National Institute for Health and Care Excellence

Consultation

Renal and ureteric stones: assessment and management

Prevention of recurrence

NICE guideline

Intervention evidence review

July 2018

Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

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1 Prevention of recurrence

1.1 Review question: What is the most clinically-effective and cost-effective non-surgical management for preventing the recurrence of future renal and ureteric stones?

1.2 Introduction

It is estimated that about one third of people affected by renal and ureteric stones will experience a recurrence at five years without treatment of the underlying cause. This rate of recurrence rises to 75% after 20 years with no treatment (reference Phillips, 2015 Cochrane review). As such, it is crucial to determine the most clinically and cost effective long-term management options for people who have, or who have had renal and ureteric stones.

Currently, there is variation in practice on the use of pharmacological management in the UK for the prevention of stone recurrence. Some patients are given general dietary advice while others are manged with medication to lower urinary calcium, increase urinary citrate levels, or alter urinary pH. Developing recommendations from evidence worldwide could help to inform clinical practice and future research studies in the UK.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People with renal and ureteric stones
Interventions	• Potassium citrate supplements • Sodium citrate supplements • Allopurinol • Thiazides • Oral bicarbonate • Chelating agents: D-penicillamine , Tiopronin (or Thiola or mercaptopropionylglycine) (for cystinuria) • Captopril (for cystinuria) • Ca supplements, pyridoxine, • Magnesium supplement • Methionine • Prophylactic antibiotics
Comparisons	• Each other • No treatment/ Placebo /Fluid only
Outcomes	Critical outcomes at longest time point: • Recurrence rate • Stone episodes/stone interventions • Use of healthcare services • Quality of life • Major Adverse events (if admission to hospital • Minor adverse events (no admission to hospital) • Important outcomes at longest time point: • Kidney function • Pain intensity (visual analogue scale)
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for observational studies for children

Key confounders	• Previous stones • Type of stone • Size of stone • Metabolic abnormality

1.4 Clinical evidence

1.4.1 Included studies

Seventeen studies (19 papers) were included in the review;[2, 7, 13, 16, 17, 25, 28, 45, 47, 66, 69, 70, 83, 84, 104, 106, 119, 125, 130] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

One Cochrane review was identified however it was excluded as it included drugs that were not included in this review protocol.

As per the protocol, for strata where there was no RCT evidence for children, the search was widened to include cohort studies. Two cohort studies were identified for inclusion.[83,104] Both of these compared potassium citrate to no intervention. See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Heterogeneity

For the comparison of thiazides versus placebo in adults, there was heterogeneity between the studies when they were meta-analysed for the outcome of recurrence rate. Pre-specified subgroup analyses (see Appendix A:) were unable to be performed, so a random effects meta-analysis was applied to this outcome, and the evidence was downgraded for inconsistency in GRADE.

1.4.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Ahlstrand 1996[2]	Intervention (n=17): Thiazides (hydrochlorothiazide 25 mg x2) Comparison (n=16): combination therapy, thiazide + magnesium supplement (hydrochlorothiazide 25 mg x 2 (frequency of dose not reported) + magnesium-aspartate-hydrochloride 1.23 g x 2 (=10 mmol Mg2+ /d) Comparison (n=24): no intervention	n=57 People with recurrent calcium stone formation and with hypercalciuria or hypomagnesia Age (mean, SD): thiazide group 31 (not reported); thiazide + magnesium supplement 36 (not reported); no intervention 38 (not reported) Gender (M:F): 47:10 Sweden	Recurrence (5 years): number of people free from recurrence Minor adverse events (5 years): treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction	Concurrent medication/care: All groups were advised to increase fluid intake and to decrease oxalate intake
Ala-Opas 1987[7]	Intervention (n=28): Thiazides (hydrochlorothiazide 50 mg twice a day) Comparison (n=45): No intervention	n=73 People with recurrent urinary calcium stones Absorptive hypercalciuria 44% Age (mean, range): 48 (28-70) Gender (M:F): 60:13 Finland	Recurrence (5 months treatment with thiazides; 2 years intervention and follow-up): defined as the number of people with recurrences (based on passage, surgical removal of stone, or visualisation on x-ray)	Concurrent medication/care: both groups were on a low calcium and low oxalate diet and ate unprocessed bran (40d/day) for 24 months. A high fluid intake was recommended (approx. 2.5l daily)
Arrabal-Martin 2006[13]	Intervention (n=50): Thiazides. 50 mg/24hr hydrochlorothiazide Comparison (n=50): Placebo (details not reported)	n=100 Adults with calcium lithiasis who had residual lithiasis 3 months after SWL Age: Not reported	Stone episodes (36 months): Residual fragments or growth Stone interventions (36 months): SWL Minor adverse events (36 months): Intracellular acidosis	Concurrent medication/care: both intervention and comparison groups had SWL three months prior

Study	Intervention and comparison	Population	Outcomes	Comments
		Gender (M:F): Not reported Spain	and hypocitraturia induced by hypopotassemia secondary to administration of thiazides)	
Baggio 1983[16]	Intervention (n=28): Thiazides (hydrochlorothiazide 50mg and amiloride 5mg, daily) Intervention (n=28): Allopurinol (200mg/day) Intervention (n=28): Combination allopurinol + thiazide (allopurinol 200mg, hydrochlorothiazide 50mg, amiloride 5mg, daily) Comparison (n=29): placebo, no further details	n=96 Adults with recurrent calcium oxalate stone disease who had passed at least one stone in the two months preceding the study Age not reported Gender: 50/46 Italy	Recurrence (2 months): not defined	Concurrent medication/care: Patients were allowed a free diet and water as desired except for 4 days before the first and second controls, when they were placed on a standard diet containing 800mg calcium, 75mg oxalate, 85mg purines and 900mg phosphate
Barcelo 1993[17]	Intervention (n=28): Citrate supplements (potassium citrate, 20 mEq (4 tablets), 3 times a day, shortly after meals) Comparison (n=29): placebo, no further details	n=57 Adults with active calcium nephrolithiasis concomitant with an isolated hypocitraturic abnormality Age (mean, range): citrate group 44 (29-61); placebo group 47 (27-64) Gender (M:F): 17/21 Spain	Recurrence rate (36 months): defined as stone formation rate (per patient per year during 3 years), where stone formation was determined by spontaneous passage in the absence of pre-existing stones, stone passage without change in the number of stones, appearance of new stones on a roentgenogram, or new stone requiring SWL or surgical removal Recurrence (36 months): defined as the number of patients with a new stone formation Recurrence (36 months): defined as	Concurrent medication/care: Both groups were advised on increased ingestion of fluids (2-3l a day) and reduced sodium intake

Study	Intervention and comparison	Population	Outcomes	Comments
			number of patients remaining stone free Stone interventions (36 months): defined as treatments to remove stones Minor adverse events (36 months)	
Borghi 1993[25]	Intervention (n=25): thiazide (indapamide, 2.5mg/day) Intervention (n=25): thiazide (indapamide, 2.5mg/day) + allopurinol (300mg/day) Comparison (n=25): no intervention	n=75 People who were idiopathic recurrent stone formers (pure calcium oxalate or <20% calcium phosphate) Age (mean, SD): thiazide group 46.5 (11.4); thiazide + allopurinol group 46.2 (11.6), no intervention group 42.8 (11.3) Gender (M:F): 59:16 Italy	Recurrence rate (3 years: not defined Recurrence (3 years): defined as the number of participants stone free at the end of treatment Minor adverse events (3 years) (study discontinuation due to clinical hypotension: dizziness and hypotension) Minor adverse events (3 years) (study discontinuation due to silent severe hypokalaemia) Kidney function (3 years) (creatinine clearance - ml/min)	Concurrent medication/care: All participants received diet and fluid treatment, which involved advice to avoid high salt intake, high and/or regular ingestion of foods containing too much calcium, oxalate and purines. High fluid intake was recommended using water with a very low mineral content
Ettinger 1986[47]	Intervention (n=36): allopurinol (100mg, three times daily) Comparison (n=36): placebo identical in appearance	n=72 Adults with calculi that were composed of more than 79% calcium oxalate Age (mean, SD): Allopurinol group 48.9 (10.1); placebo group 46.4 (9.9)	Recurrence rate (39 months): defined as new calculous events (development of new stone only) Stone episode (39 months): defined as new calculous events (growth of residual calculi and/or development of new stone)	Concurrent medication/care: Patients were encouraged to increase fluid intake, no dietary advice was given

Study	Intervention and comparison	Population	Outcomes	Comments
		Gender (M:F): Not reported USA		
Ettinger 1988[45]	Intervention (n=51): magnesium supplement (milk of magnesia, 650mg x2 or 325g x2 daily) Intervention (n=42): thiazide (chlorthalidone, 25g x2 daily or 50 mg x 2 daily) Comparison (n=31): placebo	n=124 Adults with active recurrent calculous disease and no secondary causes for nephrolithiasis, with calculi that were composed of more than 79% calcium oxalate Age: placebo group 48.9 (12.5); 650mg magnesium group 47.1 (9.6); 1300mg magnesium group 41.1 (9.9) Gender (M:F): 109/15 USA	Recurrence rate (36 months): number of calculous events per uyear based on radiographic evidence of new or enlarging calculi or passage of calculi Recurrence (36 months): defined as new calculus events (growth of residual calculi, appearance of new calculi or passage of new calculi)	Concurrent medication/care: All participants were advised to increase the fluid intake sufficient to produce a daily urine output of 2000ml and all were given written dietary instructions that recommended restriction of salt, refined sugar, animal protein, and foods high in oxalate with encouraging high cereal fibre intake. Dairy products were limited to 2 servings daily and vitamin C was prescribed
Kohri 1990[66]	Intervention (n=43): combined thiazide and allopurinol treatment: 2mg trichloromethiazide (Fluitran) once every morning and 100mg allopurinol (Zyroric) three times daily Comparison (n=44): 100mg allopurinol (Zyroric) three times daily	n=87 People with idiopathic calcium oxalate or calcium phosphate urinary stones and no history of primary hyperparathyroidism, renal tubular acidosis (type 1), urinary infection, hypercalcaemia or diseases of the gastrointestinal tract Age: Not reported Gender (M:F): male only Japan	Recurrence rate (mean 4.6-4.9 years) Recurrence (mean 4.6-4.9 years): number of people with stones formed during treatment)	Concurrent medication/care: recommendations from the stone clinic, such as diet and fluid intake. The stone clinic restricted calcium intake, but did not encourage citrate ingestion nor restrict oxalate ingestion
Laerum 1984[69, 70]	Intervention (n=25): 25mg	n=50	Recurrence (median 3 years): new stone	Concurrent medication/care:

Study	Intervention and comparison	Population	Outcomes	Comments
	hydrochlorothiazide as Esidrex-K (containing 0.6g potassium chloride) twice daily Comparison (n=25): Matching placebo tablets	People with recurrent calcium stones Age - Mean (range): 44 (16-75 years) Gender (M:F): 38/10 Norway	formation (verified and probable) Minor adverse events (median 3 years): attack of gouty arthritis (transient and characterised as mild) Minor adverse events (median 3 years): general discomfort as nausea, dyspepsia, fatigue and vertigo (transient and characterised as mild) Minor adverse events (median 3 years): impotence (transient and characterised as mild) Minor adverse events: hypopotassemia (K<3mmol/litre)	All patients were advised to reduce oxalate, calcium (milk <1/2 litre/day), purine and salt intake. High fluid intake was recommended in order to achieve a 24-hour urine volume of two litres or more
Oguz 2013[83]	Intervention (n-22): Potassium citrate (1mEq/kg oral with 5mEq citrate per tablet, per day) Comparison (n=20): no intervention	n=42 Children with calcium oxalate stone disease who underwent PNL and detected to be stone-free Age – mean (range): citrate group 7.9 (3-16), no intervention group 7.5 (4-16) Gender (M:F): 29:13 Turkey	Recurrence rate (12-42 months): defined as stone formation rate after PNL, per patient per year Recurrence (12-42 months): defined as number of children with stone recurrence defined as new detection of stone or spontaneous passage of non-pre-existing stone	Non-randomised study Concurrent medication/care: all participants were informed about the food that included oxalates and they were advised to avoid these foods. They were asked to take fluids to achieve a minimum urine output of 25mL/kg/day. Red meat protein was not restricted.

Study	Intervention and comparison	Population	Outcomes	Comments
Ohkawa 1992[84]	Intervention (n=105): Thiazide (2mg trichlormethiazide for 1 week, followed by 4mg) Comparison (n=105): no intervention	n=210 Adults with calcium urolithiasis with idiopathic hypercalciuria without signs of hyperparathyroidism Stone composition: calcium oxalate stones: 16.57%; calcium oxalate and calcium phosphate stones 83.4% Age - Mean (SD): Thiazide group 48.7 (12.3); control group 46.9 (13.8) Gender (M:F): 97/78 Japan	Recurrence rate (mean 2.21 years): defined stone formation rate (number of stones per patient per year) Recurrence (mean 2.21 years): defined as the number of patients without new stone formation	Population includes first time stone formers Concurrent medication/care: Both groups received the same dietary and fluid advice (no further information)
Sarica 2006[104]	Intervention (n=48): Potassium citrate (1mEq/kg orally per day either in tablet or liquid form) Comparison (n=48) 'no specific medication or preventive measure' control group	n=96 Children with or without stones following SWL Age – mean (range): citrate group 6.6 (4-14), no intervention group 7.4 (4-14) Gender (M:F): 58:38 Turkey	Recurrence (12-36.6 months): defined as new stone formation in children stone-free following SWL) Recurrence (12 - 36.6months): defined as stone recurrence or regrowth in children with residual fragments following SWL) Stone episodes (12-36.6 months): defined as stone stability in children with residual fragments following SWL	Non-randomised study Concurrent medication/care: SWL was performed four weeks prior, using the Stonelith V5 lithotripter with the child under general anaesthesia. In addition to enforced fluid intake, the dietary content of each child was evaluated, and avoidance of excessive dairy products and oxalate-rich foods was advised
Scholz 1982[106]	Intervention (n=25): Thiazide (hydrochlorothiazide	n=51	Recurrence (12 months): defined as spontaneous	Concurrent medication/care: No drugs were

Study	Intervention and comparison	Population	Outcomes	Comments
	25mg, twice daily). Participants took one tablet in the morning and one in the evening Comparison (n=26): Placebo twice daily	Adults with metabolically active calcium stone formation but without signs of primary hyperparathyroidism Age: thiazide group 46 (29-63); placebo group 41 (20-64) Gender: 31/20 Germany	passage of newly formed stone Minor adverse events (12 months)	allowed that could influence mineral metabolism. Additional potassium was given orally to patients in whom serum potassium decreased to <3 mEq./l during the study
Soygür 2002[119]	Intervention (n=46): potassium citrate 60 mEq per day. Potassium citrate tablets 5 mEq were administered in three doses after meals. Comparison (n=44): No intervention	n=110 enrolled in study; 90 randomised in trial Adults with calcium oxalate stones. They had lower caliceal stones and were stone free or had residual stone fragments <5mm in diameter 4 weeks after SWL. All patients had documented calcium oxalate stones without urinary tract infection. Age - Median (range): 41.7 (range 18.4 to 62.5 years) Gender (M:F): 60/30 Turkey	Recurrence (12 months): stone-free Stone episodes (12 months): stone size unchanged Stone episodes (12 months): stone size increased	Concurrent medication/care: Patients underwent SWL (with Dornier MPL lithotripter) before the trial. During the trial, all patients were advised to have a high fluid intake to achieve a minimum daily urine output of 2.1 litres and to avoid excess oxalate-rich foods and salty foods. They were instructed to limit their daily meat intake to 8 ounces or less, to substitute whole wheat bread for white bread, and to eat natural fibre cereals
Tosukhowong 2008[125]	Intervention (n=13): oral potassium citrate, in powder form packed in sachets. Participants were instructed to consume one sachet daily by dissolving	n=39 People who were post-operative and had nephrolithiasis with no residual stones	Kidney function (3 months): creatinine clearance – ml/min Kidney function (3 months): fractional excretion of magnesium - %	Concurrent medication/care: All patients received advice to increase water intake as well as avoid high salt and high purine

Study	Intervention and comparison	Population	Outcomes	Comments
	the medication in 200ml water throughout the treatment period Comparison (n=13): placebo (lactose) in powder form packed in sachets. Participants were instructed to consume one sachet daily by dissolving the medication in 200ml water throughout the treatment period.	Age - Mean (SD): Intervention group 47.8 (10.1); comparison group 54.1 (8.6). Gender (M:F): 17/14 Thailand	Kidney function (3 months): urine NAG activity – U/g Cr Kidney function (3 months): urine proteins – g/day	diets.
Wolf 1983[130 28]	Intervention (n=33): Thiazides (Bendroflumethiazide, 2.5mg three times daily) Comparison (n=29): placebo tablet, three times daily	n=62 Adults with stones of the upper urinary tract, who had no well-defined metabolic causes of renal stone formation Age >16 years Gender not reported Denmark	Recurrent (36 months): defined as new stone formation	Concurrent medication/care: Not reported

See appendix D for full evidence tables.

