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REVIEW

Thiazide and thiazide-like diuretics for kidney stones recurrence: a systematic review and network meta-analysis of randomised controlled trials

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Abstract

Purpose Thiazide (THZ) and thiazide-like (TL) diuretics are routinely prescribed and considered to be the gold-standard prophylaxis for kidney stones (KS) recurrence in current guidelines despite having limited evidence. Thus, we aimed to investigate the efficacy and safety of different doses of THZ and TL diuretics in preventing KS recurrence.

Methods We searched for randomised controlled trials in PubMed, Web of Science, Embase, CENTRAL, and clinical trials registries from their inception through January 2025. The clinical or radiological KS recurrence was the primary endpoint, while the occurrence of adverse effects at any time was the secondary endpoint. We estimated odds ratio (OR) in a frequentist random-effects network meta-analysis with $P<0.05$. This study was prospectively registered (CRD42025650062).

Results Nine trials ($n=999$) were included. Chlorthalidone 50 mg/d (OR: 0.18, 95% confidence interval [CI] 0.04–0.88), hydrochlorothiazide 50 mg/d (OR: 0.52, CI 0.29–0.93), and trichlormethiazide 4 mg/d (OR: 0.26, CI 0.10–0.68) were different from placebo in terms of KS recurrence. There was no evidence of dose-dependent effect when comparing hydrochlorothiazide 50 mg/d to 12.5 mg/d (OR: 0.58, CI 0.25–1.34) or 25 mg/d (OR: 0.65, CI 0.28–1.48), nor comparing chlorthalidone 50 mg/d to 25 mg/d (OR: 0.80, CI 0.12–5.20). Only trichlormethiazide 4 mg/d (OR: 49.96, CI 1.78–1 402.80) provoked more adverse effects than placebo.

Conclusion Although some therapies were statistically different from placebo, the current evidence does not support their use in preventing KS recurrence due to several limitations, indicating that THZ and/or TL diuretics should not be routinely prescribed. Further well-designed trials are urgently needed to address head-to-head comparisons and provide high-quality evidence.

Keywords Kidney calculi · Nephrolithiasis · Network meta-analysis · Systematic review · Thiazides

Introduction

Kidney stone (KS) disease is a disorder characterised by the formation of solid crystalline masses within urinary tract [1, 2], being a known risk factor for various comorbidities, including chronic kidney disease [3], metabolic syndrome, and cardiovascular diseases [1, 2]. There are often debilitating symptoms during an acute episode, significantly impacting patients' quality of life [4], yielding pain, nausea, vomiting, and – in some cases – kidney failure [4]. Modern treatment options for KS disease include lithotripsy, ureteroscopy, and percutaneous nephrolithotomy [5], which are chosen according to the size and stone location, symptom severity, insurance coverage, and patients' preference

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[4]. Despite existence of various modern treatments, stone recurrence remains a significant clinical challenge [5], with recurrence rates up to 50% within 5–10 years, and 75% within 20 years of first episode [2]. Moreover, KS disease and its recurrence strongly impact on the economy, as $9 billion dollars was the inflation-adjusted cost of treating KS disease in 2021 in the United States, in addition to an indirect cost of $1.5 billion per year due to missed workdays [4]. Thus, decreasing the number of new and recurrent KS episodes would reduce the overall cost of this disease management and financial burden [5].

The European Association of Urology (EAU) and the American Urological Association (AUA) recommend fluid intake, nutritional advice for a balanced diet, and lifestyle advice to normalise general risk factors [6, 7] as general preventive measures for KS disease, however, further stone analysis should be undertaken, in addition to stratifying patients in low-risk and high-risk for KS formation [6]. Thus, despite general preventive measures, high-risk patients may benefit from further specific prophylaxis to reduce stone formation [6]. To address this, prophylaxis has been proposed and routinely performed by using thiazide (THZ) and thiazide-like (TL) diuretics to reduce new and recurrent calcium stone formation [5–7], which are based on these drugs' mechanism to reduce urinary calcium excretion by increasing sodium and calcium reabsorption in proximal tubules and calcium reabsorption in distal tubules [8].

However, previously published reviews and meta-analysis focused solely on comparing THZ and/or TL diuretics to placebo or no treatment [6, 7, 9–11], overlooking comparisons between treatments and their doses. A deeper understanding of these drugs' effect on KS recurrence is essential, since inappropriate doses may not only fail to prevent recurrent KS disease, but also lead to severe outcomes, including hypokalaemia [12], hyponatremia [13], hypomagnesemia [14], and increased risk for skin cancer [15]. The increase in sodium reabsorption by THZ and/or TL diuretics promotes a lumen negative gradient that favours potassium excretion, exhibiting a dose-dependent effect and a worse hypokalaemia with long-acting agents, including chlorthalidone [12]. Moreover, THZ and TL diuretics act by blocking sodium chloride cotransport in distal convoluted tubules, impairing free water clearance and preventing achievement of maximally diluted urine, in addition to reducing the paracellular reabsorption of magnesium ions in the thick ascending loop of Henle [12]. In the opposite direction, underdosing may lead to inadequate KS prophylaxis [6, 7].

In current guidelines [6, 7], THZ and TL diuretics are considered as standard prophylaxis for recurrent calcium KS in current guidelines, however, the recently published NOSTONE trial [16] contested this practice and instigated for further and more meticulous analyses. Understanding how different drugs and doses may affect KS recurrence may impact on current approach on prophylaxis for KS disease, in addition to improving patient care, as current recommendations are mostly based on these drugs' mechanism of action rather than on clinical evidence of recurrence rates.

Thus, we aimed to investigate the efficacy and safety of different doses of THZ and TL diuretics in preventing KS recurrence.

