADEpro Guideline Development Tool. We resolved any discrepancies by consensus, or, if needed, by arbitration by a third review author (NF). For each comparison, we presented a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about: the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011, Schünemann 2011)). If meta-analysis is not possible, we presented results in a narrative 'Summary of findings' table. We used the controlled vocabulary suggested by Glenton 2010 to summarize the findings of the Summary of Findings table in the Plain Language Summary.

We summarized the evidence for the comparison "Diuretics versus control" and "Diuretics versus alendronate" for the following outcomes:

- stone-free patients
- Urinary symptoms
- Severe adverse events
- Stone formation rate

### *Subgroup analysis and investigation of heterogeneity*

No subgroup analyses were planned in the review.

### *Sensitivity analysis*

We planned to conduct the following sensitivity analyses to assess robustness of the main analysis to the methods applied:

- Sensitivity analysis to identify individual studies that were contributing to significant heterogeneity ($I^2$ value greater than 50%);
- Sensitivity analysis applying the fixed-effect model;
- Sensitivity analysis restricted to trials at an overall low risk of bias across all domains for the main outcomes.

## IV. Risk of bias in included studies and reasons for exclusion

| Ala-Opas 1987: risk of bias table | | |
|---|---|---|
| **Risk of Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation process to permit judgement. See "other biases" for further exploration of selection bias. |
| Allocation concealment (selection bias) | Unclear risk | No information on the method for allocation was available. |
| Blinding of participants and personnel (performance bias) | High risk | Not blinded. |
| Blinding of outcome assessment (detection bias)<br>Stone free patients / stone formation rate | High risk | There is no information about blinding of the professional who reported the x-ray or ultrasound evaluations. |
| Blinding of outcome assessment (detection bias)<br>Adverse events | High risk | Not blinded. |
| Blinding of outcome assessment (detection bias)<br>Calciuria | Low risk | No blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Incomplete outcome data (attrition bias)<br>Stone free patients / stone formation rate | Low risk | All randomised patients were included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Adverse events | Unclear risk | The adverse events are not clearly specified. |
| Incomplete outcome data (attrition bias)<br>Calciuria | Low risk | All randomised patients were included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Selective reporting (reporting bias) | Unclear risk | We were unable to find the protocol to check if all the pre-specified outcomes were reported in the published manuscript. |
| Other biases | High risk | Only the subgroup of hyper calciuric patients included in the RCT is analysed in this review. The distribution of these patients across the intervention and control group was not similar (50% and 40% of participants in each group, respectively), suggesting the possibility of a selection bias derived from analysing this subgroup of participants. The stone formation/year in the pre-treatment period was different in the bran vs bran+ thiazides group: 0.784+/-0.943 vs 0.516+/-0.258 P = 0.047. |

| Borgi 1993: risk of bias table | | |
|---|---|---|
| **Risk of Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation process to permit judgement. |
| Allocation concealment (selection bias) | Unclear risk | No information on the method used is available. |
| Blinding of participants and personnel (performance bias) | High risk | Not blinded. |
| Blinding of outcome assessment (detection bias)<br>Stone free patients / stone formation rate | High risk | There is no information about blinding of the professional who reported the x-ray or ultrasound evaluations. |
| Blinding of outcome assessment (detection bias)<br>Adverse events | High risk | Not blinded. |
| Blinding of outcome assessment (detection bias)<br>Calciuria | Low risk | No blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Incomplete outcome data (attrition bias)<br>Stone free patients / stone formation rate | Unclear risk | Almost 15% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Adverse events | Unclear risk | Almost 15% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Calciuria | Unclear risk | Almost 15% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Selective reporting (reporting bias) | Unclear risk | We were unable to find the protocol to check if all the pre-specified outcomes were reported in the published manuscript. |
| Other biases | Low risk | No other biases were detected. |