1.4.5 Quality assessment of clinical studies included in the evidence review

1.4.5.1 Adults

Table 3: Clinical evidence profile: potassium citrate versus no intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Potassium citrate (95% CI)
Recurrence (new stone formation of patients stone-free at baseline)	56 (1 study) 12 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Peto OR 0.1 (0.02 to 0.45)	Moderate	
				286 per 1000	247 fewer per 1000 (from 133 fewer to 278 fewer)
Recurrence (stone-free of patients stone-free at baseline)	56 (1 study) 12 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.39 (1.09 to 1.77)	Moderate	
				714 per 1000	278 more per 1000 (from 64 more to 550 more)
Recurrence (stone-free of patients with residual stones at baseline)	34 (1 study) 12 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 3.56 (0.88 to 14.35)	Moderate	
				125 per 1000	320 more per 1000 (from 15 fewer to 1000 more)
Stone episodes (stone size increased in patients with residual fragments <5mm at baseline)	34 (1 study) 12 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Peto OR 0.05 (0.01 to 0.23)	Moderate	
				625 per 1000	548 fewer per 1000 (from 348 fewer to 609 fewer)
Stone episodes (stone size unchanged in patients with residual fragments <5mm at baseline)	34 (1 study) 12 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 2.22 (0.86 to 5.71)	Moderate	
				250 per 1000	305 more per 1000 (from 35 fewer to 1000 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 4: Clinical evidence profile: potassium citrate versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Potassium citrate (95% CI)
Recurrence rate (stone formation/patient/year)	38 (1 study) 36 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Rate Ratio 0.09 (0.04 to 0.20)	Moderate	
				1100 per 1000	1001 fewer events per 1000 people treated (from 1056 fewer to 880 fewer)
Recurrence (new stone formation)	38 (1 study) 36 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.4 (0.18 to 0.88)	Moderate	
				700 per 1000	420 fewer per 1000 (from 84 fewer to 574 fewer)
Recurrence (number remaining stone-free)	38 (1 study) 36 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 3.61 (1.44 to 9.08)	Moderate	
				200 per 1000	522 more per 1000 (from 88 more to 1000 more)
Stone episodes (increase in stone size)	38 (1 study) 36 months	⊕⊖⊖⊖ VERY LOW1 due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 1.38)	Moderate	
				150 per 1000	128 fewer per 1000 (from 148 fewer to 46 more)
Stone interventions (procedures to remove stones)	38 (1 study) 36 months	⊕⊕⊕⊖ MODERATE due to risk of bias	RR 0.09 (0.01 to 0.64)	Moderate	
				600 per 1000	546 fewer per 1000 (from 216 fewer to 594 fewer)
Minor adverse events (unspecified; causing withdrawal from study)	38 (1 study) 36 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 2.22 (0.22 to 22.49)	Moderate	
				50 per 1000	61 more per 1000 (from 39 fewer to 1000 more)
Kidney function (creatinine clearance - ml/min)	18 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW1 due to risk of		The mean kidney function (creatinine clearance - ml/min) in	The mean kidney function (creatinine clearance - ml/min) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Potassium citrate (95% CI)
		bias, imprecision		the control groups was 80.6 ml/min	0.8 higher (64.75 lower to 66.35 higher)
Kidney function (fractional excretion of magnesium - %)	18 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean kidney function (fractional excretion of magnesium - %) in the control groups was 3 %	The mean kidney function (fractional excretion of magnesium - %) in the intervention groups was 0.7 higher (1.63 lower to 3.03 higher)
Kidney function (urine NAG activity - U/g Cr)	18 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean kidney function (urine nag activity - u/g cr) in the control groups was 3.6 U/g Cr	The mean kidney function (urine nag activity - u/g cr) in the intervention groups was 0.2 lower (4.44 lower to 4.04 higher)
Kidney function (urine proteins - g/day)	18 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean kidney function (urine proteins - g/day) in the control groups was 0.17 g/day	The mean kidney function (urine proteins - g/day) in the intervention groups was 0.04 lower (0.24 lower to 0.16 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 5: Clinical evidence profile: Magnesium supplement versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Magnesium supplement 650mg (95% CI)
Recurrence rate	82			Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Magnesium supplement 650mg (95% CI)
	(1 study) 36 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Rate Ratio 0.74 (0.36 to 1.54)	220 per 1000	57 fewer events per 1000 (from 141 fewer 119 more)
Recurrence (calculi observed)	82 (1 study) 36 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.65 (0.37 to 1.16)	Moderate	
				452 per 1000	158 fewer per 1000 (from 285 fewer to 72 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: Clinical evidence profile: allopurinol versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Allopurinol (95% CI)
Recurrence rate (rate of calculous events per patient per year)	60 (1 study) 39 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Rate Ratio 0.46 (0.16 to 1.33)	Moderate	
				260 per 1000	140 fewer events per 1000 people treated (from 218 fewer to 86 more)
Recurrence (new stones)	60 (1 study) 39 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.49 (0.19 to 1.23)	Moderate	
				355 per 1000	181 fewer per 1000 (from 288 fewer to 82 more)
Recurrence (unspecified)			Not estimable4	Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Allopurinol (95% CI)
	52 (1 study) 2 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias,		0 per 1000	0 fewer per 1000 (from 73 fewer to 73 more)3
Stone episodes (number of people with stone size increase)	60 (1 study) 39 months	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.61 (0.2 to 1.87)	Moderate	
				226 per 1000	88 fewer per 1000 (from 181 fewer to 197 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager
4 Could not be calculated as there were no events in the intervention or comparison arms

Table 7: Clinical evidence profile: thiazides versus no intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Thiazides (95% CI)
Recurrence rate	175 (1 study) 2.21 years	⨁⨁⨀⨀ LOW1 due to risk of bias	Rate Ratio 0.42 (0.26 to 0.68)	Moderate	
				295 per 1000	171 fewer events per 1000 people treated (from 218 fewer to 94 fewer)
Recurrence (stone free)	40 (1 study) 36 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.47 (0.97 to 2.24)	Moderate	
				571 per 1000	268 more per 1000 (from 17 fewer to 708 more)
Recurrence (patients without new stone formation per number of cumulative year of observation)	175 (1 study) 2.21 years	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 1.06 (0.96 to 1.18)	Moderate	
				860 per 1000	52 more per 1000 (from 34 fewer to 155 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Thiazides (95% CI)
Recurrence (number of people free from recurrence)	41 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 3.76 (1.17 to 12.16)	Moderate	
				125 per 1000	345 more per 1000 (from 21 more to 1000 more)
Recurrence (number of patients with recurrences) - Normocalciuric patients	41 (1 study) 24 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.29 (0.43 to 3.82)	Moderate	
				222 per 1000	64 more per 1000 (from 127 fewer to 626 more)
Recurrence (number of patients with recurrences) - Hypercalciuric patients	32 (1 study) 24 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.43 (0.1 to 1.81)	Moderate	
				333 per 1000	190 fewer per 1000 (from 300 fewer to 270 more)
Minor adverse events (study discontinuation due to clinical hypotension: dizziness and hypotension)	50 (1 study) 36 months	⨁⨁⊖⊖ LOW1 due to imprecision	Peto OR 7.39 (0.15 to 372.38)	Moderate	
					40 more per 1000 (from 64 fewer to 144 more)3
Minor adverse events (study discontinuation due to silent severe hypokalaemia)	50 (1 study) 36 months	⨁⨁⊖⊖ LOW1 due to imprecision	Peto OR 7.39 (0.15 to 372.38)	Moderate	
					40 more per 1000 (from 64 more to 144 more)3
Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction)	41 (1 study) 5 years	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 14.58 (2.24 to 95.12)	Moderate	
				0 per 1000	294 more per 1000 (from 74 more to 514 more)3
Kidney function (creatinine clearance - ml/min)	40 (1 study) 36 months	⨁⨁⊖⊖ LOW1 due to imprecision		The mean kidney function (creatinine clearance - ml/min) in the	The mean kidney function (creatinine clearance - ml/min) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Thiazides (95% CI)
				control groups was 120 ml/min	6.00 lower (20.26 lower to 8.26 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Risk difference calculated in Review Manager

Table 8: Clinical evidence profile: thiazides versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Thiazides (95% CI)
Recurrence rate	135 (2 studies) 36 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Rate Ratio 0.50 (0.14 to 1.84)	Moderate	
				155 per 1000	77 fewer events per 1000 people treated (from 133 fewer to 130 more)
Recurrence (unspecified)	50 (1 study) 2 months	⨁⨁⊖⊖ LOW1 due to risk of bias	Not estimable4	Moderate	
				0 per 1000	0 fewer per 1000 (from 76 fewer to 76 more)3
Recurrence (verified and probable new stone/ spontaneous passage of newly formed stones/calculi observed)	169 (3 studies) 1-3 years	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.50 (0.3 to 0.82)	Moderate	
				452 per 1000	226 fewer per 1000 (from 81 fewer to 316 more)
Stone interventions (SWL) with previous SWL	100 (1 study) 36 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.43 (0.22 to 0.84)	Moderate	
				420 per 1000	239 fewer per 1000 (from 67 fewer to 328 fewer)
				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Thiazides (95% CI)
Stone episodes (residual fragments or growth) with previous SWL	100 (1 study) 36 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.53 (0.36 to 0.76)	760 per 1000	357 fewer per 1000 (from 182 fewer to 486 fewer)
Minor adverse events (attack of gouty arthritis)	48 (1 study) 37-38 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 8.06 (0.16 to 407.6)	Moderate	
				0 per 1000	44 more per 1000 (from 67 fewer to 154 more)3
Minor adverse events (impotence - transient and characterised as mild)	48 (1 study) 37-38 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 8.06 (0.16 to 407.6)	Moderate	
				0 per 1000	44 more per 1000 (from 67 fewer to 154 more)3
Minor adverse events (hypopotassemia)	48 (1 study) 38-40 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 8.06 (0.16 to 407.6)	Moderate	
				0 per 1000	44 more per 1000 (from 67 fewer to 154 more)4
Minor adverse events (general discomfort as nausea, dyspepsia, fatigue and vertigo)	48 (1 study) 37-38 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.63 (0.3 to 8.9)	Moderate	
				80 per 1000	50 more per 1000 (from 56 fewer to 632 more)3
Minor adverse events (weariness, nausea and symptoms of low blood pressure)	48 (1 study) 12 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 2.39 (0.98 to 5.84)	Moderate	
				200 per 1000	278 more per 1000 (from 4 fewer to 968 more)
Minor adverse events (intracellular acidosis and hypocitraturia induced by hypopotassemia secondary to administration of thiazides)	100 (1 study) 36 months	⊕⊕⊕⊖ MODERATE2 due to imprecision	Peto OR 8.04 (1.34 to 48.12)	Moderate	
				0 per 1000	100 more per 1000 (from 10 more to 190 more)4

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Thiazides (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. 3 Risk difference calculated in Review Manager					

Table 9: Clinical evidence profile: thiazides versus magnesium

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Magnesium (any dose)	Risk difference with Thiazide (95% CI)
Recurrence	93 (1 study) 36 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.49 (0.21 to 1.14)	Moderate	
				294 per 1000	150 fewer per 1000 (from 232 fewer to 41 more)
Recurrence rate	93 (1 study) 36 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Rate ratio 0.35 (0.13 to 0.9)	Moderate	
				163 per 1000	106 fewer per 1000 (from 142 fewer to 16 fewer)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 10: Clinical evidence profile: thiazides versus allopurinol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Allopurinol	Risk difference with Thiazides (95% CI)
Recurrence (unspecified)	46 (1 study) 2 months	⊕⊕⊖⊖ LOW1 due to risk of bias	Not estimable2	Moderate	
				0 per 1000	0 per 1000 (from 80 fewer to 41 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Could not be calculated as there were no events in the intervention or comparison group

3 Risk difference calculated in Review Manager

Table 11: Clinical evidence profile: allopurinol + thiazides versus no intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Allopurinol + thiazide (95% CI)
Recurrence (stone free)	45 (1 study) 36 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.53 (1.03 to 2.28)	Moderate	
				571 per 1000	303 more per 1000 (from 17 more to 731 more)
Kidney function (creatinine clearance - ml/min)	45 (1 study) 36 months	⊕⊕⊖⊖ LOW1 due to imprecision		The mean kidney function (creatinine clearance - ml/min) in the control groups was 120 ml/min	The mean kidney function (creatinine clearance - ml/min) in the intervention groups was 2.00 higher (11.01 lower to 15.01 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 12: Clinical evidence profile: allopurinol + thiazides versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Allopurinol + thiazides (95% CI)
Recurrence (unspecified)	50 (1 study) 2 months	⊕⊕⊖⊖ LOW1 due to risk of bias	Not estimable2	Moderate	
				0 per 1000	0 per 1000 (from 76 fewer to 76 more)3

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Could not be calculated as there were no events in the intervention or comparison group
3 Risk difference calculated in Review Manager

Table 13: Clinical evidence profile: allopurinol + thiazides versus allopurinol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Allopurinol	Risk difference with Allopurinol + thiazides (95% CI)
Recurrence rate	87 (1 study) 4.7 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Rate Ratio 0.84 (0.56 to 1.27)	Moderate	
				240 per 1000	38 fewer events per 1000 people treated (from 105 fewer to 65 more)
Recurrence (number of people with new stones)	87 (1 study) 4.7 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.24 (0.8 to 1.92)	Moderate	
				432 per 1000	104 more per 1000 (from 86 fewer to 397 more)
Recurrence (unspecified)	46 (1 study) 2 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Not estimable3	Moderate	
				0 per 1000	0 more per 1000 (from 81 fewer to 81 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Risk difference calculated in Review Manager

Table 14: Clinical evidence profile: thiazides + allopurinol versus thiazides

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Thiazides	Risk difference with Thiazides + allopurinol (95% CI)
Recurrence (unspecified)	44 (1 study) 2 months	⊕⊕⊖⊖ LOW1 due to risk of bias	Not estimable3	Moderate	
				0 per 1000	0 per 1000 (from 84 fewer to 43 more)4
Recurrence (number of stone-free participants)	43 (1 study) 36 months	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.04 (0.81 to 1.33)	Moderate	
				842 per 1000	34 more per 1000 (from 160 fewer to 278 more)
Minor adverse events (study discontinuation due to clinical hypotension: dizziness and hypotension)	50 (1 study) 36 months	⊕⊕⊖⊖ LOW2 due to imprecision	Peto OR 7.39 (0.15 to 372.38)	Moderate	
					40 fewer per 1000 (from 64 fewer to 144 more)4
Minor adverse events (study discontinuation due to silent severe hypokalaemia)	50 (1 study) 36 months	⊕⊕⊖⊖ LOW2 due to imprecision	Peto OR 7.39 (0.15 to 372.38)	Moderate	
					40 fewer per 1000 (from 64 fewer to 144 more)4
Kidney function (creatinine clearance - ml/min)	43 (1 study) 36 months	⊕⊕⊖⊖ LOW2 due to imprecision		The mean kidney function (creatinine clearance - ml/min) in the control groups was 114 ml/min	The mean kidney function (creatinine clearance - ml/min) in the intervention groups was 8.00 higher (4.72 lower to 20.72 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

3 Could not be calculated as there were no events in the intervention or comparison group

4 Risk difference calculated in Review Manager

Table 15: Clinical evidence profile: magnesium supplement (2460 mg) + thiazides versus thiazides

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with thiazides	Risk difference with magnesium + thiazides (95% CI)
Recurrence (number of people free from recurrence)	33 (1 study) 5 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.46 (0.8 to 2.67)	Moderate	
				471 per 1000	217 more per 1000 (from 94 fewer to 787 more)
Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction)	33 (1 study) 5 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.28 (0.48 to 3.37)	Moderate	
				294 per 1000	82 more per 1000 (from 153 fewer to 697 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 16: Clinical evidence profile: magnesium supplement (2460 mg) + thiazides versus no intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Magnesium + thiazides (95% CI)
Recurrence (number of people free from recurrence)	40 (1 study) 5 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 5.5 (1.81 to 16.67)	Moderate	
				125 per 1000	562 more per 1000 (from 101 more to 1000 more)
Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction)	40 (1 study) 5 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 17.6 (3.06 to 101.18)	Moderate	
				0 per 1000	375 more per 1000 (from 138 more to 612 more)3

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Magnesium + thiazides (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. 3 Risk difference calculated in Review Manager					

1.4.5.2 Children

Table 17: Clinical evidence profile: potassium citrate versus no intervention (non-randomised studies)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Potassium citrate (95% CI)
Recurrence rate (stone formation rate in children after PNL, per patient per year)	42 (1 study) 12-42 months	⊕⊖⊖⊖ VERY LOW1 due to risk of bias	Rate Ratio 0.17 (0.04 to 0.79)	Moderate	
				200 per 1000	166 fewer events per 1000 people treated (from 192 fewer to 42 fewer)
Recurrence (new detection of stone or spontaneous passage of non-pre-existing stone in children following PNL)	42 (1 study) 12-42 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.26 (0.06 to 1.11)	Moderate	
				350 per 1000	259 fewer per 1000 (from 329 fewer to 39 more)
Recurrence (new stone formation in children stone-free following SWL)	52 (1 study) 12-36.6 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.22 (0.05 to 0.93)	Moderate	
				346 per 1000	270 fewer per 1000 (from 24 fewer to 329 fewer)
Recurrence (stone recurrence or regrowth in children with residual fragments following SWL)	44 (1 study) 12-36.6 months	⊕⊖⊖⊖ VERY LOW1 due to risk of bias	RR 0.25 (0.1 to 0.63)	Moderate	
				727 per 1000	545 fewer per 1000 (from 269 fewer to 654 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No intervention	Risk difference with Potassium citrate (95% CI)
Stone episodes (stone stability in children with residual fragments following SWL)	44 (1 study) 12-36.6 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 3 (1.47 to 6.1)	Moderate	
				273 per 1000	546 more per 1000 (from 128 more to 1000 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6 Unit costs

Illustrations of unit costs for the interventions identified in the clinical review are demonstrated below.

Table 18: UK costs of drugs

Drug	Medicinal form	Daily dose	Cost – 28 days	Cost – annual	Source
Sodium citrate	sachets of granules 4g, 6 sachets £2.79	4g (1 sachet)	£14.14	£169.73	Dose: clinical review Cost: BNF
Citric acid with Potassium citrate	Oral solution 200ml 300mg per 1ml £1.33	10ml twice a day (= 6g per day)	£4.05	£48.55	Dose: clinical review Cost: BNF
Potassium citrate	Oral solution 200ml 300mg per 1ml £2.49	10ml twice a day (= 6g per day)	£7.57	£90.89	Dose: clinical review Cost: Online pharmacy (a)
Milk of magnesia	Oral solution, 200ml £5.29	10ml = 830mg	£8.05	£96.54	Dose: clinical review Cost: Online pharmacy (b)
Allopurinol	Tablet 28 tablets, 100g, £0.69	200mg per day	£1.50	£17.99	Dose: clinical review Cost: BNF
Bendroflumethiazide (c)	Tablet, 28 tablets, 2.5mg, £0.62	7.5mg	£2.02	£24.25	Dose: clinical review Cost: BNF

Source: BNF[63], other sources listed below.

(a) http://www.lloydspharmacy.com/en/care-potassium-citrate-mixture-200ml April 2018

(b) http://www.boots.com/phillips-milk-of-magnesia-liquid-traditional-mint-flavour-200ml-10007028 Feb 2018

(c) Thiazides with potassium chloride, amiloride, or hydrochlorothiazide alone were not in the BNF.

1.6.1 Economic considerations: trade-off between net clinical effects and costs

Some illustrative examples of cost offset calculations are demonstrated below.

Example 1:

These medications will most likely have to be taken for the lifetime of the patient, hence large costs can accrue.

There is therefore a trade-off with regards to;

- potential intervention avoided from stones that do not recur (because of the treatment),
- and whether that would outweigh the costs of the preventative treatment.

Say for someone aged 45, likely to live for another 40 years, then that is 40 years of the treatment. Depending on the cost of the treatment, this is likely to be roughly around the cost of 1 or 2 surgeries (if we say a conservative £100 per year multiplied by 40 years = £4,000). So the intervention would have to be effective enough for each individual to avoid possibly several stone recurrences.

Example 2:

If we have data on the recurrence of stones in terms of how long before another stone forms, or the average number of stones a person will have in their lifetime, and we knew how effective the interventions were, we could work out the trade-off. For example;

Sakhaee 2009[102] states that the median time for a recurrence after the first event is approximately every 5 years. Over a 40 year period this would be 8 episodes. Robertson 2006[100] states that the average stone patient will have between 3 or 4 episodes over their lifetime. Let's take the midpoint of say 6 episodes over the lifetime of an average patient.

Let us also use a rate ratio of 0.7 (the average of all the studies that report rate ratios).

This means there would be 1.8 stone episodes avoided with pharmacological prevention of recurrence interventions. If these episodes would cost an average of £2,000 each to treat, and assuming that only 50% would require treatment, then that would be £1,800 of treatment costs avoided over the patient's lifetime. To make the preventative treatments cost neutral, then over a 40 year period these interventions would have to cost less than £45 per year.

Example 3:

Let's assume we can use the rates/probabilities from the review and put them all in the same timeframe of 1 year. Then we could compare effectiveness across the interventions.

We could also assume, that each year the probability of developing a stone would be the same, and that someone who develops a stone within a year is treated, and then they will go back into the pool of people who are at risk of developing a stone. So below is just a 1 year example assuming this would be the same repeatedly over time.

Table 19 below is using the outcomes that are reported as rates from the clinical review, and these have all been converted to 1 year probabilities using the following formula;

(Equation 1): P = 1-EXP(-instantaneous rate*t) where P = probability, t = time

Rates may be more appropriate than probabilities because; a person can develop more than one stone over time, and also it is the stones that will be treated rather than the people, that

will influence resource use (unless multiple stones in one individual can be treated at the same time).