Materials and methods

Search strategy and eligibility criteria

This systematic review and network meta-analysis (NMA) was registered (CRD42025650062) and conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for NMA (Table S1) [17]. We searched for randomised controlled trials (RCTs) published in PubMed, Web of Science, Embase, CENTRAL, ClinicalTrials.gov, EU Clinical Trials, and International Clinical Trial Registry Platform from their inceptions through January 2025. We also searched for further RCTs by screening the reference list of the included studies. Search strategies were performed using PICOT acronym [18] and are available in Table S2.

We have included RCTs that compared any THZ or TL diuretics to each other, placebo, or no treatment without considering publication language or date as exclusion criteria. Therefore, we included RCTs that: (1) population was male or female adults at any ages with previous history of KS composed of calcium phosphate, oxalate, or both; (2) used THZ or TL at any dose as active treatment; (3) used placebo, no treatment, or another THZ or TL diuretic as control; (4) had an endpoint of clinically or radiologically diagnosed KS recurrence. Studies conducted with paediatric population (< 15 years old), and patients with secondary hypercalciuria were excluded.

Two researchers (A.V.O and A.L.N.S) independently screened articles by title and abstract, followed by full-text screening. Data were independently collected with a prespecified table with authors' name, year of publication, country, sample size, group distribution, drug and dose used, follow-up time, number of patients with recurrence, and number of patients with adverse effects. All disagreements were presented to a third reviewer (R.W.M.J or L.O.A.D.P) and discussed until consensus was reached.

We considered the KS recurrence as primary endpoint, defined by (1) a newly diagnosed episode of symptomatic or asymptomatic KS that required surgical intervention, or by (2) new stones or enlargement of baseline stones on any radiological method. Moreover, the occurrence of

any adverse effect at any time was the secondary endpoint, including but not limited to hypokalaemia, hyponatremia, hypomagnesemia, gout, skin allergy, and new-onset diabetes mellitus.

Statistical analysis

We performed a frequentist NMA to explore direct and indirect comparisons between different doses and drugs [19]. Odds ratio (OR) and 95% confidence interval (CI) were used as summary statistics for primary and secondary endpoints. We used an inverse-variance random-effects model with the DerSimonian and Laird estimator for calculating the between-study variance. Heterogeneity was assessed by τ^2, H, Q-statistic, and their respective degrees of freedom (df) values to evaluate total, within designs, and between designs heterogeneity. We assessed consistency by using the Separating Indirect from Direct Evidence approach for node-splitting [20], where the difference between direct and indirect evidence was used to assess incoherence. Furthermore, treatments were ranked according to 1 000 simulations of the Surface Under the Cumulative Ranking (SUCRA) [21], ranging from zero (worst) to one (best) and multiplied by 100, resulting in percentage values. SUCRA values of a given treatment are computed by the probability distribution of its possible ranks, which are then integrated into the cumulative ranking probabilities to determine a final value, reflecting how likely a treatment is to rank among the best options [21]. RCTs with no treatment as a control were analysed as if they were conducted with a placebo group to unify treatments network. Sensitivity analyses were performed by excluding studies that had high risk of bias, without adequate placebo group, and including only hypercalciuric patients. Publication bias was assessed by funnel plot visual inspection and by Egger's test [22].

All analyses were performed with two-sided tests in R v4.4.1 using the "netmeta" package, considering $P<0.05$ as a threshold.

Risk of bias and certainty of evidence

To evaluate the risk of bias in individual studies, we used the Revised Cochrane Risk-of-Bias Tool for Randomised Trials (RoB-2) [23] and to evaluate the certainty of evidence we used the Confidence in Network Meta-Analysis (CINeMA) guideline [24].

Results

Study characteristics

We identified 1 804 reports and included nine of them in the synthesis (Fig. 1), while 58 were excluded with reasons (Table S3). There were nine different interventions: bendroflumethiazide 7.5 mg per day (BFTZ 7.5 mg/d), chlorthalidone 25 mg per day (CLTD 25 mg/d), chlorthalidone 50 mg per day (CLTD 50 mg/d), hydrochlorothiazide 12.5 mg per day (HCTZ 12.5 mg/d), hydrochlorothiazide 25 mg per day (HCTZ 25 mg/d), hydrochlorothiazide 50 mg per day (HCTZ 50 mg/d), indapamide 2.5 mg per day (IND 2.5 mg/d), trichlormethiazide 4 mg per day (TCTZ 4 mg/d), and placebo (PLC). There were no disagreements on study selection, data extraction, or risk of bias assessment.

Six studies had a PLC arm [16, 25–29] and three had a no treatment group as a control [30–32], only two studies [16, 29] had a multi-arm design with two or more active treatment arms and one control group. A total of 999 patients were included in the primary endpoint; the minimum number of patients among the included RCTs was 22 patients [28], and the maximum was 416 patients [16]. The median percentage of males was 76% (interquartile range: 68–83%), two studies did not report the proportion of males [29, 32], moreover, the maximum follow-up period among studies ranged from 12 months [26] to 68 months [30]. Five studies reported a threshold in 24 h urine for defining hypercalciuria, ranging from 5 mmol [16] to 7.5 mmol in males and 6.25 mmol in females [29, 31], with a median percentage of hypercalciuric patients of 38% (interquartile range: 25–52%). Further characteristics are in Table 1.