| Fernandez-Rodriguez 2006:: risk of bias table | | |
|---|---|---|
| **Risk of Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation process to permit judgement. See "other biases" for further exploration of selection bias. |
| Allocation concealment (selection bias) | Unclear risk | Randomisation stated but no information on method used is available. |
| Blinding of participants and personnel (performance bias) | High risk | Not blinded. |
| Blinding of outcome assessment (detection bias)<br>Stone free patients / stone formation rate | High risk | There is no information about blinding of the professional who reported the x-ray or ultrasound evaluations. |
| Blinding of outcome assessment (detection bias)<br>Adverse events | Unclear risk | No information provided. |
| Blinding of outcome assessment (detection bias)<br>Calciuria | Low risk | No blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Incomplete outcome data (attrition bias)<br>Stone free patients / stone formation rate | Low risk | All randomised patients were included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Adverse events | Unclear risk | No information provided. |
| Incomplete outcome data (attrition bias)<br>Calciuria | Low risk | All randomised patients were included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Selective reporting (reporting bias) | Unclear risk | We were unable to find the protocol to check if all the pre-specified outcomes were reported in the published manuscript. |
| Other biases | High risk | Only the subgroup of hyper calciuric patients included in the RCT is analysed in this review. The distribution of these patients across the intervention and control group was not similar (42% and 34% of participants in each group, respectively), suggesting the possibility of a selection bias derived from analysing this subgroup of participants. |

| Giusti 2009: risk of bias table | | |
|---|---|---|
| **Risk of Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Patients underwent "computer generated block randomisation". |
| Allocation concealment (selection bias) | Unclear risk | No information on the method for allocation was available. |
| Blinding of participants and personnel (performance bias) | Low risk | No blinding but the co-intervention was controlled and measured strictly in the three groups. |
| Blinding of outcome assessment (detection bias)<br>Stone free patients / stone formation rate | Unclear risk | No information provided. Outcome not assessed. |
| Blinding of outcome assessment (detection bias)<br>Adverse events | High risk | Not blinded. |
| Blinding of outcome assessment (detection bias)<br>Calciuria | Low risk | No blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>Bone mineral density | Low risk | No blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding. |
| Incomplete outcome data (attrition bias)<br>Stone free patients / stone formation rate | Unclear risk | No information provided. Outcome not assessed. |
| Incomplete outcome data (attrition bias)<br>Adverse events | Unclear risk | Almost 13% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Calciuria | Unclear risk | Almost 13% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Bone mineral density | Unclear risk | Almost 13% of randomised patients were not included in the final analyses. |
| Selective reporting (reporting bias) | Unclear risk | We were unable to find the protocol to check if all the pre-specified outcomes were reported in the published manuscript. |
| Other biases | Low risk | No other biases were detected. |

| Ohkawa 1992: risk of bias table | | |
|---|---|---|
| **Risk of Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation process to permit judgement. |
| Allocation concealment (selection bias) | Unclear risk | No information on method for allocation was available. |
| Blinding of participants and personnel (performance bias) | High risk | No blinding. |
| Blinding of outcome assessment (detection bias)<br>Stone free patients / stone formation rate | High risk | No blinding. |
| Blinding of outcome assessment (detection bias)<br>Adverse events | High risk | Not blinding. |
| Blinding of outcome assessment (detection bias)<br>Calciuria | Low risk | No blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding. |
| Blinding of outcome assessment (detection bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Incomplete outcome data (attrition bias)<br>Stone free patients / stone formation rate | Unclear risk | Almost 17% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Adverse events | Unclear risk | Almost 17% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Calciuria | High risk | More than 20% of randomised patients were not included in the final analyses. |
| Incomplete outcome data (attrition bias)<br>Bone mineral density | Unclear risk | No information provided. Outcome not assessed. |
| Selective reporting (reporting bias) | Unclear risk | We were unable to find the protocol to check if all the pre-specified outcomes were reported in the published manuscript. |
| Other biases | Low risk | No other biases were detected. |