Table 20 is using probabilities from the review (rather than rates) and these have all been converted to 12 month probabilities, using the following method;

A probability over time is converted to an instantaneous rate using the formula;

(Equation 2): R = -[LN(1-P)]/t where R = rate, P = probability, t = time

Then as above, an instantaneous rate can be used to convert to a 1 year probability.

Table 19: Illustrating if interventions are cost saving over a year using rates from clinical review

Comparison	Intervention: 1 year probability of developing stone	Control: 1 year probability of developing stone	No. of stones that develop with intervention (per 1000 people)	No. of stones that develop with control (per 1000 people)	1) Intervention incremental cost per 1000 people (a)	2) Cost of stone treatments avoided (b)	Is intervention cost saving? (2-1)
Potassium citrate vs placebo	0.09	0.67	94	667	£90,885	£572,872	cost saving
Magnesium 650g vs placebo	0.14	0.20	145	197	£96,540	£52,869	
Magnesium 1300g vs placebo	0.16	0.20	158	197	£96,540	£39,797	
Allopurinol vs placebo	0.11	0.23	113	229	£17,990	£116,224	cost saving
Allopurinol + thiazide vs allopurinol	0.18	0.21	183	213	£24,250	£30,794	cost saving
Thiazide vs no intervention	0.12	0.26	117	255	£24,250	£138,937	cost saving
Thiazide vs placebo	0.08	0.09	84	86	£24,250	£1,647	

(a) Costs are based on those reported in the unit cost table (Table 18). For potassium citrate the higher cost is used. For the different doses of magnesium citrate, the same cost is used – this may overestimate costs for the 650g dose but a unit of 8ml for example is an unusual dose so a round 10ml has been used. This will not overestimate costs to the extent that the intervention will be cheaper than the cost of treatment avoided. For potassium citrate, the most conservative cost of the intervention is used.

(b) Cost of stone treatment is assuming this cost £2,000, and that 50% of people will need intervention

Table 20: Illustrating if interventions are cost saving over a year using probabilities from clinical review

Comparison (a)	Outcome	Intervention: 1 year probability of developing stone	Control: 1 year probability of developing stone	No. of stones that develop with intervention (per 1000 people)	No. of stones that develop with control (per 1000 people)	1) Intervention incremental cost per 1000 people (a)	2) Cost of stone treatments avoided (b)	Is intervention cost saving? (2-1)
Potassium citrate vs no intervention	new stone in pts stone free at baseline	0.03	0.29	29	286	£90,885	£257,400	cost saving

Comparison (a)	Outcome	Intervention: 1 year probability of developing stone	Control: 1 year probability of developing stone	No. of stones that develop with intervention (per 1000 people)	No. of stones that develop with control (per 1000 people)	1) Intervention incremental cost per 1000 people (a)	2) Cost of stone treatments avoided (b)	Is intervention cost saving? (2-1)
Potassium citrate versus placebo	new stone formation	0.10	0.33	104	331	£90,885	£226,848	cost saving
Allopurinol vs placebo	Recurrence (new stones)	0.06	0.13	57	126	£17,990	£69,114	cost saving
Allopurnol + thiazides vs no intvn	Recurrence (stone free) - used reciprocal	0.04	0.17	44	170	£42,240	£126,347	cost saving
Allopurinol + thiazides vs allopurinol	Recurrence (number of people with new stones)	0.15	0.11	151	113	£24,250	-£37,216	
Thiazides vs no intervention	Recurrence (number of patients with recurrences) - Hypercalciuric patients	0.07	0.18	74	183	£24,250	£108,940	cost saving

Some comparisons are not included here because; studies pooled are at different time points, or there was no clinical difference in outcome, or there were not many outcomes reported.

(a) Costs are based on those reported in the unit cost table. For potassium citrate, the most conservative cost of the intervention is used.

(b) Where the cost of treatment avoided is negative, this is because there are more stones in the intervention group than the control group. Cost of stone treatment is assuming this cost £2,000, and that 50% of people will need intervention

1.6.2 Resource costs

The committee has made recommendations based on this review (see section **Error! eference source not found.**) that potassium citrate, and thiazides, should be 'considered'.

Unlike for stronger recommendations stating that interventions should be adopted, it is not possible to make a judgement about the potential resource impact to the NHS of recommendations regarding interventions that could be used, as uptake is too difficult to predict.

However, the committee noted that where this recommendation is implemented there is not expected to be a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

1.7.1.1 Adults

Potassium citrate versus no intervention

One study compared potassium citrate with no intervention. This study reported recurrence as new stone formation in patients who were stone-free at baseline; the evidence suggested a clinically important benefit in favour of potassium citrate (n=56). The same study also reported recurrence as number of stone-free patients of those who were stone-free at baseline (n=34) and those who had residual stones at baseline (n=56); this evidence suggested a clinically important benefit in favour of potassium citrate. Further stone episode outcomes were reported for increased and unchanged stone size in patients with residual stones <5mm at baseline; this evidence suggested a clinically important benefit in favour of potassium citrate (n=34).The quality of the evidence was Moderate to Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Potassium citrate versus placebo

Two studies compared potassium citrate with placebo. One study reported the outcome recurrence rate (stone formation per patient per year); this evidence suggested a clinically important benefit in favour of potassium citrate (n=38). One study reported outcomes for recurrence, defined as new stone formation and stone-free; this evidence suggested a clinically important benefit in favour of potassium citrate (1 study; n=38). Further stone episode and intervention outcomes included increased stone size and procedures to remove stones, for which the evidence suggested a clinically important benefit in favour of potassium citrate (1 study; n=38). One study reported the outcome minor adverse events (unspecified; causing withdrawal from study) and the evidence suggested a clinically important benefit in favour of placebo (n=38). One study reported outcomes for kidney function. This evidence suggested no clinical difference between potassium citrate and placebo (n=18). The quality of the evidence ranged from Moderate to Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Magnesium supplement () versus placebo

One study compared magnesium supplementation with placebo. The evidence suggested a clinically important benefit in favour of magnesium in terms of recurrence, defined as calculi observed and recurrence rate (n=82). The quality of the evidence was Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Allopurinol versus placebo

Two studies compared allopurinol with placebo. One study reported the outcome recurrence rate as the rate of calculous events per patient per year, and the evidence suggested a clinically important benefit in favour of allopurinol (n=60). There was a suggested clinically important benefit of allopurinol when recurrence was defined as new stones (1 study; n= 60), and no clinical difference between the interventions when recurrence was not defined (1 study; n =52). In terms of stone episodes, defined as number of people with increased stone size, there was a suggested clinically important benefit in favour of allopurinol (1 study; n=60). The quality of the evidence ranged from Moderate to Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Thiazides versus no intervention

Four studies compared thiazides versus no intervention. One study reported the outcome recurrence rate as the number of stones per patient per year and this evidence suggested a clinically important benefit in favour of thiazides (n=175). There was a suggested clinically important benefit of thiazides in terms of recurrence when the outcome was defined across different time-points as the number of participants stone free (1 study; n=175), the number of participants without a new stone formation (1 study; n=41), the number of participants free from recurrence (1 study; n=41), and the number of hypercalciuric patients with recurrences (1 study; n=32). There was a clinically important benefit of no intervention in terms of recurrence defined as the number of normocalciuric patients with recurrence (1 study; n=41). In terms of adverse events, one study reported two minor adverse events, including study discontinuation due to clinical hypotension (dizziness and hypotension), and study discontinuation due to silent severe hypokalaemia; this evidence suggested no clinical difference between thiazides and no intervention in adults (1 study; n=50). Another study reported minor adverse events as treatment discontinued due to side effects including orthostatic reaction, dizziness, gastrointestinal symptoms, muscle cramp and erectile dysfunction; this evidence suggested a clinically important benefit in favour of no intervention when compared with thiazides (1 study; n=41). One study reported the outcome creatinine clearance, as a measure of kidney function; this evidence suggested no clinical difference between thiazides and no intervention (1 study; n=40). The quality of the evidence was Moderate to Very Low to . The main reasons for downgrading evidence included risk of bias and imprecision.

Thiazides versus placebo

Six studies compared thiazides with placebo. There was a clinically important benefit of thiazides in terms of recurrence rate (2 studies; n=135). There was no clinical difference between thiazides and placebo in terms of recurrence when the definition was not specified (1 study; n=50). When recurrence was defined as verified and probable stone or spontaneous passage of newly formed stone, there was a clinically important benefit of thiazides (3studies; n=169). One study reported stone interventions (SWL) and the evidence suggested a clinically important benefit of thiazides (n=100). One study reported stone episodes as residual fragments or growth; this evidence suggested a clinically important benefit in favour of thiazides (n=100). Three studies reported minor adverse events. The evidence suggested no clinical difference between thiazides and placebo for minor adverse events including an attack of gouty arthritis, impotence characterised as transient and mild, and hypopotassaemia (1 study; n=48); one study reported general discomfort, nausea, dyspepsia, fatigue and vertigo as a minor adverse event and this evidence suggested a clinical benefit in favour of placebo when compared with thiazides (n=48). One study reported weariness, nausea and symptoms of low blood pressure as a minor adverse event; this evidence suggested a clinically important benefit of placebo when compared with thiazides (n=48). One study reported intracellular acidosis and hypocitraturia induced by hypopotassemia secondary to administration of thiazides as a minor adverse event; this evidence suggested a clinically important benefit in favour of placebo when compared with thiazides (n=100). The quality of the evidence ranged from Moderate to Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Thiazide versus magnesium

One study compared thiazides with magnesium. There was a clinically important benefit in terms of recurrence rate, and in terms of recurrence defined as calculi observed (1 study; n=93). The quality of the evidence was Very Low. The main reason for downgrading the evidence was risk of bias.

Thiazides versus allopurinol

One study compared thiazides with allopurinol. This study reported the outcome recurrence (unspecified) and the evidence suggested no clinical difference between the interventions (n=46). The quality of the evidence was Low. The main reason for downgrading the evidence was risk of bias.

Allopurinol plus thiazides versus no intervention

One study compared allopurinol plus thiazides with no intervention. The study reported the outcome recurrence as the number of stone-free patients; this evidence suggested a clinically important benefit in favour of allopurinol plus thiazides when compared with no intervention (1 study; n=45). This study also reported the outcome creatinine clearance, as a measure of kidney function; the evidence suggested no clinical difference between allopurinol plus thiazides and no intervention (1 study; n=45). The quality of the evidence was Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Allopurinol plus thiazides versus placebo

One study compared allopurinol plus thiazides with placebo. This study reported the outcome recurrence (unspecified), and the evidence suggested no clinical difference between allopurinol plus thiazides and placebo (1 study; n=50). The quality of the evidence was Low. The main reason for downgrading evidence was risk of bias.

Allopurinol plus thiazides versus allopurinol

Two studies compared allopurinol plus thiazides with allopurinol. The evidence suggested no clinical difference between allopurinol plus thiazides and allopurinol in terms of recurrence rate (1 study; n=87). In terms of recurrence, there was a suggested clinically important benefit of allopurinol alone when compared with allopurinol plus thiazides when recurrence was defined as the number of people with new stones (1 study; n=87), and no clinical difference when recurrence was not defined (1 study; n=46). The quality of the evidence was Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Thiazides plus allopurinol versus thiazides

Two studies compared thiazides plus allopurinol with thiazides. The evidence suggested no clinical difference between the interventions in terms of recurrence (unspecified) (1 study; n=44) or recurrence when defined as the number of stone-free patients (1 study; n=43). One study reported two minor adverse events, including study discontinuation due to clinical hypotension, and study discontinuation due to silent severe hypokalaemia; this evidence suggested no clinical difference between thiazides plus allopurinol and thiazides (1 study; n=50). One study reported creatinine clearance, as a measure of kidney function; this evidence suggested no clinical difference between thiazides plus allopurinol and thiazides (1 study; n=43). The quality of the evidence was Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Magnesium supplement (2460mg) + thiazides versus thiazides

One study compared magnesium supplement plus thiazide with thiazide alone. This study reported the outcome recurrence, defined as the number of people free from recurrence. The evidence suggested a clinically important benefit in favour of combined magnesium and thiazide. The same study also reported minor adverse events as treatment discontinued due

to side effects including orthostatic reaction, dizziness, gastrointestinal symptoms, muscle cramp and erectile dysfunction; this evidence suggested a clinically important benefit in favour of thiazide alone (n=33). The quality of the evidence was Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

Magnesium supplement (2460mg) + thiazides versus no intervention

One study compared magnesium supplement plus thiazide with no intervention. This study reported the outcome recurrence, defined as the number of people free from recurrence. The evidence suggested a clinically important benefit in favour of combined magnesium and thiazide. The same study also reported minor adverse events as treatment discontinued due to side effects including orthostatic reaction, dizziness, gastrointestinal symptoms, muscle cramp and erectile dysfunction; this evidence suggested a clinically important benefit in favour of no intervention (n=40). The quality of the evidence was Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

1.7.1.2 Children

Potassium citrate versus no intervention

Two non-randomised studies in children compared potassium citrate with no intervention. One of the studies reported the outcome recurrence rate (stone formation rate in children after PNL, per patient per year); this evidence suggested a clinically important benefit in favour of potassium citrate (n=42). One study reported recurrence as the new detection of a stone or spontaneous passage of a non-pre-existing stone in patients following PNL; this evidence suggested a clinically important benefit in favour of potassium citrate (n=42). One study reported recurrence as new stone formation in patients stone-free following SWL; this evidence suggested a clinically important benefit in favour of potassium citrate (n=52). One study reported stone recurrence or regrowth, and stone stability in children with residual fragments following SWL; this evidence suggested a clinically important benefit in favour of potassium citrate (n=44). The quality of the evidence was Very Low. The main reasons for downgrading evidence included risk of bias and imprecision.

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.8 Recommendations

The following recommendations apply alongside the recommendations on dietary and lifestyle advice.

K1. Consider potassium citrate[a] for adults with a recurrence of stones that are predominantly (more than 50%) calcium oxalate.

K2. Consider potassium citrate for children and young people with a recurrence of stones that are predominantly (more than 50%) calcium oxalate and with hypercalciuria or hypocitraturia.

[a] At the time of consultation (July 2018), potassium citrate did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Thiazides

K3. Consider thiazides[b] for adults with a recurrence of stones that are predominantly (more than 50%) calcium oxalate and hypercalciuria after restricting their sodium intake to no more than 6 g a day.

1.8.1 Research recommendations

What is the clinical and cost-effectiveness of empirical potassium citrate or bendroflumethiazide as preventative therapies for patients with small residual fragments following shockwave lithotripsy to renal and ureteric stones.

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

Evidence showed that potassium citrate reduced the recurrence of calcium oxalate and calcium oxalate/calcium phosphate stones in adults compared with no intervention or placebo. There were more adverse events with potassium citrate and the committee agreed that there may be concerns about hyperkalaemia in some groups. However, the benefits in terms of stones avoided are likely to outweigh any harm. Potassium citrate is currently used in UK practice and so the committee agreed it could be considered to prevent stone recurrence in adults with calcium oxalate stones.

Limited evidence in children showed that potassium citrate reduced stone recurrence after PCNL and SWL. There was no information on adverse events or on the type of stone or results of urine testing. The committee discussed that in UK practice potassium citrate is used for children based on the levels of calcium or citrate in urine. They agreed that it could be considered for children with recurrence of calcium oxalate stones or hypercalciuria or hypocitraturia.

Limited evidence showed that thiazides reduced stone recurrence in adults with hypercalciuria compared with no intervention. There was no benefit for adults with normal levels of urinary calcium, and evidence was mixed when the biochemical abnormality was mixed or not defined. The committee agreed that thiazides tend to be well tolerated but should only be used after salt has been restricted. They agreed that thiazides could be considered for adults with hypercalciuria and recurrent calcium oxalate stones, but only after reducing salt intake to recommended levels.

There was not enough evidence for the committee to make recommendations on allopurinol or combined therapy of allopurinol and thiazides. Although limited evidence suggested a potential benefit of magnesium, the committee knew from their experience that magnesium may cause adverse effects. Magnesium is not commonly used in UK practice for people with renal or ureteric stones and the committee agreed that the limited evidence and potential for adverse events did not justify a recommendation.

Limited evidence from a single study of thiazides compared with placebo in people who had had previous SWL showed some benefit of thiazides in reducing the need for further SWL and for stone growth. The committee agreed that this is not usual practice and that further research would be beneficial to inform future practice.

[b] At the time of consultation (July 2018), thiazides did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

1.9.2 Impact of the recommendations on practice

The committee considered the impact the recommendations would have on practice including metabolic laboratory testing. Testing to identify stone composition or metabolic abnormalities would be a prerequisite to the recommendations and this would have a cost as well as potential service impact. Recommending the interventions also has a monitoring impact.

There is variation in current practice in terms of the use of thiazides and potassium citrate for people with renal or ureteric stones.

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

The committee agreed that recurrence rate, stone episodes/stone interventions, use of healthcare services, quality of life, major adverse events (if admission to hospital) and minor adverse events (no admission to hospital) were the outcomes critical for decision making. Kidney function and pain intensity (visual analogue scale) were also considered as important outcomes.

Evidence was reported for recurrence rate, stone episodes, stone interventions and minor adverse events. There was no evidence for the quality of life, use of healthcare services, major adverse events or pain intensity. For the purposes of this review, stone episodes and stone interventions were considered as two separate outcomes, and 'recurrence' was considered as a further outcome of critical importance.

1.10.1.2 The quality of the evidence

In adults, the quality of the evidence in this review ranged from a GRADE rating of very low to moderate. In children, the quality of the evidence was very low, based on two non-randomised studies. The main reasons for downgrading the quality of the evidence were risk of bias and imprecision. The presence of selection bias in terms of a lack of adequate randomisation and allocation concealment commonly resulted in a high or very high risk of bias rating.

No evidence was found for the following comparisons listed in the protocol: sodium citrate; oral bicarbonate; chelating agents: D-penicillamine, Tiopronin (or Thiola or mercaptopropionylglycine) (for cystinuria); captopril (for cystinuria); Ca supplements, pyridoxine; methionine; prophylactic antibiotics.

1.10.1.3 Benefits and harms

Evidence for people with both symptomatic and asymptomatic stones was searched for; however no evidence was identified for the asymptomatic population. The committee therefore agreed that the recommendations should only apply to those with symptomatic stones.

Potassium citrate in adults

The committee considered the evidence for potassium citrate in adults compared to no intervention or placebo and noted there was very low to moderate quality evidence in favour of potassium citrate for outcomes related to stone recurrence, stone episodes and stone intervention. These outcomes were measured at 12 and 36 months. The committee considered that 12 months is a short follow up period, and may not be a sufficient length of

time to measure stone recurrences. However, the committee noted that the results at 36 months were consistent with the 12 month evidence. It was noted that there was no clinically important difference between the interventions in terms of kidney function. The committee discussed that these outcomes were measured at 3 months, which may not be a sufficient length of time to capture meaningful changes in these outcomes. There were more adverse events leading to study discontinuation in the potassium citrate group, however no reasons were given for these events, therefore it was not possible to fully consider the trade-off between benefits and harms of intervention. The committee considered that there may be concerns associated with potassium citrate in some populations, as increased potassium in patients with impaired renal function can cause hyperkalaemia which is associated with adverse events. Overall, they concluded that there was not enough evidence to make a conclusion regarding safety.