KS recurrence

Regarding efficacy, most of the 999 patients were allocated in HCTZ 12.5 mg/d ($n=105$), HCTZ 25 mg/d ($n=108$), HCTZ 50 mg/d ($n=201$), and PLC ($n=391$) groups, with four studies comparing HCTZ 50 mg/d to PLC, one study comparing HCTZ 25 mg/d to PLC, and two studies comparing BFTZ 7.5 mg/d to PLC (Fig. 2A). We found that CLTD 50 mg/d (OR: 0.18, CI 0.04–0.88), HCTZ 50 mg/d (OR: 0.52, CI 0.29–0.93), and TCTZ 4 mg/d (OR: 0.26, CI 0.10–0.68) were statistically superior to PLC, whereas BFTZ 7.5 mg/d (OR: 0.51, CI 0.13–2.03), CLTD 25 mg/d (OR: 0.23, CI 0.05–1.12), HCTZ 12.5 mg/d (OR: 0.90, CI 0.39–2.07), HCTZ 25 mg/d (OR: 0.81, CI 0.35–1.85), and IND 2.5 mg/d (OR: 0.24, CI 0.05–1.10) did not differ from PLC. Regarding dose-dependent effect among same drugs with different doses, HCTZ 50 mg/d was not superior to HCTZ 12.5 mg/d (OR: 0.58, CI 0.25–1.34) or to HCTZ 25 mg/d (OR: 0.65, CI 0.28–1.48), neither was CLTD 50 mg/d

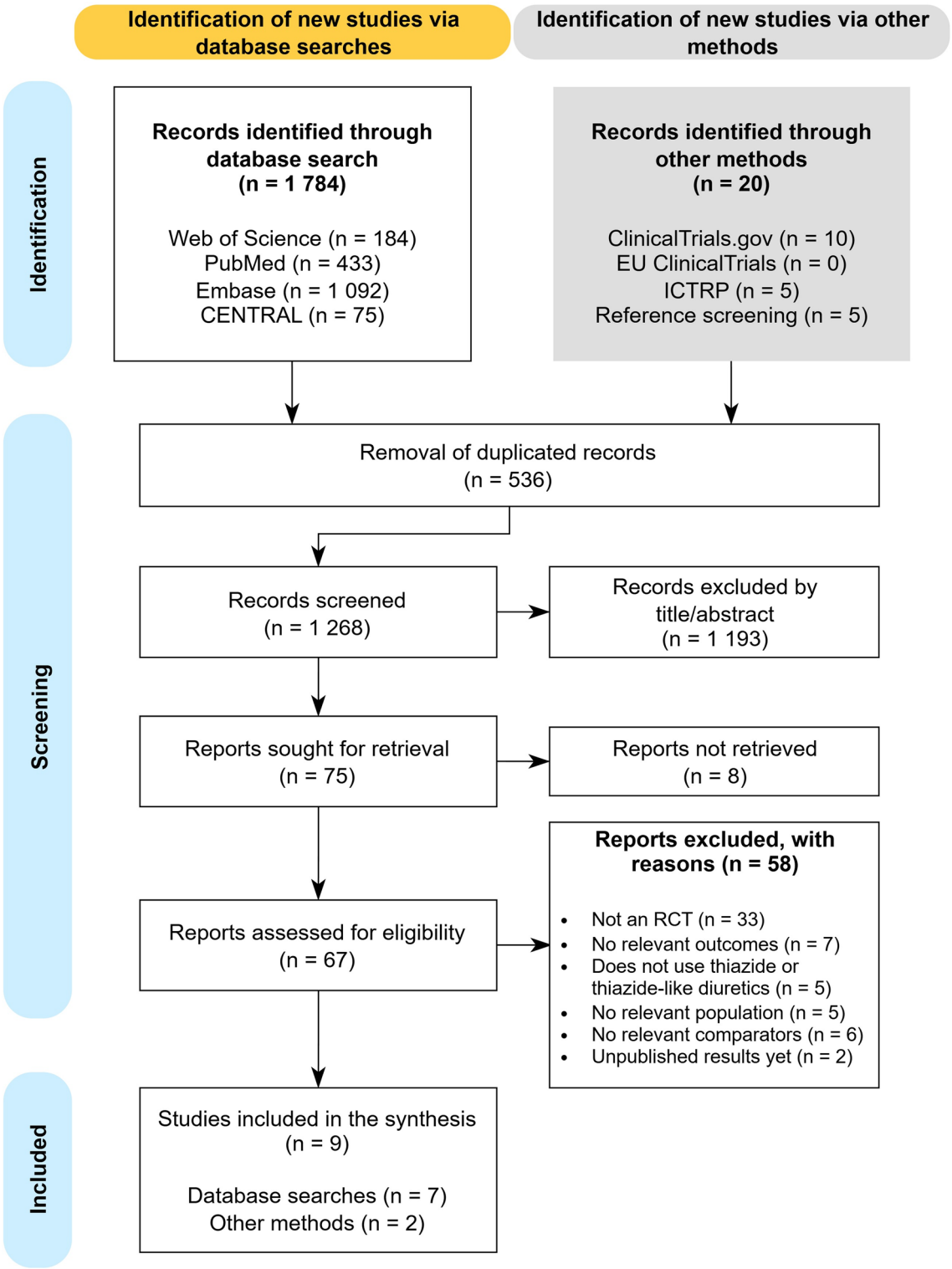

Fig. 1 PRISMA flowchart of the identification screening, and inclusion of reports. ICTRP = International Clinical Trial Registry Platform, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomised controlled trials

Table 1 Characteristics of the randomised controlled trials included in the network meta-analysis synthesis