***Characteristics of excluded studies***

| Excluded study | Reason for exclusion |
|---|---|
| Ahlstard 1995 | Unable to get data on hyper calciuric patients |
| Arrabal-Martin 2016 | Not an RCT |
| Arrabal-Polo 2013 | Not an RCT |
| Borghi 1996 | No pharmacologic intervention (only water intake increase) |
| Breslau 1998 | Treatment and follow-up lasted three months |
| Brocks 1981 | No patients with hypercalciuria |
| Caudarella 2015 | Not an RCT |
| Cicerello 1994 | Although 14 among the 70 included participants had hypercalciuria, outcome data was not available for this subgroup. We were unable to get data on hyper calciuric patients after contacting the authors |
| Coe 1988 | Not an RCT |
| Ettinger 1976 | Unable to get data on hyper calciuric patients after contacting the authors |
| Ettinger 1988 | Unable to get data on hyper calciuric patients after contacting the authors |
| Ettinger 1997 | Unable to get data on hyper calciuric patients after contacting the authors |
| Ferroni 2015 | Short intervention period and follow-up (6 weeks) and no specific data of hyper calciuric patients subgroup |
| Heller 1998 | Not an RCT |
| Herrmann 1999 | No patients with hypercalciuria |
| Jaeger 1986 | Not an RCT |
| Jaipakdee 2004 | Unable to get data on hyper calciuric patients after contacting the authors |
| Jiménez Verdejo 2001 | No patients with hypercalciuria |
| Kato 2004 | No patients with hypercalciuria |
| Laerum 1984 | Unable to get data on hyper calciuric patients after contacting the authors |
| Lamid 1984 | Patients with spinal cord injury. No idiopathic hypercalciuria. Treatment only last two weeks |
| Lau 1977 | Single arm study. Very short intervention period (7 days). |
| Legroux-Gerot 2004 | Compares patients with hypercalciuria and patients with osteoporosis without hypercalciuria |
| Leone 1987 | Impossible to extract data. Only graphical representation of the results. |
| Lojanapiwat 2011 | Unable to get separated data on hyper calciuric patients |
| Lynam 2015 | Not an RCT |
| Martins 1996 | Treatment and follow-up only lasted three months |
| Mortensen 1986 | There were no patients with hypercalciuria |
| Niroomand 2016 | Treatment and follow-up only lasted four weeks |
| NCT00004284 | No data available. Only a protocol of a RCT registered |
| Nishiura 2004 | Treatment and follow-up only lasted three months |
| No authors 2017 | None of the screened abstracts met the inclusion criteria |
| Osther 2010 | Not an RCT. No treatment follow-up. Only punctual effect of acid overload on calciuria |
| Osther 2010a | Not an RCT. No treatment follow-up. Only punctual effect of acid overload on calciuria |
| Parks 2003 | Not an RCT |
| Raja 2002 | No patients with idiopathic hypercalciuria |
| Reusz 1998 | There was no control group |

| | |
|---|---|
| Ruml 1995 | Bedrest immobilization patients. No patients with idiopathic hypercalciuria. Treatment only lasts 5 weeks |
| Sami 2017 | Unable to get data after contacting the authors |
| Scholz 1982 | Unable to get separated data on hyper calciuric patients |
| Smith 1983 | No patients with idiopathic hypercalciuria |
| Soygür 2002 | Unable to get data on hyper calciuric patients after contacting the authors |
| Tasian 2014 | Not an RCT |
| Yousefi 2011 | Treatment and follow-up only last three months |
| Yousefi 2013 | Treatment and follow-up only last three months |
| Yousefichaijan 2017 | Treatment and follow-up only last three months |
| Zhang 2015 | No patients with hypercalciuria |
| Zoccali 1993 | No access to the whole original study document |

## V. Differences between protocol and review

### *Objectives*

- The objectives were simplified in a single objective covering the two previous ones

### *Methods*

- This section has been extensively modified in order to comply with the current methodological expectations for the conduct of systematic reviews of interventions (MECIR).
- We deleted the section on minimum duration of the intervention as an inclusion criteria (this has not affected the inclusion decisions).
- We added a sentence "Measurement of outcomes assessed was not used as an eligibility criterion"
- The outcomes of the review were re-assessed in order focus on patient-centered outcomes: stone-free patients and urinary symptoms. Additionally an outcome addressing adverse events was added as a primary outcome. We placed those outcomes addressing surrogate markers (stone formation rate, changes in bone mass density and calciuria) as secondary outcomes.
- The search methods were updated.
- The methods for the assessment of Risk of Bias were updated to the current tool provided by Cochrane.
- A section under Data Synthesis was added to describe GRADE methods for Summary of Findings Table
- Three options for sensitivity analysis were added.