The evidence was discussed with reference to the available information on study participants' stone composition and biochemical abnormalities. The committee noted that all the evidence was based on people with calcium oxalate or calcium oxalate and calcium phosphate stones, however included a mixture of urine metabolic abnormalities. All of the evidence came from a population of recurrent stone formers.

The committee highlighted that potassium citrate is currently used in UK clinical practice off-licence for calcium oxalate stones, although practice can vary, and that there may be issues with availability and long term prescription. From clinical experience, the committee also noted that the taste of potassium citrate might be a negative factor for treatment adherence.

Overall, the committee agreed that both the evidence and clinical experience supported the use of potassium citrate based on stone composition and irrespective of urine biochemical abnormalities. However, there were concerns regarding the size of the studies and the amount of evidence, as well as concerns relating to safety and the adverse events evidence; therefore a consider recommendation was made.

Potassium citrate in children

The committee considered the evidence for potassium citrate in children compared with no intervention and noted this was of very low quality, from non-randomised studies. They also noted that both studies were based on a population who had undergone previous treatment with either PCNL or SWL. The evidence favoured potassium citrate for the prevention of recurrence when compared with no intervention. There was no evidence for major or minor adverse events; therefore the committee were not able to consider potential harms. However it was noted that as with the adult population, potassium citrate is not very palatable and therefore there are sometimes problems with adherence to treatment.

The committee also discussed the evidence with reference to the available information on study participants' stone composition and urine biochemical abnormalities. Although the evidence did not relate to specific urine biochemical abnormalities, the committee agreed these would be tested as part of standard UK clinical practice in the paediatric population, typically at a specialist centre. The committee also noted that if hypercalciuria and/or hypocitraturia are identified in the urine during metabolic testing, potassium citrate is likely to be used in the paediatric population. The committee considered that the evidence suggested that potassium citrate is beneficial regardless of urine metabolic abnormality, however agreed that the evidence was not sufficiently convincing to change current practice and the expert opinion of the committee by recommending its use for all children with a calcium oxalate stone regardless of urine metabolic abnormality. Therefore, the committee recommended that potassium citrate should only be considered in children with a specific stone composition and urine biochemical abnormality. They also agreed that although the evidence was based on those who had had previous treatment with SWL or PCNL, based on consensus and clinical experience, the recommendations should apply to this population irrespective of previous treatment, as child stone formers are much more likely to have a metabolic abnormality and are therefore a high risk group.

Thiazides in adults

When compared to no intervention, there was a benefit of thiazides in terms of all outcomes relating to recurrence, when the population was people with hypercalciuria. One study included a subgroup of people with normocalciuria, and for this population there was a benefit of no intervention in terms of recurrence, suggesting that thiazides are only beneficial for those with hypercalciuria.

When compared to placebo, there was no difference between interventions in terms of recurrence rate, based on a population with no well-defined metabolic cause of renal stone formation. This also suggests that thiazides may only be beneficial for people with a specific urine metabolic abnormality. There was no clinical difference between groups in terms of recurrence when the definition of recurrence was not specified and measured at 2 months. However the committee agreed that this was not a sufficient length of time to see a recurrence of stones, therefore no conclusions could be drawn from this outcome. When recurrence was measured at between 1 and 3 years, there was a benefit of thiazides over no intervention. This evidence was based on a population of people with mixed or unspecified urine metabolic abnormalities. In terms of stone interventions and stone episodes, one study showed a benefit of thiazides in terms of reducing the need for SWL and in terms of changes in stone size. The committee noted that the population included a mix of urine metabolic abnormalities, but the majority of participants had hypercalciuria. They also discussed that this study used thiazides as an adjunct to SWL, and suggested that using thiazides in this way reduces the need for repeat procedures. They considered that this is not usual practice, and agreed that further research to replicate these findings may be of benefit to inform future practice.

When compared to allopurinol, there was no clinical difference between interventions in terms of recurrence, however this outcome was measured at 2 months and therefore the committee again agreed that they could not draw conclusions from this evidence.

When compared to magnesium, there was a benefit of thiazides in terms of recurrence and recurrence rate, however the committee did note that this was based on a single study.

Across all comparisons there was no clinical difference or a harm of thiazides in terms of adverse events; however the committee noted that these events were generally not serious. From clinical experience they noted that thiazides tend to be well tolerated. The committee noted that thiazides are currently used in UK clinical practice for adults with recurrent calcium oxalate stones and hypercalciuria, but as an off-licence treatment.

All of the evidence was based on a population with either calcium oxalate stones, a mixture of calcium oxalate and calcium phosphate stones, or calcium stones with no further detail. The majority of calcium stones have a composition of predominantly calcium oxalate. The committee noted that pure calcium oxalate stones are rare, and therefore most stones labelled calcium or calcium oxalate will usually be a mixture of calcium oxalate and calcium phosphate. They noted that stones containing over 50% calcium phosphate are also a small group compared to calcium oxalate stones, and would generally not be treated with thiazides as calcium phosphate stones are associated with rare distal tubulopathies and certain infections. They agreed that the recommendation should apply to those with predominantly calcium oxalate stones.

Overall, the committee noted that there seems to be some benefit of thiazides, and that the majority of the evidence favouring thiazides was based on a population of purely or majority hypercalciuria. They noted that evidence from normocalciurics showed no benefit of thiazides, and there was conflicting evidence when the population had a mix of urine metabolic abnormalities. Therefore, they agreed thiazides should be considered for those with hypercalciuria. They discussed that thiazides work by inducing a natriuresis, and that if more sodium is ingested this will cancel out the effect of the thiazide. Therefore, they agreed that sodium intake should be restricted as a prerequisite to treatment with thiazides.

Magnesium supplementation in adults

The committee highlighted that magnesium supplementation has limited use within current UK clinical practice. They indicated that magnesium levels would typically be measured in cases of hypocalcemia, and that this is a small and targeted population. Very low quality evidence favoured magnesium 650mg supplementation for the prevention of recurrence in adults when compared with placebo. For magnesium 1300mg supplementation, the evidence suggested no clinical difference for recurrence rate while favouring the higher dose supplement over placebo and 650mg for recurrence; it was suggested that this inconsistency might relate to 'recurrence rate' referring to the number of stones while 'recurrence' referred to the number of participants with stones.

The committee discussed that over half of participants had no urine biochemical abnormality, yet there was a potential benefit in terms of recurrence, suggesting that magnesium may be beneficial regardless of urine biochemical abnormality. However, the committee was aware from clinical expertise and experience that magnesium may lead to adverse events relating to the bowels, and as there was no evidence for adverse events to inform this, did not feel that it could be recommended. Further, the evidence showing a potential benefit of magnesium was of very low quality and based on a single study. The committee agreed that recommending magnesium was not justified on the basis of the evidence, and on the consensus of the committee.

Allopurinol in adults

The committee discussed that allopurinol is not commonly used in UK clinical practice but agreed that evidence for this treatment should be considered. They noted that very low to low quality evidence in a population of predominantly calcium oxalate stones favoured allopurinol for outcomes related to the prevention of recurrence when compared with placebo, and moderate quality evidence showed no clinical difference. The committee discussed how this evidence did not seem to make clinical sense, as allopurinol is used to alter uric acid and may in some way modulate calcium, but the mechanism of effect on calcium stones was unclear to the committee. The committee considered this evidence and the absence of any replicated evidence since this was published over 30 years ago. There was no evidence for the major or minor adverse events outcomes, but the committee highlighted potentially serious side effects with using allopurinol, such as acute kidney injury and problems with the blood cell count.

Combined therapy (allopurinol and thiazides) in adults

Low quality evidence favoured combined therapy for the prevention of recurrence when compared with no intervention, while very low quality evidence favoured allopurinol alone when compared with combined therapy. Also, very low to low quality evidence showed no clinical difference for other recurrence outcomes when combined therapy was compared with allopurinol alone, thiazides alone and placebo. The committee noted that evidence of harms in terms of minor adverse events was of low quality and showed no clinical difference between combined therapy (allopurinol and thiazides) when compared with thiazides alone. There were no major adverse events reported.

The committee noted that combined therapy, consisting of allopurinol and thiazides, is not routinely used in UK clinical practice. They noted that this combination may be used if urine metabolic laboratory tests have been done. The results of each test are then treated for, individually. However, they noted that thiazides are usually used to treat calcium stones, whereas allopurinol is usually used to treat uric acid stones, therefore this combination may not make clinical sense. Overall, the committee considered the evidence and agreed that there seemed to be no additional benefit of combined therapy over either intervention alone, in overall biochemically unselected patients.

1.10.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

Unit costs were presented to the committee to illustrate the variation in costs of the interventions in the clinical review. These ranged from below £20 per year for Allopurinol for example, to over £100 per year for the more supplement based interventions.

These interventions are likely to have to be taken for the patient's lifetime. There is therefore a cost trade-off with regards to the cost of the interventions over the patient's lifetime, versus the costs saved from stone events avoided if the treatment is successful.

Some cost-offset examples were presented to the committee to aid their consideration of cost effectiveness in the absence of evidence;

If the average age of onset of stones is 45, and the individual is likely to live for another 40 years, then an estimate of the number of recurrences a patient might have over their remaining lifetime is 6 episodes (see section 1.6.1 for more detail on assumptions). If we apply the average rate ratio from all the interventions that reported rates in the clinical review (for adults) (0.7) this means there would be 1.8 stone episodes avoided with prevention of recurrence interventions. If these episodes would cost an average of £2,000 each to treat, and assuming that only 50% would require treatment, then that would be £1,800 of treatment costs avoided over the patient's lifetime. To make the preventative treatments cost neutral, over a 40 year period these interventions would have to cost less than £45 per year. It may be however that the number of recurrences is overestimated as some people may never develop another stone, and some are more likely to keep developing stones because of an underlying abnormality. Therefore, the cost of a preventative intervention would have to be even lower to offset fewer events avoided.

The clinical data for individual interventions (for adults) was also used to estimate some cost offsets. Using a cohort of 1000 people, and the same assumptions that intervention to remove a stone would cost £2,000 but only 50% of stones would need intervention, applying the costs of the interventions based on the unit costs presented; showed that interventions likely to be offset are potassium citrate, allopurinol, allopurinol plus thiazides, and thiazides. These informal calculations are highly dependent on the clinical data and the assumptions made and should be interpreted with caution.

The clinical data was sometimes difficult to interpret because some studies had populations that were in people with specific urine abnormalities (e.g. hypocitraturia), and some were in populations with mixed urine abnormalities (although still within predominantly one type of stone composition e.g. calcium oxalate stones). The committee opinion was that this showed there to be a benefit of prescribing to a mixed group of people who have had renal stones and not necessarily just those with certain urine metabolic abnormalities.

The potassium citrate data for adults showed a benefit to giving the intervention regardless of the presence of specific abnormalities. However an adverse event that might be a concern would be hyperkalemia. It was acknowledged that it would be a change in practice to recommend potassium citrate to all individuals who have ever had calcium stones, regardless of whether they had a metabolic abnormality.

It is also important to note that in order to identify the type of stone a stone analysis would be necessary, and there is a large variation in practice with regards to whether stone analysis takes place. Although, It is only possible to do a stone analysis if the stone is available for testing which would be in about 50% of patients – therefore this reduces the population eligible for stone analysis. It is important to consider the cost effectiveness of the pathway as a whole, because tests can be expensive and would only be cost effective if there is adequate benefit from the treatment that would be given to those identified from the test.

For example; potassium citrate could be given to those with a predominantly calcium oxalate stone, as that is what the evidence suggests (so based on stone composition regardless of urine metabolic abnormality presence). It costs around £25 to undertake a stone analysis, if 1000 people with renal stones had their stone analysed, then that would cost around £25,000. If the prevalence of a calcium oxalate stone was around 70%, then 700 people could benefit from potassium citrate. Giving potassium citrate for 1 year to 700 people would cost around £64,000, which leads to total costs of testing and treatment of around £89,000. To offset this cost, around 44 stones that would need treatment in those 700 people would need to be prevented (if treatment cost £2,000), to offset the cost of identifying those people who could benefit from the potassium citrate. This means avoiding around 6% of stones in a year in those people being treated. The effectiveness difference between the intervention and control arm for potassium citrate versus placebo or no treatment was higher than this 6%. As mentioned earlier these are informal calculations and need to be viewed with caution.

Other interventions also considered to be effective from the clinical review were thiazides. These are low cost interventions, but would require some monitoring if prescribed. Thiazides are used for hypertension, therefore some patients would already be prescribed thiazides, given the high prevalence of hypertension.

Given concerns around; the quality of the evidence, that evidence for most outcomes came from single studies, concerns around adverse events that were not captured in the clinical review, uncertainty around cost effectiveness, and acknowledgment that any strong recommendations would be a change in current practice – the committee decided to make consider recommendations for the interventions they felt were clinically effective from the clinical review. The populations the interventions were recommended in were limited to recurrent stone formers, and limited further by stone compositions or metabolic abnormalities the committee felt the clinical evidence was demonstrated in. The use of potassium citrate and thiazides for renal stones is already current practice in some areas, resource impact is therefore likely to be small.

In children, only non-randomised evidence was identified comparing potassium citrate to no intervention. Children are a much smaller population, and it is standard practice to undertake screening for metabolic abnormalities in children, as they tend to be seen in specialist centres. The committee felt the evidence demonstrated effectiveness in children with mixed urine metabolic abnormalities. The recommendation might result in a change in practice as currently potassium citrate would be given in children with calcium in their urine or dependent on stone composition. However as a consider recommendation was made, the impact on practice is dependent on uptake, and children are a small population.

As mentioned above when discussing stone analysis, there is an implied pre-requisite that in order to treat by a specific stone composition or abnormality, then tests have taken place to identify these factors. No evidence was identified on the cost effectiveness of metabolic tests, and also as mentioned; the cost effectiveness of a test is dependent on the downstream factors such as prevalence of conditions identified from the tests and effectiveness of subsequent management. Clinical questions often assess individual parts of a pathway, but these need to be taken together when assessing cost effectiveness because individual parts of a pathway have an impact on the rest of the pathway. It has been shown that prevention of recurrence can be effective, and these costs may be offset by stones avoided, but the cost effectiveness of the whole testing pathway has not been formally proven. Therefore the recommendations from this review are ‘consider’ recommendations, from the perspective that; should composition or metabolic abnormality information be available for a patient, then a clinician might want to consider the treatments recommended in this review.

1.10.3 Other factors the committee took into account

The committee agreed that all pharmacological management approaches should be considered alongside dietary advice.

References

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Appendices

Appendix A: Review protocols

Table 21: Review protocol: What is the most clinically-effective and cost-effective non-surgical management for preventing the recurrence of future renal and ureteric stones?

Field	Content
Review question	What is the most clinically-effective and cost-effective non-surgical management for preventing the recurrence of future renal and ureteric stones?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To find the most effective management preventing the recurrence of future renal and ureteric stones for people who have had renal or ureteric stones
Eligibility criteria – population / disease / condition / issue / domain	People (adults, children and young people) with symptomatic and asymptomatic renal or ureteric stones
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Potassium citrate supplements • Sodium citrate supplements • Allopurinol • Thiazides • Oral bicarbonate • Chelating agents: D-penicillamine , Tiopronin (or Thiola or mercaptopropionylglycine) (for cystinuria) • Captopril (for cystinuria) • Ca supplements, pyridoxine, • Magnesium supplement • Methionine • Prophylactic antibiotics
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Each other • No treatment/ Placebo /Fluid only
Outcomes and prioritisation	Critical outcomes at longest time point: • Recurrence rate • Stone episodes/stone interventions • Use of healthcare services • Quality of life • Major Adverse events (if admission to hospital • Minor adverse events (no admission to hospital) • Important outcomes at longest time point: • Kidney function • Pain intensity (visual analogue scale)
Eligibility criteria – study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for observational studies for children
Other inclusion exclusion criteria	Bladder stones Open surgery for renal (kidney and ureteric) stones

	Laparoscopic nephrolithotomy and pyelolithotomy Non-English language studies

Proposed sensitivity / subgroup analysis, or meta-regression	Strata:
	• Population
	  ○ Adults (≥16 years)
	  ○ Children and young people (<16 years)
	• Stone composition:
	  ○ cystine
	  ○ urate
	  ○ calcium oxalate
	  ○ calcium phosphate/brushite
	  ○ struvite
	• Abnormal biochemistry :
	  ○ hypercalciuria
	  ○ hypocitraturia
	  ○ hyperuricosuria/ hyperuricaemia
	  ○ hyperoxaluria
	  ○ hypomagnesaemia
	Subgroups:
	• Pregnant women
	• People who are HIV positive and having treatment with protease inhibitors

Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Endnote for bibliography, citations, sifting and reference management • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10033
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B

Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Andrew Dickinson in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1 **Table 22: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis).

	• Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G *[in the Full guideline]*.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the 2014 NICE guidelines manual.[81] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable). • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations.

	Year of analysis: • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 23: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 24 October 2017	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 24 October 2017	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 10 of 12 CENTRAL to 2017 Issue 9 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.

5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	exp Citrates/
28.	((potassium or sodium or K or Na) adj3 citrate*).ti,ab.
29.	or/27-28
30.	Allopurinol/
31.	(allopurinol or Uricto or Zyloric).ti,ab.
32.	or/30-31
33.	exp Thiazides/
34.	exp Bendroflumethiazide/ or exp Hydrochlorothiazide/ or exp Chlorothiazide/ or exp Cyclopenthiazide/ or exp Hydroflumethiazide/ or exp Methyclothiazide/ or exp Polythiazide/
35.	(thiazide* or Bendroflumethiazide or Hydrochlorothiazide or Chlorothiazide or Cyclopenthiazide or Hydroflumethiazide or Methyclothiazide or Polythiazide).ti,ab.
36.	or/33-35
37.	exp Sodium Bicarbonate/
38.	bicarb*.ti,ab.
39.	((baking or bicarbonate) adj5 soda).ti,ab.
40.	((Na or sodium acid or sodium hydrogen) adj5 carbonate).ti,ab.
41.	NaHCO3.ti,ab.
42.	or/37-41
43.	Cystinuria/
44.	((high* or raise* or elevate*) adj3 cystine).ti,ab.
45.	exp Chelating Agents/
46.	Chelation Therapy/

47.	(chelation adj3 (agent* or therap*)).ti,ab.
48.	(D-Penicillamine or Penicillamine or Tiopronin or Thiola or mercaptopropionylglycine).ti,ab.
49.	exp Angiotensin-Converting Enzyme Inhibitors/
50.	(angiotensin-converting adj3 inhibitor*).ti,ab.
51.	(Captopril or Capoten or Ecopace or Noyada).ti,ab.
52.	or/43-51
53.	Calcium/
54.	Calcium, Dietary/
55.	((calcium or Ca) adj3 (oral or supplement*)).ti,ab.
56.	or/53-55
57.	Pyridoxine/
58.	(pyridoxine or pyridoxal phosphate or vitamin B6 or vit B6 or B 6 or Pyrid).ti,ab.
59.	or/57-58
60.	exp Vitamin D/
61.	((vitamin D or vit D) adj3 (oral or supplement*)).ti,ab.
62.	or/60-61
63.	Magnesium/
64.	((magnesium or Mg) adj3 (oral or supplement*)).ti,ab.
65.	or/63-64
66.	exp Methionine/
67.	methionine.ti,ab.
68.	or/66-67
69.	exp Anti-bacterial Agents/
70.	Antibiotic Prophylaxis/
71.	antibiotic*.ti,ab.
72.	or/69-71
73.	29 or 32 or 36 or 42 or 52 or 56 or 59 or 62 or 65 or 68 or 72
74.	26 and 73
75.	randomized controlled trial.pt.
76.	controlled clinical trial.pt.
77.	randomi#ed.ti,ab.
78.	placebo.ab.
79.	randomly.ti,ab.
80.	Clinical Trials as topic.sh.
81.	trial.ti.
82.	or/75-81
83.	Meta-Analysis/
84.	exp Meta-Analysis as Topic/
85.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
86.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
87.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
88.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
89.	(search* adj4 literature).ab.