Study	Country	Type of calcium stone	Drug and dose	Group distribution	Percentage of men (%)	Percentage of hypercalciuric patients (%)	Definition of hypercalciuria (mmol/24 h)	Age range	No. patients with kidney stones recurrence (events/total)	No. patients with adverse effects (events/total)	Follow-up (months)
Brocks 1981 [25]	Denmark	NR	Arm A: BFTZ 2.5 mg t.i.d, Arm B: Placebo	Arm A: 33, Arm B: 29	NR	NR	NR	16–49	Arm A: 5/33, Arm B: 5/29	NR	48
Scholz 1982 [26]	Germany	NR	Arm A: HCTZ 25 mg b.i.d, Arm B: Placebo	Arm A: 25, Arm B: 26	61	24	NR	20–64	Arm A: 6/25, Arm B: 6/26	Arm A: 11/25, Arm B: 5/26	12
Laerum 1984 [27]	Norway	NR	Arm A: HCTZ 25 mg b.i.d, Arm B: Placebo	Arm A: 25, Arm B: 25	76	26	6.0	16–75	Arm A: 5/25, Arm B: 12/25	Arm A: 6/25, Arm B: 2/25	36
Mortensen 1986 [28]	Denmark	NR	Arm A: BFTZ 2.5 mg t.i.d, Arm B: Placebo	Arm A: 12, Arm B: 10	100	NR	NR	20–49	Arm A: 0/12, Arm B: 4/10	Arm A: 2/12, Arm B: 0/10	24
Ettinger 1988 [29]	United States	Oxalate	Arm A: CLTD 25 mg u.i.d, Arm B: CLTD 50 mg u.i.d, Arm C: Placebo	Arm A: 19, Arm B: 23, Arm C: 31	86	12	7.5 (men) or 6.25 (women)	NR	Arm A: 3/19, Arm B: 3/23, Arm C: 14/31	Arm A: 5/19, Arm B: 5/23, Arm C: 1/31	36
Ohkawa 1992 [30]	Japan	NR	Arm A: TCTZ 4 mg u.i.d, Arm B: no agent	Arm A: 82, Arm B: 93	55	100	7.0 [a]	16–77	Arm A: 24/82, Arm B: 57/93	Arm A: 17/82, Arm B: 0/93	68
Borghi 1993 [31]	Italy	Oxalate	Arm A: IND 2.5 mg u.i.d, Arm B: no agent	Arm A: 25, Arm B: 25	76	100	7.5 (men) or 6.25 (women)	NR	Arm A: 4/25, Arm B: 11/25	Arm A: 2/25, Arm B: 0/25	36
Fernández-Rodríguez 2001 [32]	Spain	Oxalate and phosphate	Arm A: HCTZ 50 mg u.i.d, Arm B: no agent	Arm A: 50, Arm B: 50	NR	38	NR	18–65	Arm A: 16/50, Arm B: 28/50	NR	36
Dhayat 2023 [16]	Switzerland	Oxalate and phosphate	Arm A: HCTZ 12.5 mg u.i.d, Arm B: HCTZ 25 mg u.i.d, Arm C: HCTZ 50 mg u.i.d, Arm D: Placebo	Arm A: 105, Arm B: 108, Arm C: 101, Arm D: 102	80	63	5.0	35–57	Arm A: 62/105, Arm B: 61/108, Arm C: 49/101, Arm D: 60/102	Arm A: 28/105, Arm B: 42/105, Arm C: 30/101, Arm D: 38/102	36

Notes: BFTZ = bendroflumethiazide, b.i.d. = twice a day, CLTD = chlorthalidone, HCTZ = hydrochlorothiazide, IND = indapamide, NR = not reported, TCTZ = trichlormethiazide, t.i.d. = three times a day, u.i.d. = once a day, [a]calculated by the formula given by the authors (0.1 mmol/kg) for a 70 kg person