### *Results*

With respect to the previous version of the review:

- The comparison "thiazides vs. comparator" has been divided in two comparisons (vs. control and vs. alendronate).
- We re-assessed the eligibility of Breslau et al., excluding this study from this review
- We did not perform sensitivity analysis to assess clinical heterogeneity or risk of bias due to the scarcity of information

## Supplementary file references

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**Apendix 1: electronic search strategies**

| Database searched | Search terms |
|---|---|
| CENTRAL | To update this Systematic review we performed two searches. The first was performed following the recommendations of the Cochrane Renal Group Search strategies included those bibliographic references up to April 2015. Afterwards, in April 2018 we expanded the search including all 2015, 2016, 2017 as well as part of 2018 bibliographic references following the Cochrane Urology Group search strategies recommendations.<br><br>The Cochrane Library<br><br>Cochrane Central Register of Controlled Trials: Issue 6 of 12, April 2015<br><br>1. MeSH descriptor: [Hypercalciuria] this term only<br>2. MeSH descriptor: [Calcium Metabolism Disorders] this term only<br>3. hypercalciuri*:ti,ab,kw in Trials<br>4. #1 or #2 or #3 in Trials<br><br>The Cochrane Library<br><br>Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2018<br><br>#1 MeSH descriptor: [Hypercalciuria] explode all trees<br><br>#2 MeSH descriptor: [Calcium Metabolism Disorders] explode all trees<br><br>#3 hypercalciur*:ti,ab<br><br>#4 hypercalcinur*:ti,ab<br><br>#5 #1 or #2 or #3 or #4<br><br>#6 #1 or #2 or #3 or #4 Publication Year from 2014 to 2018, in Trials |
| MEDLINE | Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <2008 to 2014><br><br>1. Hypercalciuria/<br>2. hypercalciuri$.tw.<br>3. Calcium Metabolism Disorders/<br>4. or/1-3<br><br>Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to April 17th 2018><br><br>1. Hypercalciuria/<br>2. Calcium Metabolism Disorders/<br>3. hypercalciur*.ti,ab.<br>4. hypercalcinur*.ti,ab.<br>5. 1 or 2 or 3 or 4<br>6. randomized controlled trial.pt.<br>7. controlled clinical trial.pt. |

| | |
|---|---|
| | 8. randomized.ab.<br>9. placebo.ab.<br>10. drug therapy.fs.<br>11. randomly.ab.<br>12. trial.ab.<br>13. groups.ab.<br>14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13<br>15. exp animals/ not humans.sh.<br>16. 14 not 15<br>17. 5 and 16<br>18. limit 17 to yr="2014 -Current" |
| EMBASE | Ovid Embase <1974 to 2015 April 30><br><br>1. Idiopathic Hypercalciuria/<br>2. hypercalciuria$.tw.<br>3. or/1-2<br><br>Ovid Embase <1974 to April 17th 2018><br><br>1. exp hypercalciuria/<br>2. hypercalciur*.ti,ab.<br>3. hypercalcinur*.ti,ab..<br>4. 1 or 2 or 3<br>5. random:.tw. or clinical trial:.mp. or exp health care quality/<br>6. 4 and 5<br>7. limit 6 to yr="2014 -Current" |
| GREY LITERATURE | Open Grey (http:/www.opengrey.eu) (up to April 17th 2018)<br><br>1. hypercalciuria<br><br>Grey Literature Report (http:\www.greylit.org/about) (up to April 17th 2018)<br><br>1. hypercalciuria |
| CLINICAL TRIAL REPORTS | International Clinical Trials Register (ICTRP) Search Portal as well as Clinical trial.gov for on-going studies (up to April 17th 2018)<br><br>1. hypercalciuria |

## Appendix 2: Searches in conferences

| Conference | Website (last access April 2018) |
|---|---|
| American Urology Association May 2017 | www.jurology.com/issue/S0022-5347(17)X0003-7 |
| American Urology Association May 2016 | www.jurology.com/issue/S0022-5347(16)X0004-3 |
| American Urology Association May 2015 | www.jurology.com/issue/S0022-5347(14)X0014-5 |
| American Urology Association May 2014 | www.jurology.com/issue/S0022-5347(13)X0019-9 |
| American Urology Association May 2013 | www.jurology.com/issue/S0022-5347(13)X0013-8 |
| European Association of Urology 2018 | eau18.uroweb.org/ |
| European Association of Urology 2017 | eau17.uroweb.org/ |
| European Association of Urology 2016 | eaumunich2016.uroweb.org/resource-centre/ |
| European Association of Urology 2015 | eaumadrid2015.uroweb.org/ |
| European Association of Urology 2014 | eaustockholm2014.uroweb.org/ |
| American Society of Nephrology 2017, 2016, 2015, 2014, 2013 | www.asn-online.org/education/kidneyweek/archives/ |