90.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
91.	cochrane.jw.
92.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
93.	or/83-92
94.	Epidemiologic studies/
95.	Observational study/
96.	exp Cohort studies/
97.	(cohort adj (study or studies or analys* or data)).ti,ab.
98.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
99.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
100.	Controlled Before-After Studies/
101.	Historically Controlled Study/
102.	Interrupted Time Series Analysis/
103.	(before adj2 after adj2 (study or studies or data)).ti,ab.
104.	or/94-103
105.	exp case control study/
106.	case control*.ti,ab.
107.	or/105-106
108.	104 or 107
109.	Cross-sectional studies/
110.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
111.	or/109-110
112.	104 or 111
113.	104 or 107 or 111
114.	74 and 82
115.	74 and 93
116.	114 or 115
117.	74 and 113
118.	117 not 116

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.

12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	exp citric acid/
26.	citric acid.ti,ab.
27.	((potassium or sodium or K or Na) adj3 citrate*).ti,ab.
28.	or/25-27
29.	allopurinol sodium/
30.	(allopurinol or Uricto or Zyloric).ti,ab.
31.	or/29-30
32.	exp thiazide diuretic agent/
33.	bendroflumethiazide/ or hydrochlorothiazide/ or chlorothiazide/ or cyclopenthiazide/ or hydroflumethiazide/ or methyclothiazide/ or polythiazide/
34.	(thiazide* or Bendroflumethiazide or Hydrochlorothiazide or Chlorothiazide or Cyclopenthiazide or Hydroflumethiazide or Methyclothiazide or Polythiazide).ti,ab.
35.	or/32-34
36.	exp bicarbonate sodium/
37.	bicarb*.ti,ab.
38.	((baking or bicarbonate) adj5 soda).ti,ab.
39.	((Na or sodium acid or sodium hydrogen) adj5 carbonate).ti,ab.
40.	NaHCO3.ti,ab.
41.	or/36-40
42.	cystinuria/
43.	((high* or raise* or elevate*) adj3 cystine).ti,ab.
44.	exp chelating agent/
45.	chelation therapy/
46.	(chelation adj3 (agent* or therap*)).ti,ab.
47.	(D-Penicillamine or Penicillamine or Tiopronin or Thiola or mercaptopropionylglycine).ti,ab.
48.	exp dipeptidyl carboxypeptidase inhibitor/
49.	(angiotensin-converting adj3 inhibitor*).ti,ab.
50.	(Captopril or Capoten or Ecopace or Noyada).ti,ab.
51.	or/42-50
52.	calcium/
53.	calcium intake/
54.	((calcium or Ca) adj3 (oral or supplement*)).ti,ab.

55.	or/52-54
56.	pyridoxine/
57.	(pyridoxine or pyridoxal phosphate or vitamin B6 or vit B6 or B 6 or Pyrid).ti,ab.
58.	or/56-57
59.	exp vitamin D/
60.	((vitamin D or vit D) adj3 (oral or supplement*)).ti,ab.
61.	or/59-60
62.	magnesium/
63.	((magnesium or Mg) adj3 (oral or supplement*)).ti,ab.
64.	or/62-63
65.	exp methionine/
66.	methionine.ti,ab.
67.	or/65-66
68.	exp antibiotic agent/
69.	antibiotic prophylaxis/
70.	antibiotic*.ti,ab.
71.	or/68-70
72.	28 or 31 or 35 or 41 or 51 or 55 or 58 or 61 or 64 or 67 or 71
73.	24 and 72
74.	random*.ti,ab.
75.	factorial*.ti,ab.
76.	(crossover* or cross over*).ti,ab.
77.	((doubl* or singl*) adj blind*).ti,ab.
78.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
79.	crossover procedure/
80.	single blind procedure/
81.	randomized controlled trial/
82.	double blind procedure/
83.	or/74-82
84.	systematic review/
85.	meta-analysis/
86.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
87.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
88.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
89.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
90.	(search* adj4 literature).ab.
91.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
92.	cochrane.jw.
93.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
94.	or/84-93
95.	Clinical study/
96.	Observational study/
97.	family study/

98.	longitudinal study/
99.	retrospective study/
100.	prospective study/
101.	cohort analysis/
102.	follow-up/
103.	cohort*.ti,ab.
104.	102 and 103
105.	(cohort adj (study or studies or analys* or data)).ti,ab.
106.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
107.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
108.	(before adj2 after adj2 (study or studies or data)).ti,ab.
109.	or/95-101,104-108
110.	exp case control study/
111.	case control*.ti,ab.
112.	or/110-111
113.	109 or 112
114.	cross-sectional study/
115.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
116.	or/114-115
117.	109 or 116
118.	109 or 112 or 116
119.	73 and 83
120.	73 and 94
121.	119 or 120
122.	73 and 118
123.	122 not 121

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Urolithiasis] explode all trees
#2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s):ti,ab
#3.	((renal or kidney* or urinary or ureter* or urethra*) near/3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)):ti,ab
#4.	stone disease*:ti,ab
#5.	((calculi or calculus or calcium oxalate or cystine) near/3 (crystal* or stone* or lithiasis)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Citrates] explode all trees
#8.	((potassium or sodium or K or Na) near/3 citrate*):ti,ab
#9.	(or #7-#8)
#10.	MeSH descriptor: [Allopurinol] this term only
#11.	(allopurinol or Uricto or Zyloric):ti,ab
#12.	(or #10-#11)
#13.	MeSH descriptor: [Thiazides] explode all trees
#14.	MeSH descriptor: [Bendroflumethiazide] explode all trees
#15.	MeSH descriptor: [Hydrochlorothiazide] explode all trees

#16.	MeSH descriptor: [Chlorothiazide] explode all trees
#17.	MeSH descriptor: [Cyclopenthiazide] explode all trees
#18.	MeSH descriptor: [Hydroflumethiazide] explode all trees
#19.	MeSH descriptor: [Methyclothiazide] explode all trees
#20.	MeSH descriptor: [Polythiazide] explode all trees
#21.	(thiazide* or Bendroflumethiazide or Hydrochlorothiazide or Chlorothiazide or Cyclopenthiazide or Hydroflumethiazide or Methyclothiazide or Polythiazide):ti,ab
#22.	(or #13-#21)
#23.	MeSH descriptor: [Sodium Bicarbonate] explode all trees
#24.	bicarb*:ti,ab
#25.	((baking or bicarbonate) near/5 soda):ti,ab
#26.	((Na or sodium acid or sodium hydrogen) near/5 carbonate):ti,ab
#27.	NaHCO3:ti,ab
#28.	(or #23-#27)
#29.	MeSH descriptor: [Cystinuria] this term only
#30.	((high* or raise* or elevate*) near/3 cystine):ti,ab
#31.	MeSH descriptor: [Chelating Agents] explode all trees
#32.	MeSH descriptor: [Chelation Therapy] this term only
#33.	(chelation near/3 (agent* or therap*)):ti,ab
#34.	(D-Penicillamine or Penicillamine or Tiopronin or Thiola or mercaptopropionylglycine):ti,ab
#35.	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#36.	(angiotensin-converting near/3 inhibitor*):ti,ab
#37.	(Captopril or Capoten or Ecopace or Noyada):ti,ab
#38.	(or #29-#37)
#39.	MeSH descriptor: [Calcium] this term only
#40.	MeSH descriptor: [Calcium, Dietary] this term only
#41.	((calcium or Ca) near/3 (oral or supplement*)):ti,ab
#42.	(or #39-#41)
#43.	MeSH descriptor: [Pyridoxine] this term only
#44.	(pyridoxine or pyridoxal phosphate or vitamin B6 or vit B6 or B 6 or Pyrid):ti,ab
#45.	(or #43-#44)
#46.	MeSH descriptor: [Vitamin D] explode all trees
#47.	((vitamin D or vit D) near/3 (oral or supplement*)):ti,ab
#48.	(or #46-#47)
#49.	MeSH descriptor: [Magnesium] this term only
#50.	((magnesium or Mg) near/3 (oral or supplement*)):ti,ab
#51.	(or #49-#50)
#52.	MeSH descriptor: [Methionine] explode all trees
#53.	methionine:ti,ab
#54.	(or #52-#53)
#55.	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#56.	MeSH descriptor: [Antibiotic Prophylaxis] this term only
#57.	antibiotic*:ti,ab
#58.	(or #55-#57)
#59.	(or #9, #12, #22, #28, #38, #42, #45, #48, #51, #54, #58)

#60.	#6 and #59

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to renal and ureteric stones population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 24: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 9 March 2018	Exclusions Health economics studies
Embase	2014 – 9 March 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 9 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.

24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	exp urolithiasis/
2.	(nephrolitiasis or nephrolith or nephroliths or urolithias?s or ureterolithias?s).ti,ab.
3.	((renal or kidney* or urinary or ureter* or urethra*) adj3 (stone* or calculi or calculus or calculosis or lithiasis or c?olic*)).ti,ab.
4.	stone disease*.ti,ab.
5.	((calculi or calculus or calcium oxalate or cystine) adj3 (crystal* or stone* or lithiasis)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/

19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

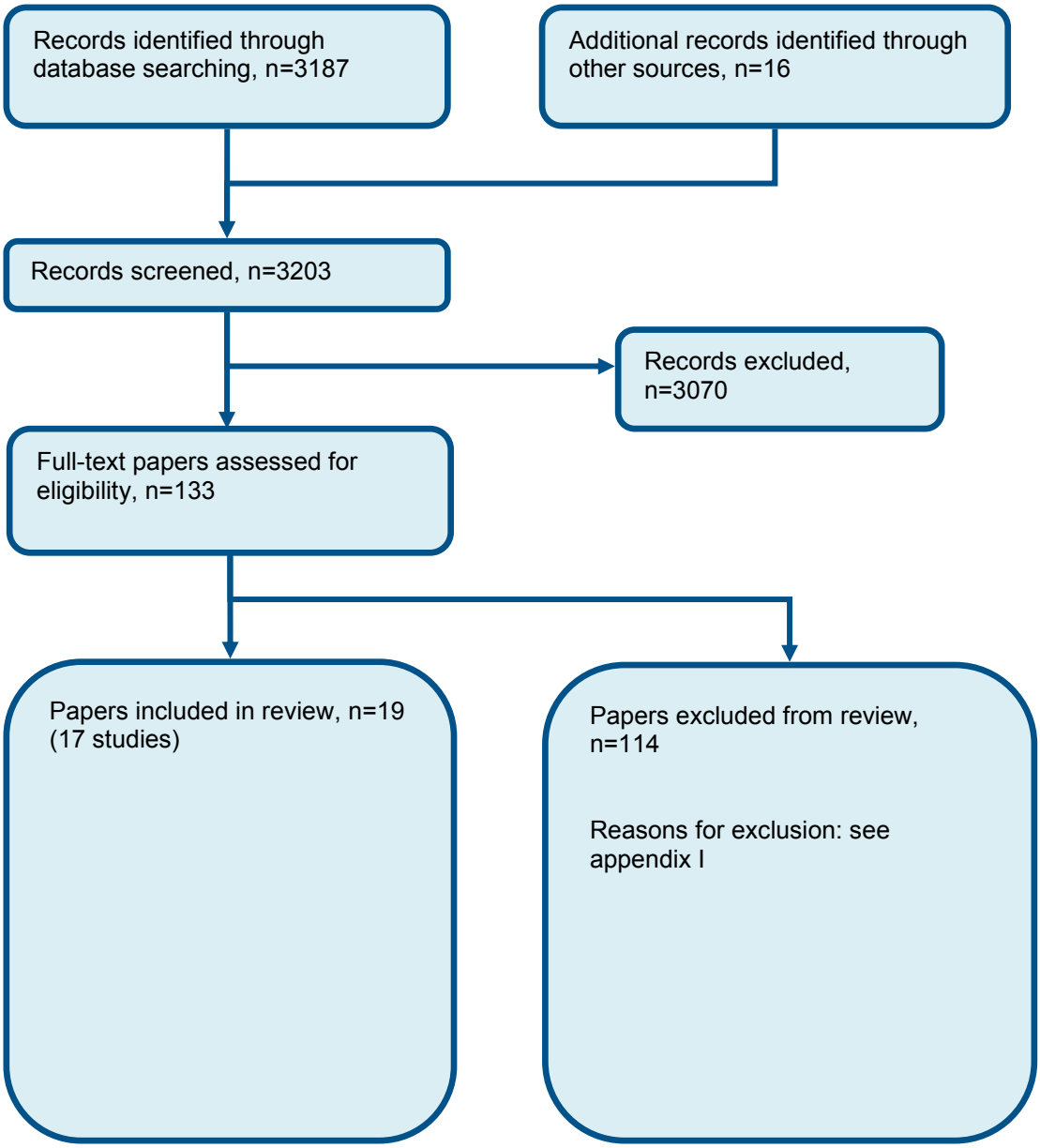
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR urolithiasis EXPLODE ALL TREES
#2.	(((nephrolitiasis or nephrolith or urolithiasis)))
#3.	((((renal or kidney or urinary or ureteric or ureteral or ureter or urethra*) adj2 (stone* or calculi or calculus or calculosis or lithiasis or colic))))
#4.	((stone disease*))
#5.	((((calculi or calculus) adj2 (stone* or lithiasis))))
#6.	(#1 OR #2 OR #3 OR #4 OR #5)

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of prevention of recurrence



Appendix D: Clinical evidence tables

Study	Ahlstrand 1996{#1221}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Unclear (57 reported in table, 55 reported in text))
Countries and setting	Conducted in Sweden; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 'The clinical outcome was analyzed 5 years after the start of treatment'
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not reported
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: hydrochlorothiazide: mean 31 yrs (no SD); hydrochlorothiazide + magnesium supplement: mean 36 yrs (no SD); no intervention: mean 38 yrs (no SD). Gender (M:F): 47/10 (hydrochlorothiazide:16/1; hydrochlorothiazide + magnesium supplement: 13/3; no intervention: 18/6). Ethnicity: Not reported
Further population details	
Extra comments	'Patients with recurrent calcium stone formation and with hypercalciuria or hypomagnesiuria'
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Thiazides. 'Hydrochlorothiazide 25 mg x2'. Frequency of dose not reported.. Duration 5 years. Concurrent medication/care: Advice to increase fluid intake and to decrease oxalate intake. Indirectness: No indirectness (n=16) Intervention 2: Magnesium supplement . 'Hydrochlorothiazide 25 mg x 2 (frequency of dose not reported) + magnesium-aspartate-hydrochloride 1.23 g x 2 (=10 mmol Mg2+ /d)'. Duration 5 years. Concurrent medication/care: Advice to increase fluid intake and to decrease oxalate intake. Indirectness: No indirectness (n=24) Intervention 3: Placebo/No intervention/Fluid only - No intervention. '0'. Duration 5 years. Concurrent

Study	Ahlstrand 1996{#1221}
	medication/care: Advice to increase fluid intake and to decrease oxalate intake. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus MAGNESIUM SUPPLEMENT

Protocol outcome 1: Minor adverse events (no admission to hospital) at Define
- Actual outcome for Adults (≥18 years): Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction) at 5 years; Group 1: 5/17, Group 2: 6/16; Comments: Number analysed recorded from table
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline comparability between groups was not reported but the 'no intervention' group had a higher mean age and greater proportion of women than the intervention groups. Stratification was made according to the rate of stone formation; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Recurrence at Define
- Actual outcome for Adults (≥18 years): Recurrence (number of people free from recurrence) at 5 years; Group 1: 8/17, Group 2: 11/16
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline comparability between groups was not reported but the 'no intervention' group had a higher mean age and greater proportion of women than the intervention groups. Stratification was made according to the rate of stone formation; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus NO INTERVENTION

Protocol outcome 1: Minor adverse events (no admission to hospital) at Define
- Actual outcome for Adults (≥18 years): Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction) at 5 years; Group 1: 5/17, Group 2: 0/24; Comments: Number analysed recorded from table
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline comparability between groups was not reported but the 'no intervention' group had a higher mean age and greater proportion of women than the intervention groups. Stratification was made according to the rate of stone formation; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Recurrence at Define
- Actual outcome for Adults (≥18 years): Recurrence (number of people free from recurrence) at 5 years; Group 1: 8/17, Group 2: 3/24
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement -

Study	Ahlstrand 1996{#1221}
High; Indirectness of outcome: No indirectness ; Baseline details: Baseline comparability between groups was not reported but the 'no intervention' group had a higher mean age and greater proportion of women than the intervention groups. Stratification was made according to the rate of stone formation; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MAGNESIUM SUPPLEMENT versus NO INTERVENTION Protocol outcome 1: Minor adverse events at Define - Actual outcome for Adults (≥18 years): Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction) at 5 years; Group 1: 6/16, Group 2: 0/24; Comments: Number analysed recorded from table Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline comparability between groups was not reported but the 'no intervention' group had a higher mean age and greater proportion of women than the intervention groups. Stratification was made according to the rate of stone formation; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Recurrence at Define - Actual outcome for Adults (≥18 years): Recurrence (number of people free from recurrence) at 5 years; Group 1: 11/16, Group 2: 3/24 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline comparability between groups was not reported but the 'no intervention' group had a higher mean age and greater proportion of women than the intervention groups. Stratification was made according to the rate of stone formation; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Ala-opas 1987[7]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=73)
Countries and setting	Conducted in Finland; Setting: Not reported
Line of therapy	Unclear

Study	Ala-opas 1987[7]
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Patients with recurrent urinary stones were included in the study. Hypercalciuria was diagnosed as urinary calcium in two consecutive samples exceeding 7.5 mmol/l/day in men and 6.25 mmol/l/day in women
Stratum	Adults (≥18 years): 32 patients (44%) had absorptive hypercalciuria and 41 patients had normal urinary calcium excretion
Subgroup analysis within study	Not stratified but pre-specified: absorptive hypercalciuria and normocalciuria
Inclusion criteria	Recurrent urinary calcium stones
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 48 (28-70 years). Gender (M:F): 60/13. Ethnicity: Not reported
Further population details	
Extra comments	Included participants had absorptive hypercalciuria and normocalciuria
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Thiazides. Hydrochlorothiazide (50 mg twice daily) . Duration 5 months . Concurrent medication/care: Patients were on a low-calcium and low-oxalate diet and ate unprocessed bran (40g/day) for 24 months. A high fluid intake (approximately 2.5 litres daily) was recommended for all patients . Indirectness: No indirectness (n=45) Intervention 2: Placebo/No intervention/Fluid only - No intervention. No intervention. Duration 5 months . Concurrent medication/care: Patients were on a low-calcium and low-oxalate diet and ate unprocessed bran (40g/day) for 24 months. A high fluid intake (approximately 2.5 litres daily) was recommended for all patients . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus NO INTERVENTION