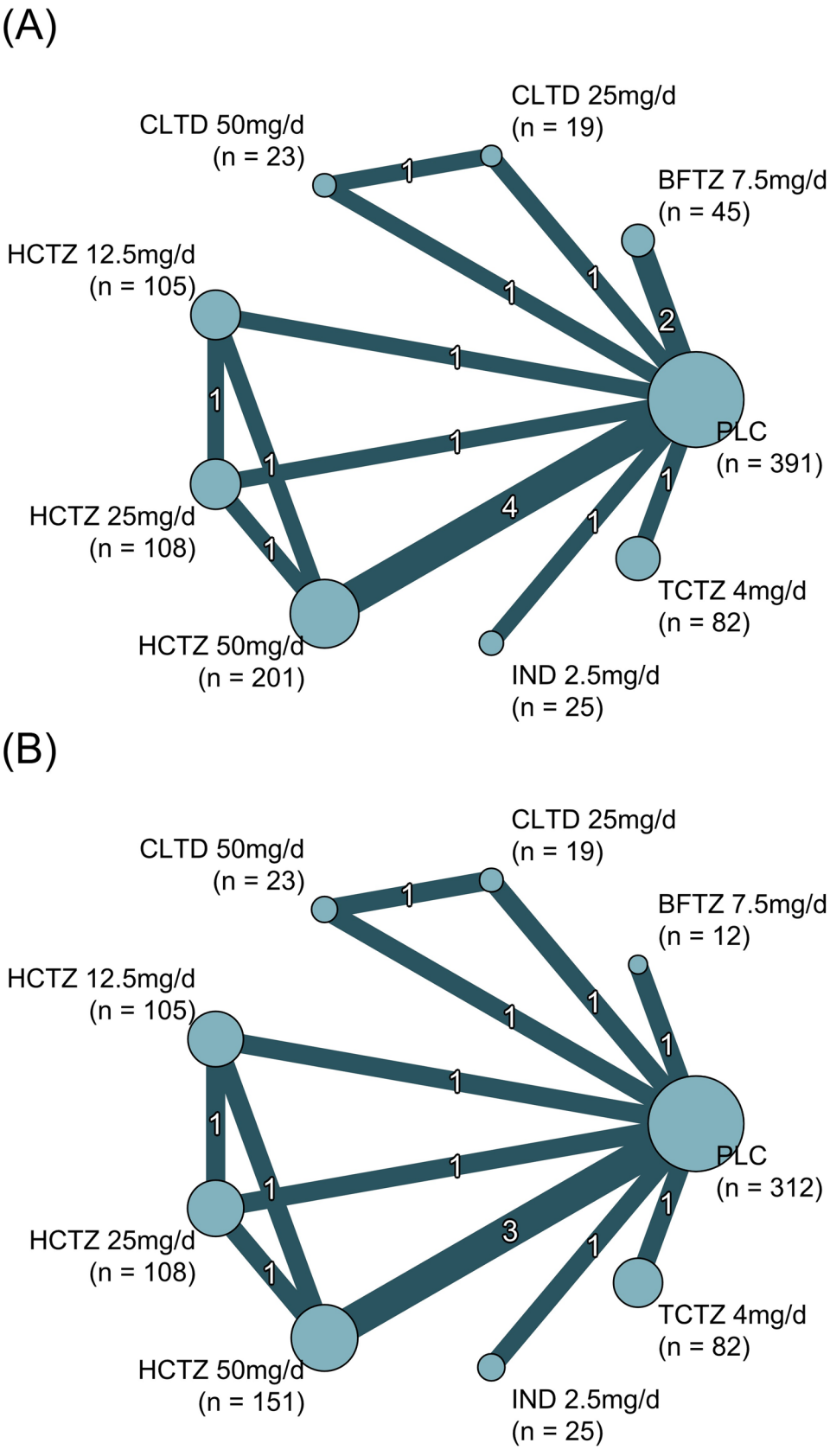

Fig. 2 Network of the treatments included in the synthesis according to the (A) efficacy and (B) safety endpoint Notes: BFTZ = bendroflumethiazide, CLTD = chlorthalidone, HCTZ = hydrochlorothiazide, IND = indapamide, PLC = placebo, TCTZ = trichlormethiazide

superior to CLTD 25 mg/d (OR: 0.80, CI 0.12–5.20). None of the other comparisons between two different active treatments were significant. Other estimates are in Fig. 3.

Treatments' efficacy was ranked in the following order by SUCRA: CLTD 50 mg/d (82%), CLTD 25 mg/d (75%), TCTZ 4 mg/d (73%), IND 2.5 mg/d (72%), HCTZ 50 mg/d (47%), BFTZ 7.5 mg/d (44%), HCTZ 25 mg/d (24%), HCTZ 12.5 mg/d (20%), and PLC (12%). The rank of treatments is further described in Fig. S1A.

There was no evidence of publication bias in the primary endpoint (t: 0.95, df: 14, $P=0.36$) with no evidence of

Treatment vs. other	Number of patients	Network odds ratio for kidney stones recurrence (95%CI)
'BFTZ 7.5mg/d' vs other		
CLTD 25mg/d	19	2.25 (0.27–18.46)
CLTD 50mg/d	23	2.81 (0.35–22.82)
HCTZ 12.5mg/d	105	0.57 (0.11– 2.86)
HCTZ 25mg/d	108	0.63 (0.13– 3.17)
HCTZ 50mg/d	201	0.98 (0.22– 4.37)
IND 2.5mg/d	25	2.11 (0.27–16.31)
TCTZ 4mg/d	82	1.96 (0.37–10.48)
PLC	391	0.51 (0.13– 2.03)
'CLTD 25mg/d' vs other		
BFTZ 7.5mg/d	45	0.44 (0.05– 3.65)
CLTD 50mg/d	23	1.25 (0.19– 8.13)
HCTZ 12.5mg/d	105	0.25 (0.04– 1.53)
HCTZ 25mg/d	108	0.28 (0.05– 1.70)
HCTZ 50mg/d	201	0.44 (0.08– 2.37)
IND 2.5mg/d	25	0.94 (0.10– 8.42)
TCTZ 4mg/d	82	0.87 (0.14– 5.57)
PLC	391	0.23 (0.05– 1.12)
'CLTD 50mg/d' vs other		
BFTZ 7.5mg/d	45	0.36 (0.04– 2.88)
CLTD 25mg/d	19	0.80 (0.12– 5.20)
HCTZ 12.5mg/d	105	0.20 (0.03– 1.21)
HCTZ 25mg/d	108	0.23 (0.04– 1.34)
HCTZ 50mg/d	201	0.35 (0.07– 1.87)
IND 2.5mg/d	25	0.75 (0.08– 6.66)
TCTZ 4mg/d	82	0.70 (0.11– 4.40)
PLC	391	0.18 (0.04– 0.88)
'HCTZ 12.5mg/d' vs other		
BFTZ 7.5mg/d	45	1.75 (0.35– 8.76)
CLTD 25mg/d	19	3.94 (0.65–23.76)
CLTD 50mg/d	23	4.93 (0.83–29.30)
HCTZ 25mg/d	108	1.11 (0.45– 2.73)
HCTZ 50mg/d	201	1.72 (0.75– 3.96)
IND 2.5mg/d	25	3.70 (0.66–20.76)
TCTZ 4mg/d	82	3.43 (0.97–12.20)
PLC	391	0.90 (0.39– 2.07)
'HCTZ 25mg/d' vs other		
BFTZ 7.5mg/d	45	1.58 (0.32– 7.87)
CLTD 25mg/d	19	3.55 (0.59–21.35)
CLTD 50mg/d	23	4.43 (0.75–26.33)
HCTZ 12.5mg/d	105	0.90 (0.37– 2.21)
HCTZ 50mg/d	201	1.55 (0.68– 3.55)
IND 2.5mg/d	25	3.33 (0.60–18.65)
TCTZ 4mg/d	82	3.09 (0.87–10.95)
PLC	391	0.81 (0.35– 1.85)
'HCTZ 50mg/d' vs other		
BFTZ 7.5mg/d	45	1.02 (0.23– 4.53)
CLTD 25mg/d	19	2.29 (0.42–12.45)
CLTD 50mg/d	23	2.86 (0.53–15.34)
HCTZ 12.5mg/d	105	0.58 (0.25– 1.34)
HCTZ 25mg/d	108	0.65 (0.28– 1.48)
IND 2.5mg/d	25	2.15 (0.43–10.83)
TCTZ 4mg/d	82	2.00 (0.65– 6.09)
PLC	391	0.52 (0.29– 0.93)
'IND 2.5mg/d' vs other		
BFTZ 7.5mg/d	45	0.47 (0.06– 3.65)
CLTD 25mg/d	19	1.06 (0.12– 9.54)
CLTD 50mg/d	23	1.33 (0.15–11.80)
HCTZ 12.5mg/d	105	0.27 (0.05– 1.52)
HCTZ 25mg/d	108	0.30 (0.05– 1.68)
HCTZ 50mg/d	201	0.46 (0.09– 2.34)
TCTZ 4mg/d	82	0.93 (0.16– 5.53)
PLC	391	0.24 (0.05– 1.10)
'TCTZ 4mg/d' vs other		
BFTZ 7.5mg/d	45	0.51 (0.10– 2.73)
CLTD 25mg/d	19	1.15 (0.18– 7.34)
CLTD 50mg/d	23	1.43 (0.23– 9.06)
HCTZ 12.5mg/d	105	0.29 (0.08– 1.03)
HCTZ 25mg/d	108	0.32 (0.09– 1.15)
HCTZ 50mg/d	201	0.50 (0.16– 1.53)
IND 2.5mg/d	25	1.08 (0.18– 6.43)
PLC	391	0.26 (0.10– 0.68)

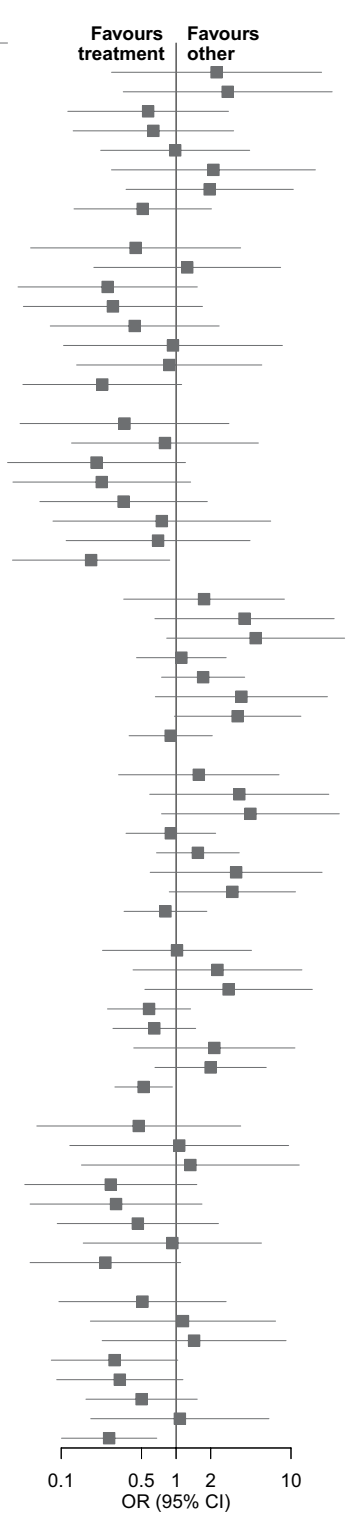

Fig. 3 Forest plot of network estimates considering direct and indirect evidence of the included treatments and doses comparisons for preventing kidney stones recurrence Notes: BFTZ = bendroflumethiazide, CI = confidence interval, CLTD = chlorthalidone, HCTZ = hydrochlorothiazide, IND = indapamide, OR = odds ratio, PLC = placebo, TCTZ = trichlormethiazide

inconsistency (Q: 1.0, df: 1, $P=0.31$) or heterogeneity (Q: 5.0, df: 3, $P=0.17$) in the overall network.

Adverse effects

Regarding safety, only seven studies ($n=837$) reported data on the occurrence of adverse effects among patients. Aside from the PLC ($n=312$) group, most patients used HCTZ 12.5 mg/d ($n=105$), HCTZ 25 mg/d ($n=108$), or HCTZ 50 mg/d ($n=151$) (Fig. 2B). The adverse effects varied across studies, with the occurrence of nausea [25], hypotension [16, 25, 30, 31], impotence [28, 29], hypokalaemia [16, 27, 30, 31], gout [16, 27], diabetes mellitus [16], and skin allergy [16]. There were no differences between BFTZ 7.5 mg/d (OR: 5.00, CI 0.13–185.83), CLTD 25 mg/d (OR: 10.71, CI 0.62–185.54), CLTD 50 mg/d (OR: 8.33, CI 0.49–142.77), HCTZ 12.5 mg/d (OR: 0.95, CI 0.17–5.37), HCTZ 25 mg/d (OR: 1.67, CI 0.30–9.30), HCTZ 50 mg/d (OR: 1.74, CI 0.51–5.92), IND 2.5 mg/d (OR: 5.43, CI 0.15–190.24) and the PLC, however, TCTZ 4 mg/d (OR: 49.96, CI 1.78–1 402.80) provoked more adverse effects than PLC. Also, patients treated with HCTZ 12.5 mg/d (OR: 0.02, CI 0.00–0.82) had less adverse effects than TCTZ 4 mg/d, nevertheless, all other comparisons were nonsignificant. All other comparisons are in Fig. 4.

Treatments' safety was ranked by SUCRA as follows: PLC (80%), HCTZ 12.5 mg/d (80%), HCTZ 25 mg/d (64%), HCTZ 50 mg/d (63%), IND 2.5 mg/d (43%), BFTZ 7.5 mg/d (43%), CLTD 50 mg/d (34%), CLTD 25 mg/d (29%), and TCTZ 4 mg/d (11%). The treatments' ranks are also plotted in Fig. S1B.

There was no evidence of publication bias in the secondary endpoint (t: −0.93, df: 12, $P=0.36$) with evidence of inconsistency (Q: 6.9, df: 1, $P=0.008$) and no evidence of heterogeneity (Q: 0.01, df: 1, $P=0.92$).