Protocol outcome 1: Recurrence at Define
- Actual outcome for Adults (≥18 years): Recurrence (number of patients with recurrences): defined as the number of people with recurrences (based on passage, surgical removal of stone, or roentgenographic visualisation of a stone-like opacity not present on a previous X-ray) at 5 months; Group 1: 6/28, Group 2: 12/45
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Ala-opas 1987[7]
Subgroups - High; Indirectness of outcome: No indirectness, Comments: Not applicable; Baseline details: Pre-treatment average frequency of stone formation adjusted to treatment period of 2 years: hypercalciuric, no intervention: 0.784 (0.943); hypercalciuric, thiazide: 0.516 (0.258); normocalciuric, no intervention: 0.466 (0.187); normocalciuric, thiazide: 0.587 (0.338) ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥18 years): Recurrence in hypercalciuric subgroup (number of patients with recurrences): defined as the number of people with recurrences (based on passage, surgical removal of stone, or roentgenographic visualisation of a stone-like opacity not present on a previous X-ray) at 5 months; Group 1: 2/14, Group 2: 6/18 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Subgroups - High; Indirectness of outcome: No indirectness, Comments: Not applicable; Baseline details: Pre-treatment average frequency of stone formation adjusted to treatment period of 2 years: hypercalciuric, no intervention: 0.784 (0.943); hypercalciuric, thiazide: 0.516 (0.258); normocalciuric, no intervention: 0.466 (0.187); normocalciuric, thiazide: 0.587 (0.338) ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥18 years): Recurrence in normocalciuric subgroup (number of patients with recurrences): defined as the number of people with recurrences (based on passage, surgical removal of stone, or roentgenographic visualisation of a stone-like opacity not present on a previous X-ray) at 5 months; Group 1: 4/14, Group 2: 6/27 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Subgroups - High; Indirectness of outcome: No indirectness, Comments: Not applicable; Baseline details: Pre-treatment average frequency of stone formation adjusted to treatment period of 2 years: hypercalciuric, no intervention: 0.784 (0.943); hypercalciuric, thiazide: 0.516 (0.258); normocalciuric, no intervention: 0.466 (0.187); normocalciuric, thiazide: 0.587 (0.338) ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Use of healthcare services at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Recurrence rate at Define

Study	Arrabal-martin 2006[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Spain; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients diagnosed with calcium lithiasis. During the study the calculus was analysed using petrographic microscopy and infrared spectography. The size and evolution of

Study	Arrabal-martin 2006[13]
	residual lithiasis were measured with a graduated template on a simple radiograph of the urinary tract by a radiologist and urologist. The absence of residual lithiasis was confirmed with renal ultrasonography after 36 months
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Both sexes, aged 18 to 65 years; the presence of calcium lithiasis treated with SWL; the absence of renal malformation or endocrine disease; informed consent
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): Not reported (male and females included). Ethnicity: Not reported
Further population details	
Extra comments	Patients diagnosed with calcium lithiasis and treated with shock waves, who presented with residual lithiasis 3 months after SWL (one to three fragments less than 4mm).
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Thiazides. 50 mg/24hr hydrochlorothiazide. Duration 36 months. Concurrent medication/care: SWL three months prior. Indirectness: No indirectness (n=50) Intervention 2: Placebo/No intervention/Fluid only - Placebo. Not reported. Duration 36 months. Concurrent medication/care: As for the thiazide group. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus PLACEBO

Protocol outcome 1: Minor adverse events (no admission to hospital) at Define
- Actual outcome for Adults (≥18 years): Intracellular acidosis and hypocitraturia induced by hypopotassemia secondary to administration of thiazides at 36 months; Group 1: 5/50, Group 2: 0/50
Risk of bias: All domain - Low, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: No age or gender reported. SWL dose not reported ; Blinding details: SWL was performed using similar indication criteria for the two groups (a significant increase in the residual lithiasis size or symptoms not controlled with medical treatment); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Stone episodes/stone interventions at Define

Study	Arrabal-martin 2006[13]
- Actual outcome for Adults (≥18 years): SWL at 36 months; Group 1: 9/50, Group 2: 21/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness, Comments: Calcium lithiasis only; Baseline details: No age or gender reported. SWL dose not reported ; Blinding details: SWL was performed using similar indication criteria for the two groups (a significant increase in the residual lithiasis size or symptoms not controlled with medical treatment); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥18 years): Residual fragments or growth at 36 months; Group 1: 20/50, Group 2: 38/50 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: No age or gender reported. SWL dose not reported ; Blinding details: SWL was performed using similar indication criteria for the two groups (a significant increase in the residual lithiasis size or symptoms not controlled with medical treatment); Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Use of healthcare services at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Recurrence rate at Define

Study	Baggio 1983[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in Italy; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with recurrent calcium oxalate stone disease who had passed at least one stone in the two months preceding the study. All patients had sterile urines, normal serum PTH, calcium, phosphate, alkalin phosphates, uric acid and potassium levels; urinary excretion of cAMP was also in the normal range
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported

Study	Baggio 1983[16]
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): 50/46. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Thiazides. Hydrochlorothiazide 50mg and amiloride 5mg . Duration 2 months. Concurrent medication/care: Patients were allowed a free diet and water as desired except for 4 days before the first and second controls, when they were placed on a standard diet containing 800mg calcium, 75mg oxalate, 85mg purines and 900mg phosphate (n=24) Intervention 2: Allopurinol. Allopurinol 200mg/day. Duration 2 months. Concurrent medication/care: Patients were allowed a free diet and water as desired except for 4 days before the first and second controls, when they were placed on a standard diet containing 800mg calcium, 75mg oxalate, 85mg purines and 900mg phosphate (n=22) Intervention 3: Allopurinol. 200mg allopurinol + hydrochlorothiazide 50mg + 5mg amiloride daily. Duration 2 months. Concurrent medication/care: Patients were allowed a free diet and water as desired except for 4 days before the first and second controls, when they were placed on a standard diet containing 800mg calcium, 75mg oxalate, 85mg purines and 900mg phosphate. Indirectness: No indirectness (n=28) Intervention 4: Placebo/No intervention/Fluid only - Placebo. placebo, no further information . Duration 2 months. Concurrent medication/care: Patients were allowed a free diet and water as desired except for 4 days before the first and second controls, when they were placed on a standard diet containing 800mg calcium, 75mg oxalate, 85mg purines and 900mg phosphate. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus ALLOPURINOL

Protocol outcome 1: Recurrence at Define
- Actual outcome for Adults (≥18 years): Stone recurrence at 2 months; Group 1: 0/22, Group 2: 0/24
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus ALLOPURINOL + THIAZIDE

Protocol outcome 1: Recurrence at Define

Study	Baggio 1983[16]
- Actual outcome for Adults (≥18 years): Stone recurrence at 2 months; Group 1: 0/22, Group 2: 0/22 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus PLACEBO Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Stone recurrence at 2 months; Group 1: 0/22, Group 2: 0/28 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus ALLOPURINOL + THIAZIDE Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Stone recurrence at 2 months; Group 1: 0/24, Group 2: 0/22 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus PLACEBO Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Stone recurrence at 2 months; Group 1: 0/24, Group 2: 0/28 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL + THIAZIDE versus PLACEBO Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Stone recurrence at 2 months; Group 1: 0/22, Group 2: 0/28 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Stone episodes/stone interventions at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Barcelo 1993[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=57)
Countries and setting	Conducted in Spain; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with documented active calcium nephrolithiasis concomitant with an isolated hypocitraturic abnormality (idiopathic hypocitraturia). Patients had moderately sever active lithiasis (2 or more stones formed during the previous 2 years composed of calcium oxalate or a mixture of calcium oxalate and calcium phosphate) and low (less than 2 mmol a day) or normal (less than 3.4 mmol a day) urinary citrate
Exclusion criteria	Participants did not suffer from other metabolic abnormalities such as hypercalciuria, hyperuricosuria, or hyperoxaluria as a cause of the nephrolithiasis, and they did not have diabetes mellitus, renal failure (creatinine clearance less than 70 ml per minute), hyperkalemia, active urinary tract infection or gastrointestinal diseases. No patients were pregnant or lactating
Recruitment/selection of patients	Patients who underwent outpatient evaluation to diagnose the metabolic cause of nephrolithiasis
Age, gender and ethnicity	Age - Mean (range): Citrate group 44 (29-61); placebo group 47 (27-64). Gender (M:F): 17/21. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Citrate supplements - Potassium citrate. 20 mEq (4 tablets), 3 times a day, shortly after meals. Duration 36 months. Concurrent medication/care: Both groups were advised on increased ingestion of fluids (2-3l a day) and reduced sodium intake. Indirectness: No indirectness (n=29) Intervention 2: Placebo/No intervention/Fluid only - Placebo. Placebo tablets of identical appearance at the same dosage and schedule . Duration 36 months. Concurrent medication/care: Both groups were advised on increased ingestion of fluids (2-3l a day) and reduced sodium intake. Indirectness: No indirectness

Study	Barcelo 1993[17]
Funding	Equipment / drugs provided by industry (Ferrer Pharma International, S.A. Barcelona, Spain, supplied the potassium citrate and placebo)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POTASSIUM CITRATE versus PLACEBO Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Number remaining stone free at 36 months; Group 1: 13/18, Group 2: 4/20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 9 - Actual outcome for Adults (≥18 years): New stone formation at 36 months; Group 1: 5/18, Group 2: 14/20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 9 - Actual outcome for Adults (≥18 years): Recurrence rate at 36 months; Group 1: mean 0.1 per patient per year during 3 years (SD 0.2); n=18, Group 2: mean 1.1 per patient per year during 3 years (SD 0.3); n=20; Comments: Baseline - potassium group 1.2 (0.6); placebo group 1.1 (0.4) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 9 Protocol outcome 2: Minor adverse events (no admission to hospital) at Define - Actual outcome for Adults (≥18 years): Unspecified (causing withdrawal from study) at 36 months; Group 1: 2/18, Group 2: 1/20 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 9 Protocol outcome 3: Stone episodes/stone interventions at Define - Actual outcome for Adults (≥18 years): Procedures to remove stones at 36 months; Group 1: 1/18, Group 2: 12/20; Comments: Potassium group ESWL; control group 10 ESWL, 1 basket, 1 open Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 9	
Protocol outcomes not reported by the study	Quality of life at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Borghi 1993[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)

Study	Borghi 1993[25]
Countries and setting	Conducted in Italy; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All participants had formed at least one stone in the previous three years, but before treatment, they were calculi-free (intravenous pyelography and renal echography)
Stratum	Adults (≥18 years): Stone composition: pure calcium oxalate or with less than 20% calcium phosphate; biochemical abnormality: hypercalciuria (Ca urine >300 mg/24h in men and >250mg/24/h in women or Ca urine >4mg/kg body weight or Ca/creatinine >0.20mg/dl in both sexes)
Subgroup analysis within study	Not applicable:
Inclusion criteria	"Idiopathic" recurrent stone formers (pure calcium oxalate or with less than 20% of calcium phosphate) characterised by hypercalciuria on their usual diet (Ca urine >300 mg/24h in men and >250mg/24/h in women or Ca urine >4mg/kg body weight or Ca/creatinine >0.20mg/dl in both sexes); all had formed at least one stone in the previous three years, but before treatment, they were calculi-free
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): thiazide group: 46.5 (11.4 years); thiazide + allopurinol group: 46.2 (11.6 years); no intervention group: 42.8(11.3 years). Gender (M:F): 59/16. Ethnicity: Not reported
Further population details	
Extra comments	Twenty participants were also affected by moderate untreated essential hypertension (systolic from 160 to 180mm Hg, diastolic from 95 to 110 mm Hg); no other disease was present in the group
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Thiazides. Indapamide 2.5mg/day. Duration 36 months. Concurrent medication/care: Diet and fluid treatment: the diet was carefully discussed with each patient to avoid a high salt intake as well as high and/or regular ingestion of foods containing too much calcium, oxalate and purines; investigators calculated that the mean daily intake should have been 120-140mEq of sodium, 400-600mg of calcium, 40-60mg of oxalate, and 200-260mg of purine. High fluid intake was recommended, using water with a very low mineral content (calcium 2.4mg/litre, sodium 9.0mg/litre). Six participants were hypertensive. Indirectness: No indirectness (n=25) Intervention 2: Allopurinol. Combined allopurinol (300mg/day) and indapamide (2.5mg/day). Duration 36 months. Concurrent medication/care: Same as for the indapamide-treated group but seven participants were hypertensive. Indirectness: No indirectness

Study	Borghi 1993[25]
	(n=25) Intervention 3: Placebo/No intervention/Fluid only - No intervention. No intervention. Duration 36 months. Concurrent medication/care: Same as for the indapamide-treated group except there were seven hypertensive participants. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus NO INTERVENTION

Protocol outcome 1: Recurrence at Define
- Actual outcome for Adults (≥18 years): Recurrence (number of stone-free participants) at 36 months; Group 1: 16/19, Group 2: 12/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: 6, Reason: Four dropouts did not feel it was worth returning because they felt in good health. Two patients did not conclude the study because of side effects (clinical symptoms of hypotension and silent severe hypokalaemia after 6 months of therapy); Group 2 Number missing: 4, Reason: The dropouts did not feel it was worth returning because they felt in good health
- Actual outcome for Adults (≥18 years): Recurrence rate (not defined) at 36 months; Rate ratio calculated from indapamide group stone rate of 1.41 (1.76) and no intervention group stone rate of 0.79 (0.48);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: 6, Reason: Four dropouts did not feel it was worth returning because they felt in good health. Two patients did not conclude the study because of side effects (clinical symptoms of hypotension and silent severe hypokalaemia after 6 months of therapy); Group 2 Number missing: 4, Reason: The dropouts did not feel it was worth returning because they felt in good health

Protocol outcome 2: Minor adverse events (no admission to hospital) at Define
- Actual outcome for Adults (≥18 years): Minor adverse events (study discontinuation due to clinical hypotension (dizziness and hypotension)) at 36 months; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults (≥18 years): Minor adverse events (study discontinuation due to silent severe hypokalaemia) at 36 months; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic

Study	Borghi 1993[25]
and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Kidney function at Define - Actual outcome for Adults (≥18 years): Kidney function (creatinine clearance (ml/min)) at 36 months; Group 1: mean 114 (SD 22); n=19, Group 2: mean 120 (SD 24); n=21 Risk of bias: All domain - ; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus THIAZIDES Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Recurrence rate (not defined) at 36 months; Rate ratio calculated from combined therapy group stone rate of 1.20 (1.43) and indapamide group stone rate of 1.41 (1.76); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: 1, Reason: The dropout did not feel it was worth returning because they felt in good health; Group 2 Number missing: 6, Reason: Four dropouts did not feel it was worth returning because they felt in good health. Two patients did not conclude the study because of side effects (clinical symptoms of hypotension and silent severe hypokalaemia after 6 months of therapy) Protocol outcome 2: Minor adverse events (no admission to hospital) at Define - Actual outcome for Adults (≥18 years): Minor adverse events (study discontinuation due to clinical hypotension (dizziness and hypotension)) at 36 months; Group 1: 0/25, Group 2: 1/25; Comments: 'Allopurinol' = combined therapy Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥18 years): Minor adverse events (study discontinuation due to silent severe hypokalaemia) at 36 months; Group 1: 0/25, Group 2: 1/25; Comments: 'Allopurinol' = combined therapy Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Kidney function at Define - Actual outcome for Adults (≥18 years): Kidney function (creatinine clearance (ml/min)) at 36 months; Group 1: mean 122 (SD 20); n=24, Group 2: mean 114 (SD 22); n=19

Study	Borghi 1993[25]
Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 4: Stone episodes/stone interventions at Define - Actual outcome for Adults (≥18 years): Recurrence (number of stone-free participants) at 36 months; Group 1: 16/19, Group 2: 21/24; Comments: 'Allopurinol'= combined therapy Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: 1, Reason: The dropout did not feel it was worth returning because they felt in good health; Group 2 Number missing: 6, Reason: Four dropouts did not feel it was worth returning because they felt in good health. Two patients did not conclude the study because of side effects (clinical symptoms of hypotension and silent severe hypokalaemia after 6 months of therapy) RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus NO INTERVENTION Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Recurrence (number of stone-free participants) at 36 months; Group 1: 21/24, Group 2: 12/21; Comments: 'Allopurinol' = combined therapy Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: 1, Reason: The dropouts did not feel it was worth returning because they felt in good health; Group 2 Number missing: 4, Reason: The dropouts did not feel it was worth returning because they felt in good health - Actual outcome for Adults (≥18 years): Recurrence rate (not defined) at 36 months; Rate ratio calculated from combined therapy group stone rate of 1.20 (1.43) and no intervention group stone rate of 0.79 (0.48); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Before treatment, groups were comparable in age, body weight, sex distribution and systolic and diastolic blood pressure; investigators also reported that height, stone rate and all serum and urine parameters were comparable at baseline; Group 1 Number missing: 1, Reason: The dropouts did not feel it was worth returning because they felt in good health; Group 2 Number missing: 4, Reason: The dropouts did not feel it was worth returning because they felt in good health Protocol outcome 2: Kidney function at Define - Actual outcome for Adults (≥18 years): Kidney function (creatinine clearance (ml/min)) at 36 months; Group 1: mean 122 (SD 20); n=24, Group 2: mean 120 (SD 24); n=21 Risk of bias: All domain - ; Indirectness of outcome: No indirectness	

Study	Borghi 1993[25]
Protocol outcomes not reported by the study	Quality of life at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Ettinger 1986[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 39 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: plain x-ray
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with calculi that were composed of more than 79% calcium oxalate. Patients in whom two or more calculi had formed within the previous five years and in whom at least one calculus had formed within the previous 2 years.
Exclusion criteria	Patients with secondary caused of nephrolithiasis (chronic urinary infection or obstruction, renal failure ,renal acidification defects, disorders of calcium metabolism, chronic gastrointestinal disorders, or the use of drugs that could affect calculous disease)
Recruitment/selection of patients	Consecutive reports on calculus analysis from medical centres
Age, gender and ethnicity	Age - Mean (SD): Allopurinol group 48.9 (10.1); placebo group 46.4 (9.9). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Allopurinol. 100mg, three times daily. Duration 39 months. Concurrent medication/care: Patients were encouraged to increase fluid intake, no dietary advice was given. Indirectness: No indirectness (n=36) Intervention 2: Placebo/No intervention/Fluid only - Placebo. Identical appearance placebo. Duration 39 months. Concurrent medication/care: Patients were encouraged to increase fluid intake, no dietary advice

Study	Ettinger 1986[47]
	was given. Indirectness: No indirectness
Funding	Other (Supported in part by the Community Service Program of Kaiser Foundation Hospitals and in part by the Burroughs Wellcome Company)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL versus PLACEBO Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): New calculous events (growth of residual calculi, development of new stone which either passed spontaneously or was seen on x-ray) at 39 months; Group 1: 9/29, Group 2: 18/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 5 - Actual outcome for Adults (≥18 years): New calculous events (development of new stone only) at 39 months; Group 1: 5/29, Group 2: 11/31 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Stone episodes/stone interventions at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Ettinger 1988[45]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: X-ray
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with active recurrent calculous disease and no secondary causes for nephrolithiasis. All patients had had 2 or more calculi within the previous 5 years and at least 1 calculus within the previous 2 years