Risk of bias

Regarding the risk of bias assessment, we classified five RCTs as high risk overall [28–32], three as some concerns [25–27], and one as low risk [16]. Most studies failed to properly describe allocation concealment [25–28, 30–32], whereas one used an inappropriate allocation method [29]. Most studies were classified as low risk in the bias due to deviations from intended intervention [16, 25–29] and missing data [16, 25–27, 30, 32]. Only one study was classified as low risk in the bias due to selection of reported result [16]. The risk of bias assessment is described in the Fig. S2.

Sensitivity analyses and certainty of evidence

We performed sensitivity analyses that encompassed pooling the estimates for the efficacy endpoint without inclusion of high risk RCTs (Fig. S3), without inclusion of RCTs that had a no treatment group instead of a PLC group (Fig. S4), and including only hypercalciuric patients (Fig. S5). Only four studies [16, 30–32] provided data on hypercalciuric patients' endpoints, nevertheless, we did not find substantial differences that could change the interpretation of our previous results, with only minimal changes to the overall pooled ORs in a few comparisons in this population.

Furthermore, only the comparisons of HCTZ 12.5 mg/d versus HCTZ 25 mg/d, and HCTZ 25 mg/d versus HCTZ 50 mg/d were classified at a low level of certainty in the efficacy endpoint, whereas all the other comparisons were classified at a very low level of certainty both in the efficacy and safety endpoints (Fig. S6).

Discussion

This is the first NMA to investigate the efficacy and safety of different doses of THZ and TL diuretics for KS recurrence, showing that CLTD 50 mg/d, HCTZ 50 mg/d, and TCTZ 4 mg/d were superior to PLC. There was no evidence of dose-response effect among drugs with different dosing. We also found that only TCTZ 4 mg/d was different from PLC regarding the occurrence of adverse effects. None of the comparisons had a high or moderate level of certainty, in which only two comparisons had a low level of certainty, whereas all others were considered to have a very low level of certainty.

Previously published meta-analyses have highlighted a positive effect of THZ or TL diuretic therapy on KS recurrence [9, 10]. However, despite being well conducted, those studies fail to provide reliable evidence on different drugs and doses, as pairwise meta-analyses only analyse direct evidence. This could explain the previously reported positive effects of these drugs due to the pooling of different substances without accounting for their particularities, which may have introduced bias on their true effectiveness. This occurred due to all treatments being combined in a single comparison against PLC or no treatment, providing – thus – evidence on the use of "any diuretic drug" indiscriminately. In this scenario, any comparison was solely based on direct evidence, thereby hindering the possibility of including indirect evidence, as most relevant literature compares an active treatment to PLC or to no treatment. Despite these differences, previous studies have reported the suboptimal quality of the evidence currently available [9]. Our findings should be interpreted with caution, as many comparisons