Study	Ettinger 1988[45]
Exclusion criteria	Not reported
Recruitment/selection of patients	Calculi analysis reported were reviewed and those with calculous composition exceeding 79% calcium oxalate were selected
Age, gender and ethnicity	Age - Mean (SD): Placebo group 48.9 (12.5); 650mg magnesium group 47.1 (9.6); 1300mg magnesium group 41.1 (9.9). Gender (M:F): 109/15. Ethnicity: 94% white
Further population details	
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Magnesium supplement . Milk of magnesia, 325g x2 daily (n=30) or 650mg x2 daily (n=21). Duration 3 years or until a new calculous event occurred. Concurrent medication/care: All subjects were advised to increase the fluid intake sufficient to produce a daily urine output of 2000ml and all were given written dietary instructions that recommended restriction of salt, refined sugar, animal protein, and foods high in oxalate with encouraging high cereal fibre intake. Dairy products were limited to 2 servings daily and vitamin C was perscribed. Indirectness: No indirectness (n=31) Intervention 2: Placebo/No intervention/Fluid only - Placebo. Placebo, identical appearing. Duration 3 years or until a new calculus event occured. Concurrent medication/care: All subjects were advised to increase the fluid intake sufficient to produce a daily urine output of 2000ml and all were given written dietary instructions that recommended restriction of salt, refined sugar, animal protein, and foods high in oxalate with encouraging high cereal fibre intake. Dairy products were limited to 2 servings daily and vitamin C was perscribed. Indirectness: No indirectness (n=42) Intervention 3: Thiazides. 25mg chlorthalidone daily (n=19) or 50mg chlorthalidone daily (n=23). Duration 3 years or until a new calculus event occured. Concurrent medication/care: All subjects were advised to increase the fluid intake sufficient to produce a daily urine output of 2000ml and all were given written dietary instructions that recommended restriction of salt, refined sugar, animal protein, and foods high in oxalate with encouraging high cereal fibre intake. Dairy products were limited to 2 servings daily and vitamin C was prescribed. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MAGNESIUM SUPPLEMENT versus PLACEBO	

Study	Ettinger 1988[45]
Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Calculi observed at 36 months; Group 1: 15/51, Group 2: 14/31 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥18 years): Recurrence rate at 36 months; Group 1: rate 0.163 per patient per year during 3 years; n=51 Group 2: rate 0.22 per patient per year during 3 years; n=31; Comments: Baseline - magnesium group 0.72; placebo group 0.57 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus MAGNESIUM SUPPLEMENT Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Calculi observed at 36 months; Group 1: 15/51, Group 2: 6/42 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥18 years): Recurrence rate at 36 months; Group 1: rate 0.057 per patient per year during 3 years; n=42, Group 2: rate 0.163 per patient per year during 3 years; n=51; Comments: Baseline - thiazide group 0.65; magnesium group 0.72 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus PLACEBO Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Calculi observed at 36 months; Group 1: 6/42, Group 2: 14/31Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Adults (≥18 years): Recurrence rate at 36 months; Group 1: rate 0.057 per patient per year during 3 years; n=42, Group 2: rate 0.22 per patient per year during 3 years; n=31; Comments: Baseline - thiazide group 0.65; placebo group 0.57 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	

Study	Ettinger 1988[45]
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Protocol outcomes not reported by the study	Quality of life at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Stone episodes/stone interventions at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Kohri 1990[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=87)
Countries and setting	Conducted in Japan; Setting: Not reported
Line of therapy	Unclear
Duration of study	Not clear: In the patients who discontinued therapy, the duration of combined thiazide and allopurinol treatment was 4.6 years (range 2-8), and 4.9 years (range one year and four months to 8 years) with allopurinol treatment
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with calcium oxalate of calcium phosphate urinary stones
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): male only. Ethnicity: Not reported
Further population details	
Extra comments	All were idiopathic stone formers with no history of primary hyperparathyroidism, renal tubular acidosis, or urinary obstruction.
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Thiazides. Combined thiazide and allopurinol treatment: 2mg trichloromethiazide (Fluitran) once every morning and 100mg allopurinol (Zyroric) three times daily. Duration In patients who

Study	Kohri 1990[66]
	discontinued therapy: 4.6 years (range 2-8). Concurrent medication/care: Other recommendations from the stone clinic, such as diet and fluid intake. The stone clinic restricted calcium intake, but did not encourage citrate ingestion nor restrict oxalate ingestion. Indirectness: No indirectness (n=44) Intervention 2: Allopurinol. 100mg allopurinol (Zyroric) three times daily. Duration In patients who discontinued therapy: 4.9 years (range one year and four months to 8 years) . Concurrent medication/care: As for the combined thiazide and allopurinol group. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus ALLOPURINOL Protocol outcome 1: Recurrence at Define - Actual outcome: Number of stones formed during treatment at In patients who discontinued therapy: combined treatment group 4.6 years (range 2-8); allopurinol group 4.9 years (range one year and four months to 8 years) ; Group 1: 40/43, Group 2: 52/44 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High; Indirectness of outcome: No indirectness; Baseline details: Age not reported. Number of stones before treatment higher in allopurinol only group (175 stones) than the combined treatment group (146 stones) ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Use of healthcare services at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Recurrence rate at Define

Study (subsidiary papers)	Laerum 1984[70] (Laerum 1984[69])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Norway; Setting: General practice serving a partly rural municipality in Norway
Line of therapy	Unclear
Duration of study	Intervention time: 'median 3 years'. The thiazide group had a median treatment duration of 40 months (range 12-51); the placebo group had a median treatment duration of 38 months (range 12-54). The study was performed between 1977 and 1981
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: X-ray examination, surgery or stone passage of most recent stone during the last 2 years

Study (subsidiary papers)	Laerum 1984[70] (Laerum 1984[69])
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Cooperative patients of both sexes above 15 years of age, with or without hypercalciuria (>6mmol/24h) and/or hyperuricosuria (>3.5 mmol/24h) and with two or more stones totally formed, were included if the most recent stone, associated with renal colic, had occurred during the last 2 years and was verified by X-ray examination, surgery or stone passage. Concretions, available from 24 patients, contained calcium oxalate alone or combined with calcium phosphate
Exclusion criteria	Chronic and/or active urinary tract infection, pyelographically verified urinary obstruction, uric acid and triple phosphate stones and chronic diseases such as heart congestion, cancer and sarcoidosis
Recruitment/selection of patients	The study comprised 50 out of 93 etiologically examined recurrent stone formers encountered in general practice (either by one of the authors or by other practitioners and referred to the author)
Age, gender and ethnicity	Age - Mean (range): thiazide group: 45.8 years (16-75); placebo group: 42.7 years (23-65). Gender (M:F): 38/12. Ethnicity: Not reported
Further population details	
Extra comments	Patients with recurrent stones
Indirectness of population	Serious indirectness: Adults and children included (aged above 15 years)
Interventions	(n=25) Intervention 1: Thiazides. 25mg hydrochlorothiazide (and 0.6g potassium chloride) twice daily. Duration median 40 months (range 12-51). Concurrent medication/care: All patients were advised to avoid a high salt intake as well as high and/or regular ingestions of food rich in calcium, oxalate and purines. High fluid intake was recommended in order to achieve a 24-hour urine volume of two litres or more. None of the patients were given drugs such as other diuretics and hormones that might interact with the treatment results. The patients were controlled every 6th month by clinical examination and analysis of blood and urine. A plain abdominal X-ray (and also i.v. pyelography and tomography when results were ambiguous) was taken yearly and at the end of the trial. Indirectness: Serious indirectness; Indirectness comment: Adults and children included (n=25) Intervention 2: Placebo/No intervention/Fluid only - Placebo. matching placebo tablets . Duration median 38 months (range 12-54). Concurrent medication/care: As for the thiazide group. Indirectness: Serious indirectness; Indirectness comment: Adults and children
Funding	Other (The study has been supported by CIBA-GEIGY Pharma A/S, Norway)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus PLACEBO	

Study (subsidiary papers)	Laerum 1984[70] (Laerum 1984[69])

Protocol outcome 1: Minor adverse events (no admission to hospital) at Define
- Actual outcome: Hypopotassemia (K<3mmol/litre) at Unclear; Group 1: 1/23, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: Serious indirectness, Comments: Adults and children included; Baseline details: Patients under 18 years included in thiazide but not placebo group; Group 1 Number missing: 2, Reason: 'Two women inthe thiazide group interrupted the treatment for pyschosocial reasons after 4 and 9 months, respectively, with no sign of recurrence. They were considered dropouts because the probability of forming a new stone while on treatment was below 0.25'; Group 2 Number missing: 0
- Actual outcome: Attack of gout at Unclear; Group 1: 1/23, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: Serious indirectness, Comments: Adults and children included; Baseline details: Patients under 18 years included in thiazide but not placebo group; Group 1 Number missing: 2, Reason: 'Two women inthe thiazide group interrupted the treatment for pyschosocial reasons after 4 and 9 months, respectively, with no sign of recurrence. They were considered dropouts because the probability of forming a new stone while on treatment was below 0.25'; Group 2 Number missing: 0
- Actual outcome: Minor side-effect such as slight fatigue and dyspepsia at Unclear; Group 1: 3/23, Group 2: 2/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - High; Indirectness of outcome: Serious indirectness, Comments: Adults and children included; Baseline details: Patients under 18 years included in thiazide but not placebo group; Group 1 Number missing: 2, Reason: 'Two women inthe thiazide group interrupted the treatment for pyschosocial reasons after 4 and 9 months, respectively, with no sign of recurrence. They were considered dropouts because the probability of forming a new stone while on treatment was below 0.25'; Group 2 Number missing: 0
- Actual outcome: Transient impotence at Unclear; Group 1: 1/23, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: Serious indirectness, Comments: Adults and children included; number of males and females not reported separately for thiazide and placebo groups; Baseline details: Patients under 18 years included in thiazide but not placebo group; Group 1 Number missing: 2, Reason: 'Two women inthe thiazide group interrupted the treatment for pyschosocial reasons after 4 and 9 months, respectively, with no sign of recurrence. They were considered dropouts because the probability of forming a new stone while on treatment was below 0.25'; Group 2 Number missing: 0

Protocol outcome 2: Recurrence at Define
- Actual outcome: New stones (verified and probable) at median treatment period of about 3 years; Group 1: 5/23, Group 2: 12/25; Comments: Figures used from the main text although a discrepancy was noted in the figures reported in the main text compared with tabulated figures for verified and probably new stones formed
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low; Indirectness of outcome: Serious indirectness, Comments: Adults and children included; Baseline details: Patients under 18 years included in thiazide but not placebo group; Group 1 Number missing: 2, Reason: 'Two women inthe thiazide group interrupted the treatment for pyschosocial reasons after 4 and 9 months, respectively, with no sign of recurrence. They were considered dropouts because the probability of forming a new stone while on treatment was below 0.25'; Group 2 Number missing: 0

Study (subsidiary papers)	Laerum 1984[70] (Laerum 1984[69])
Protocol outcomes not reported by the study	Quality of life at Define; Use of healthcare services at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Recurrence rate at Define

Study	Ohkawa 1992[84]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Japan; Setting: Department of Urology
Line of therapy	Unclear
Duration of study	Follow up (post intervention): Mean 2.21 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Stones were obtained by surgical removal and/or stone passage and anlaysed. The diagnosis of hypercalciuria was based on presence of ≥0.10mmol calcium/kg body weight in 24 hour urine
Stratum	Adults (≥18 years): Calcium oxalate stones: 16.57%; calcium oxalate and calcium phosphate stones 83.4% Hypercalciuria population
Subgroup analysis within study	Not applicable
Inclusion criteria	People with calcium urolithiasis and idiopathic hypercalciuria, who were at least 16 years old, not pregnant, without severe renal dysfunction (<0.77 mmol/L serum creatinine), free from urinary infection, with no evidence of obstruction, having hypercalciuria without signs of hyperparathyroidism
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Thiazide group 48.7 (12.3); control group 46.9 (13.8). Gender (M:F): 97/78. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=105) Intervention 1: Thiazides. Trichlormethiazide, 4mg, once a day. Half doses (2mg) were given for the first week in order to minimise side effects. . Duration Mean 2.21 years. Concurrent medication/care: Dietary and fluid advice (no further details). No drugs capable of influencing metabolism were allowed during the study. No participants received potassium supplementation. . Indirectness: No indirectness (n=105) Intervention 2: Placebo/No intervention/Fluid only - No intervention. No specific therapy other than

Study	Ohkawa 1992[84]
	supervision and follow up. . Duration Mean 2.21 years. Concurrent medication/care: Dietary and fluid advice (no further details). No drugs capable of influencing metabolism were allowed during the study. No participants received potassium supplementation. . Indirectness: No indirectness
Funding	Equipment / drugs provided by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus NO INTERVENTION Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Stone formation rate (no. of stones/patient/year) at Mean 2.21 years; Group 1: mean 0.13 (SD 0.33); n=82, Group 2: mean 0.31 (SD 0.61); n=93 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline data not reported for those who dropped out; Group 1 Number missing: 23, Reason: Voluntary withdrawal (20), side effects (2), allopurinol given (1); Group 2 Number missing: 12, Reason: Voluntary withdrawal - Actual outcome for Adults (≥18 years): Remission (patients without new stone formation per the number of cumulative year of observation) at Mean 2.21 years; Group 1: 75/82, Group 2: 80/93 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline data not reported for those who dropped out; Group 1 Number missing: 23, Reason: Voluntary withdrawal (20), side effects (2), allopurinol given (1); Group 2 Number missing: 12, Reason: Voluntary withdrawal	
Protocol outcomes not reported by the study	Quality of life at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Oguz 2013[83]
Study type	Cohort study
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Turkey; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: Medical prophylaxis: 25.9 months (12-42 months); no medical prophylaxis: 24.6 months (14-40 months)

Study	Oguz 2013[83]
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Patients underwent PNL and detected as stone-free
Stratum	Children (<18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with calcium oxalate stone disease who underwent PNL and detected as stone-free
Exclusion criteria	Children who had anatomic predisposing factors such as horseshoe kidney, ectopic kidney, ureteropelvic junction obstruction, rotation anomaly, and fusion anomaly. Those with glomerular and tubular renal disease, chronic renal failure, and systemic immunological disease were also excluded
Recruitment/selection of patients	Retrospective analysis
Age, gender and ethnicity	Age - Mean (range): medical prophylaxis group: 7.9 (3-16 years); no medical prophylaxis 7.5 (4-16 years). Gender (M:F): 29/13 overall; in medical prophylaxis group: 17/5; in no medical prophylaxis group: 12/8. Ethnicity: Not reported
Further population details	
Extra comments	Stone disease was not associated with endocrinological or gastrointestinal disorders in all patients and primary hyperparathyroidism was not detected
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Citrate supplements - Potassium citrate. Potassium citrate given at 1mEq/kg daily dose as a Urocit-K wax matrix tablet with 5mEq citrate per tablet. Duration 25.9 months (. Concurrent medication/care: Patients were informed about the food that included oxalates and they were advised to avoid these foods. They were asked to take fluids to achieve a minimum urine output of 25mL/kg/day. Red meat protein was not restricted because patients were children in the age of growth. Indirectness: No indirectness (n=20) Intervention 2: Placebo/No intervention/Fluid only - No intervention. No medical treatment. Duration 24.6 months (14-40 months). Concurrent medication/care: Same as for the citrate group. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POTASSIUM CITRATE versus NO INTERVENTION

Protocol outcome 1: Recurrence at Define
- Actual outcome for Children (<18 years): Recurrence rate (stone formation rate after PNL per patient per year) at 12-42 months; Medical prophylaxis

Study	Oguz 2013[83]
group: recurrence in two participants, each with only one recurrence (2 events); no medical prophylaxis group: recurrence in seven participants, two of whom had two recurrences (9 events). Stone formation rate (per patient per year) reported as: medical prophylaxis group: 0.034; no medical prophylaxis group: 0.2 ; Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Very high; Indirectness of outcome: No indirectness ; Baseline details: Male/female ratio higher in medical prophylaxis group; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children (<18 years): Recurrence after PNL (number of children with stone recurrence defined as new detection of stone or spontaneous passage of non-preexisting stone. Evaluation was done at follow-up with abdominal X-ray and ultrasonography; intravenous urography or computed tomography if necessary) at 12-42 months; Group 1: 2/22, Group 2: 7/20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Very high; Indirectness of outcome: No indirectness ; Baseline details: Male/female ratio higher in medical prophylaxis group; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Stone episodes/stone interventions at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Sarica 2006[104]
Study type	Cohort study
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in Turkey; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: Mean 24.4 months (range: 12 to 36.6 months)
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Idiopathic urinary calculi
Stratum	Children (<18 years):
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients with idiopathic urinary calculi treated with SWL
Exclusion criteria	'Children with anatomic abnormalities, previous stone surgery or UTI, renal tubular acidosis, renal functional disorders, cystinuria, or any other evidence metabolic abnormality (primary or secondary hyperoxaluria, hyperparathyroidism, etc.)'
Recruitment/selection of patients	Of 125 stone-forming children evaluated and treated, detailed long-term documentation was available in 96.