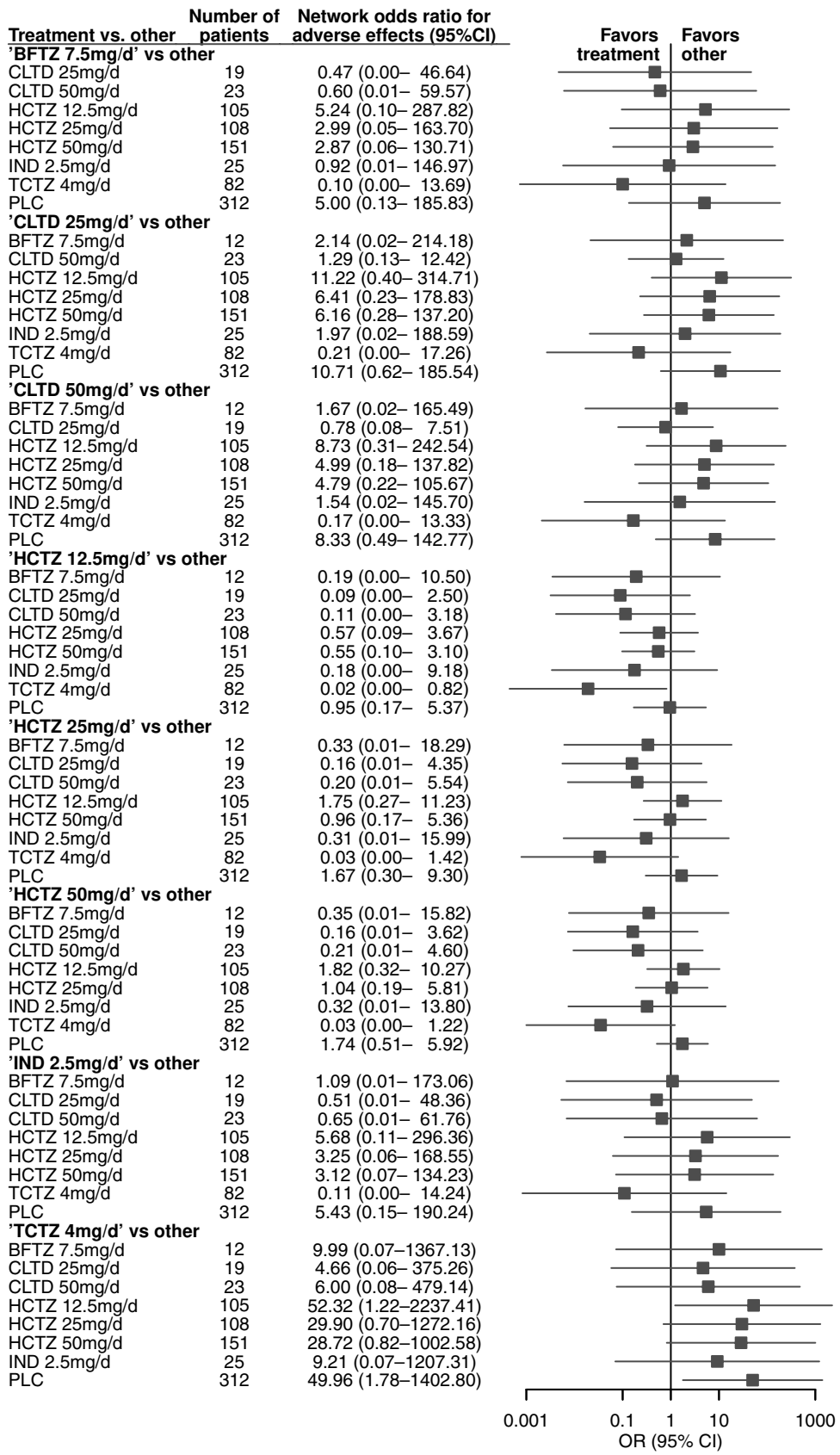

Fig. 4 Forest plot of network estimates considering direct and indirect evidence of the included treatments and doses comparisons for occurrence of adverse effects Notes: BFTZ = bendroflumethiazide, CI = confidence interval, CLTD = chlorthalidone, HCTZ = hydrochlorothiazide, IND = indapamide, OR = odds ratio, PLC = placebo, TCTZ = trichlormethiazide

had a very low level of certainty due to methodological issues in the included RCTs, in addition to several treatments pooled effects extending into the equivalence range of treatments, set at an OR of 0.8–1.25. This raises concerns regarding imprecision and suggest that, although statistically significant, some therapies may not be clinically different when compared to others – indicating uncertainty in the pooled effects and reducing overall certainty of evidence to either low or very low. Moreover, SUCRA values should be interpreted with caution, as they represent the average proportion of treatments that are worse than a given treatment in a given network of treatments [21], which should not be interpreted as an absolute measure of superiority between treatments – especially due to various limitations in the dataset. We also performed an analysis conducted only with hypercalciuric patients, which is defined as patients with > 8 mmol of calcium in 24 h urine in the EAU guideline [6]. In our study, no treatment was superior to PLC in those patients; however, none of the RCTs adopted this threshold for defining hypercalciuria. This may indicate that current recommendations [6, 7] are mostly based on the hypocalciuric effect of these drugs rather than on clinical evidence of reduction in recurrence rates, suggesting a suboptimal and unreliable evidence.

The quality of evidence has raised concerns, due to being mostly composed of outdated trials and with a very limited number of participants, which may have led to inadequate estimates due to lack of statistical power, in addition to less generalisability, more imprecision and unreliability. Moreover, follow-up may be suboptimal to detect changes in the long term, as most studies exhibit a maximum follow-up of three years. Previous cohort studies [33–35], with longer follow-up, have reported a reduction in KS recurrence with THZ and/or TL diuretics. Nonetheless, RCTs remain as the optimal study design to determine the efficacy of a given treatment by adjusting for various sources of bias [36]. It is plausible that current literature limits external validity, as most patients were males, however, KS are most prevalent in males and tend to increase with age [37], which was adequately assessed in our study. Another concern relates to the possibility of breaks in the allocation concealment, as studies comparing active treatments may exhibit higher frequencies of adverse effects compared with PLC or no treatment – suggesting which intervention is being given. Additionally, only one of the nine included studies had an overall low risk of bias [16], indicating that current evidence lacks thoroughly conducted RCTs. Most studies failed to report patients' type of calcium stones, which may impair data interpretation and its external validity. Finally, due to being outdated, most RCTs did not use computed tomography for assessing radiological recurrence, relying on less sensitive diagnostic methods.

Despite several efforts, it is possible that not all relevant studies were included. Nonetheless, we used multiple databases and registries, in addition to manually searching reference lists and not employing language or date as exclusion criteria. Moreover, we did not conduct subgroup analyses on continuous variables, as categorizing them into groups might cause spurious statistical significance and overestimation of effect size [38]. Also, despite not finding evidence of small study effects, there may be unpublished manuscripts that were not found. Furthermore, most RCTs did not compare different active treatments, which may have led to imprecise pooled effects, as comparisons that depend solely on indirect evidence may exhibit larger CIs. For instance, TCTZ 4 mg/d exhibited a very wide CI in adverse effects, indicating imprecise effects and very low certainty in the findings, which should be interpreted with caution.

Despite some limitations, this NMA is the most updated and comprehensive study on the use of THZ or TL diuretics to prevent KS recurrence, providing valuable insights on this condition. It should be noted that we made several prespecified sensitivity analyses, which did not alter the conclusions – increasing the robustness of our findings. We also adopted a random-effects NMA model, which is a more conservative approach to estimate pooled effects, accounting for study variability. Caution is needed when interpreting safety endpoint data, as there was evidence of inconsistency in the overall network.

Further RCTs are expected to be conducted with adequate statistical power and rigorous methods, as well as longer follow-up to represent long-term outcomes and multiple comparisons between diverse therapies, thereby improving the quantity of direct evidence and quality of evidence overall. We suggest a minimum of 319 patients in each arm without considering dropout rates, based on Pocock's estimation with an alpha level of 0.05 and 80% statistical power [39]. We strongly believe that THZ and TL diuretics should be further investigated prior to being routinely prescribed as standard prophylactic drug for KS recurrence, as they have been shown to exhibit many potential severe adverse effects [12–14] and are associated with a higher risk of developing skin cancer [15].

Conclusion

THZ and/or TL diuretics should not be routinely prescribed for preventing KS recurrence, as current evidence does not support their use due to several limitations, including risk of bias and limited sample sizes. Further well-designed RCTs are urgently needed to provide high-quality data on these drugs' clinical applicability for KS prophylaxis.

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Declarations

Conflict of interest The authors declare no competing interests.

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