Study	Sarica 2006[104]
Age, gender and ethnicity	Age - Mean (range): Reported as 6.6 years (range: 4 to 14 years); citrate group: 6.9 (4-12 years); no intervention group: 7.4 (4-14 years). Gender (M:F): 58/38. Ethnicity: Not reported
Further population details	
Extra comments	Patients were either stone-free or had stone(s) following SWL four weeks prior
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Citrate supplements - Potassium citrate. Potassium citrate (Urocit-K; Mission Pharmacal, San Antonio, TX) 1mEq/kg per day under close follow-up. Depending on the age of the child, the medication was given in either a tablet or a liquid form.. Duration 12 months. Concurrent medication/care: SWL was performed four weeks prior, using the Stonelith V5 lithotripter with the child under general anaesthesia. In addition to enforced fluid intake, the dietary content of each child was evaluated, and avoidance of excessive dairy products and oxalate-rich foods was advised. Indirectness: No indirectness (n=48) Intervention 2: Placebo/No intervention/Fluid only - No intervention. 'No specific medication or preventive measure and constituted the control group'. Duration 12 months. Concurrent medication/care: SWL was performed four weeks prior, using the Stonelith V5 lithotripter with the child under general anaesthesia. In addition to enforced fluid intake, the dietary content of each child was evaluated, and avoidance of excessive dairy products and oxalate-rich foods was advised. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POTASSIUM CITRATE versus NO INTERVENTION

Protocol outcome 1: Recurrence at Define
- Actual outcome for Children (<18 years): Recurrence (new stone formation in children stone-free following SWL ('true stone recurrence, defined as documentation of a new stone(s) in a child who was completely stone-free)) at 12 months intervention; 12 to 36.6 months follow-up; Group 1: 2/26, Group 2: 9/26
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Very high; Indirectness of outcome: No indirectness ; Baseline details: Groups were 'matched for sex and age'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children (<18 years): Recurrence (stone recurrence or regrowth in children with residual fragments following SWL) at 12 months intervention; 12 to 36.6 months follow-up; Group 1: 4/22, Group 2: 16/22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Very high; Indirectness of outcome: No indirectness ; Baseline details: Groups were 'matched for sex and age'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children (<18 years): Recurrence (stone stable in children with residual fragments following SWL) at 12 months intervention; 12 to

Study	Sarica 2006[104]
36.6 months follow-up; Group 1: 18/22, Group 2: 6/22 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Very high; Indirectness of outcome: No indirectness ; Baseline details: Groups were 'matched for sex and age'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Use of healthcare services at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Recurrence rate at Define

Study	Scholz 1982[106]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=51)
Countries and setting	Conducted in Germany; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with metabolically active calcium stone formation but without signs of primary hyperparathyroidism
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): Thiazide group 46 (29-63); placebo group 41 (20-64). Gender (M:F): 31/20. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Thiazides. Hydrochlorothiazide 25mg, twice daily. Participants took one tablet in the morning and one in the evening. Duration 12 months. Concurrent medication/care: No drugs were allowed that could influence mineral metabolism. Additional potassium was given orally to patients in whom serum potassium decreased to <3 mEq./l during the study. Indirectness: No indirectness

Study	Scholz 1982[106]
	(n=26) Intervention 2: Placebo/No intervention/Fluid only - Placebo. Placebo twice daily. Each participant took one tablet in the morning and one in the evening. Duration 12 months. Concurrent medication/care: No drugs were allowed that could influence mineral metabolism. Additional potassium was given orally to patients in whom serum potassium decreased to <3 mEq./l during the study. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus PLACEBO Protocol outcome 1: Recurrence at Define - Actual outcome for Adults (≥18 years): Spontaneous passage of newly formed renal stones at 12 months; Group 1: 6/23, Group 2: 6/25 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Surrogate outcome for recurrence ; Group 1 Number missing: 2; Group 2 Number missing: 1 Protocol outcome 2: Minor adverse events (no admission to hospital) at Define - Actual outcome for Adults (≥18 years): Adverse events (weariness, nausea and symptoms of low blood pressure) at 12 months; Group 1: 11/23, Group 2: 5/25 Risk of bias: All domain - High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life at Define; Kidney function at Define; Stone episodes/stone interventions at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Study	Soygür 2002[119]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110 enrolled in study; 90 randomised in trial)
Countries and setting	Conducted in Turkey; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: plain abdominal films and renal ultrasound

Study	Soygür 2002[119]
Stratum	Adults (≥18 years) with stone composition: calcium oxalate
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	110 patients enrolled in study
Age, gender and ethnicity	Age - Median (range): 41.7 (range 18.4 to 62.5 years). Gender (M:F): 60/30. Ethnicity: Not reported
Further population details	
Extra comments	Patients had lower caliceal stones and were stone free or had residual stone fragments <5mm in diameter 4 weeks after SWL. All patients had documented calcium oxalate stones without urinary tract infection. They had no anatomic abnormality of the urinary tract, no history of urologic surgery or urolithiasis, and no definitive metabolic disease such as hyperthyroidism or renal tubular acidosis.
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Citrate supplements - Potassium citrate. 60 mEq per day. Potassium citrate tablets 5 mEq were administered in three doses after meals. Duration 12 months. Concurrent medication/care: Patients underwent SWL (with Dornier MPL lithotripter) before the trial. During the trial, all patients were advised to have a high fluid intake to achieve a minimum daily urine output of 2.1 litres and to avoid excess oxalate-rich foods and salty foods. They were instructed to limit their daily meat intake to 8 ounces or less, to substitute whole wheat bread for white bread, and to eat natural fibre cereals. Indirectness: No indirectness (n=44) Intervention 2: Placebo/No intervention/Fluid only - No intervention. Duration 12 months. Concurrent medication/care: Patients underwent SWL (with Dornier MPL lithotripter) before the trial. All patients were advised to have a high fluid intake to achieve a minimum daily urine output of 2.1 litres and to avoid excess oxalate-rich foods and salty foods. They were instructed to limit their daily meat intake to 8 ounces or less, to substitute whole wheat bread for white bread, and to eat natural fibre cereals. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POTASSIUM CITRATE versus FLUID ONLY

Protocol outcome 1: Recurrence at Define
- Actual outcome for Adults (≥18 years) with stone composition: calcium oxalate: Stone free (patients stone free at baseline) at 12 months; Group 1: 28/28, Group 2: 20/28
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low;

Study	Soygür 2002[119]
Indirectness of outcome: No indirectness ; Baseline details: More patients had hypocitraturia in the citrate-treated group (n=20) than control group (n=14). There were also other metabolic differences between groups; Group 1 Number missing: , Reason: 20 patients were excluded from analysis across both groups due to noncompliance (n=10), epigastric discomfort (n=6) and reluctance to receive medication (n=4); Group 2 Number missing: - Actual outcome for Adults (≥18 years) with stone composition: calcium oxalate: Stone free (patients with residual fragments <5mm at baseline) at 12 months; Group 1: 8/18, Group 2: 2/16 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: More patients had hypocitraturia in the citrate-treated group (n=20) than control group (n=14). There were also other metabolic differences between groups; Group 1 Number missing: , Reason: 20 patients were excluded from analysis across both groups due to noncompliance (n=10), epigastric discomfort (n=6) and reluctance to receive medication (n=4); Group 2 Number missing: - Actual outcome for Adults (≥18 years) with stone composition: calcium oxalate: Stone free (patients stone free or with residual fragments <5mm at baseline) at 12 months; Group 1: 36/46, Group 2: 22/44 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: More patients had hypocitraturia in the citrate-treated group (n=20) than control group (n=14). There were also other metabolic differences between groups; Group 1 Number missing: , Reason: 20 patients were excluded from analysis across both groups due to noncompliance (n=10), epigastric discomfort (n=6) and reluctance to receive medication (n=4); Group 2 Number missing: Protocol outcome 2: Stone episodes/stone interventions at Define - Actual outcome for Adults (≥18 years) with stone composition: calcium oxalate: Stone size unchanged (patients with residual fragments <5mm at baseline) at 12 months; Group 1: 10/18, Group 2: 4/16 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: More patients had hypocitraturia in the citrate-treated group (n=20) than control group (n=14). There were also other metabolic differences between groups; Group 1 Number missing: , Reason: 20 patients were excluded from analysis across both groups due to noncompliance (n=10), epigastric discomfort (n=6) and reluctance to receive medication (n=4); Group 2 Number missing: - Actual outcome for Adults (≥18 years) with stone composition: calcium oxalate: Stone size increased (patients with residual fragments <5mm at baseline) at 12 months; Group 1: 0/18, Group 2: 10/16 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: More patients had hypocitraturia in the citrate-treated group (n=20) than control group (n=14). There were also other metabolic differences between groups; Group 1 Number missing: , Reason: 20 patients were excluded from analysis across both groups due to noncompliance (n=10), epigastric discomfort (n=6) and reluctance to receive medication (n=4); Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at Define; Use of healthcare services at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Recurrence rate at Define

Study	Tosukhowong 2008[125]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in Thailand; Setting: Department of Surgery
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Post-operative patients with nephrolithiasis; age no greater than 60 years old; x-ray KUB film was negative for residual stones; surgical removaal of stone was longer than 3 months prior to the accrual; urine culture was negative
Exclusion criteria	Patients with severe renal insufficiency (creatinine clearance <25ml/min) or other clinically significant systemic illnesses e.g. liver cirrhosis, jaundice, asthma, chronic lung disease, malabsorption syndrome, chronic diarrhea, malignancies, stroke, myocardial infarction, and congestive heart failure
Recruitment/selection of patients	Patients who came in for follow up
Age, gender and ethnicity	Age - Mean (SD): Intervention group 47.8 (10.1); comparison group 54.1 (8.6). Gender (M:F): 17/14. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Citrate supplements - Potassium citrate. Oral potassium citrate, in powder form packed in sachets. Participants were instructed to consume one sachet daily by dissolving the medication in 200ml water throughout the treatment period. Duration 3 months. Concurrent medication/care: All patients received advice to increase water intake as well as avoid high salt and high purine diets. Indirectness: No indirectness (n=13) Intervention 2: Placebo/No intervention/Fluid only - Placebo. Placebo (lactose) in powder form packed in sachets. Participants were instructed to consume one sachet daily by dissolving the medication in 200ml water throughout the treatment period. Duration 3 months. Concurrent medication/care: All patients received advice to increase water intake as well as avoid high salt and high purine diets. Indirectness: No indirectness

Study	Tosukhowong 2008[125]
Funding	Academic or government funding (Supported by Grants from Division of Nephrology, Faculty of Medicine, and from the Graduate School, Chulalongkorn University)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POTASSIUM CITRATE versus PLACEBO Protocol outcome 1: Kidney function at Define - Actual outcome for Adults (≥18 years): Creatinine clearance at 3 months; Group 1: mean 81.4 (SD 61); n=11, Group 2: mean 80.6 (SD 73.9); n=7; Comments: Baseline: Potassium citrate group 94.7 (38.8); placebo group 83.1 (45.1) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Not reported; Group 2 Number missing: 6, Reason: Not reported - Actual outcome for Adults (≥18 years): Fractional excretion of magnesium at 3 months; Group 1: mean 3.7 (SD 1.8); n=11, Group 2: mean 3 (SD 2.8); n=7; Comments: Baseline: potassium citrate group 3.4 (2); placebo group 3.2 (2.6) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Not reported; Group 2 Number missing: 6, Reason: Not reported - Actual outcome for Adults (≥18 years): Urine NAG activity (U/g Cr) at 3 months; Group 1: mean 3.4 (SD 2.4); n=11, Group 2: mean 3.6 (SD 5.4); n=7; Comments: Baseline: potassium citrate group 3.9 (3.3); placebo group 4.3 (7.2) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Not reported; Group 2 Number missing: 6, Reason: Not reported - Actual outcome for Adults (≥18 years): Urine proteins (g/day) at 3 months; Group 1: mean 0.13 (SD 0.28); n=11, Group 2: mean 0.17 (SD 0.15); n=7; Comments: Baseline: potassium citrate group 0.15 (0.26); placebo group 0.22 (0.19) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Not reported; Group 2 Number missing: 6, Reason: Not reported	
Protocol outcomes not reported by the study	Quality of life at Define; Use of healthcare services at Define; Minor adverse events (no admission to hospital) at Define; Stone episodes/stone interventions at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Recurrence rate at Define

Study (subsidiary papers)	Wolf 1983[130] (Brocks 1981[28])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=62)

Study (subsidiary papers)	Wolf 1983[130] (Brocks 1981[28])
Countries and setting	Conducted in Denmark; Setting: Department of urology
Line of therapy	Unclear
Duration of study	Intervention + follow up: 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiography
Stratum	Adults (≥18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	People with stone of the upper urinary tract, who were aged 16-49, who had passed or formed at least 2 stones in the preceding 6 years, were free from infection of the urinary tract and had no well-defined metabolic causes of renal stone formation
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Thiazides. Bendroflumethiazide, 2.5mg three times daily. Duration Mean 36 months. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=29) Intervention 2: Placebo/No intervention/Fluid only - Placebo. Placebo, three times daily. Duration Mean 36 months. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Leo Pharmaceutical Products, Ballerup, Denmark provided the study drugs)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THIAZIDES versus PLACEBO

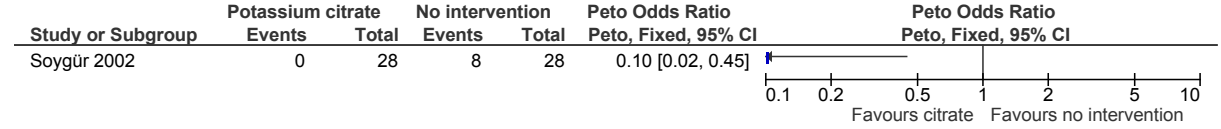
Protocol outcome 1: Recurrence at Define
- Actual outcome for Adults (≥18 years): Recurrence rate (number of stones formed) at 3 years; Group 1: 8/33, Group 2: 8/29
Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Study (subsidiary papers)	Wolf 1983[130] (Brocks 1981[28])
Protocol outcomes not reported by the study	Quality of life at Define; Minor adverse events (no admission to hospital) at Define; Kidney function at Define; Stone episodes/stone interventions at Define; Major adverse events (if admission to hospital) at Define; Pain intensity (visual analogue scale) at Define; Use of healthcare services at Define

Appendix E: Forest plots

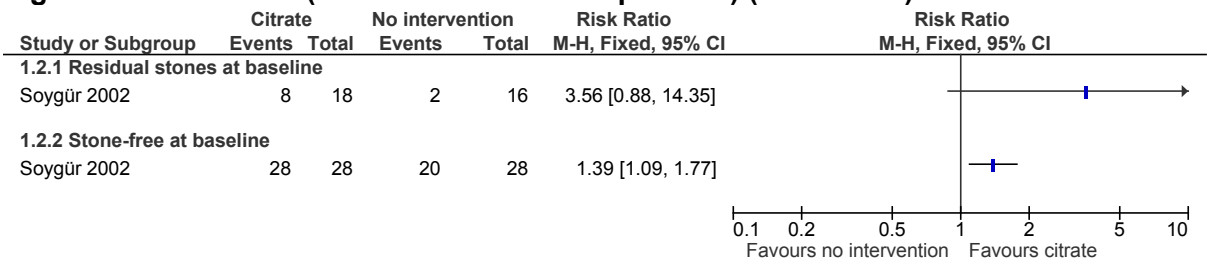
E.1 Potassium citrate versus no intervention in adults

Figure 2: Recurrence (new stone formation in patients stone-free at baseline subgroup) (12 months)



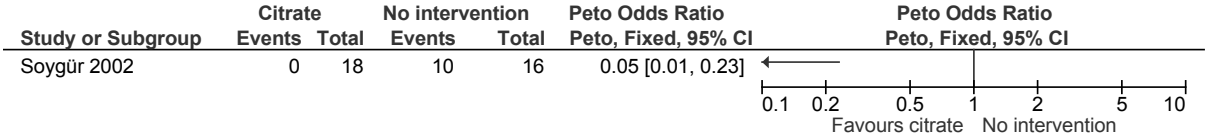
Stone composition: calcium oxalate; metabolic abnormality: hypocitraturia 28.6%, hypercalciuria 14.3%, hyperuricosuria 10.7%. At baseline, included patients were stone free or had residual fragments <5mm diameter

Figure 3: Recurrence (number of stone-free patients) (12 months)



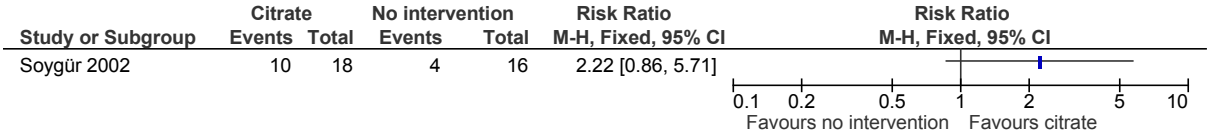
Stone composition: calcium oxalate; metabolic abnormality: stone free at baseline (hypocitraturia 28.6%, hypercalciuria 14.3%, hyperuricosuria 10.7%) residual stones at baseline (hypocitraturia 52.9%, hypercalciuria 29.4%, hyperuricosuria 29.4%), overall (hypocitraturia 37.8%, hypercalciuria 20%, hyperuricosuria 17.8%) At baseline, included patients were stone free or had residual fragments <5mm diameter

Figure 4: Stone episodes (stone size increased in patients with residual stones <5mm at baseline) (12 months)



Stone composition: calcium oxalate; metabolic abnormality: hypocitraturia 52.9%, hypercalciuria 29.4%, hyperuricosuria 29.4%. At baseline, included patients were stone free or had residual fragments <5mm diameter

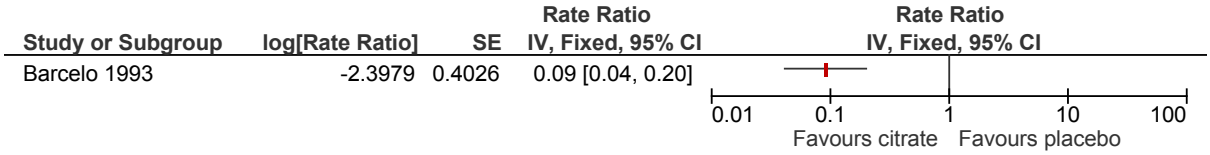
Figure 5: Stone episodes (stone size unchanged in patients with residual fragments <5mm at baseline) (12 months)



Stone composition: calcium oxalate; metabolic abnormality: hypocitraturia 52.9%, hypercalciuria 29.4%, hyperuricosuria 29.4%. At baseline, included patients were stone free or had residual fragments <5mm diameter

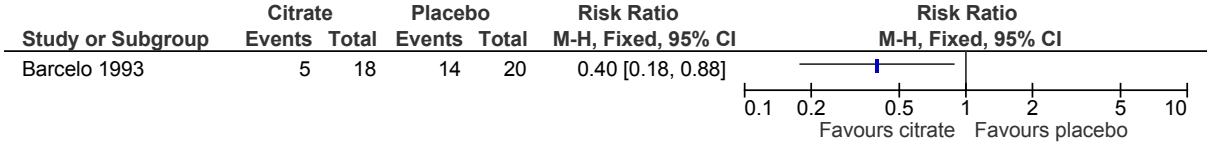
E.2 Potassium citrate versus placebo in adults

Figure 6: Recurrence rate (stone formation/patient/year) (36 months)



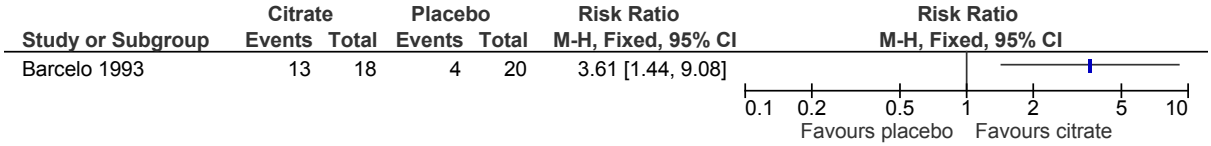
Stone composition: calcium oxalate or a mixture of calcium oxalate and calcium phosphate; biochemical abnormality: hypocitraturia. At baseline, included patients had 2 or more stones formed during the previous 2 years

Figure 7: Recurrence (new stone formation) (36 months)



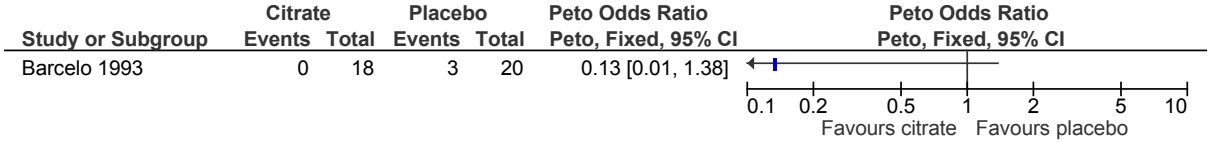
Stone composition: calcium oxalate or a mixture of calcium oxalate and calcium phosphate; biochemical abnormality: hypocitraturia. At baseline, included patients had 2 or more stones formed during the previous 2 years

Figure 8: Recurrence (stone-free) (36 months)



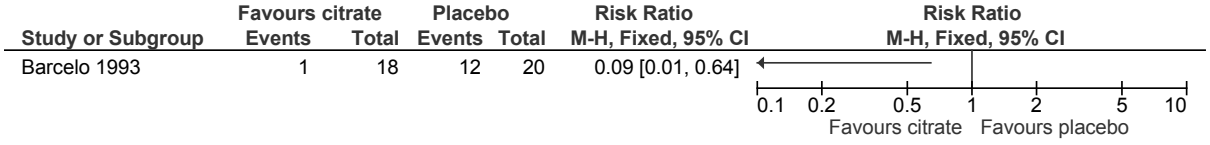
Stone composition: calcium oxalate or a mixture of calcium oxalate and calcium phosphate; biochemical abnormality: hypocitraturia. At baseline, included patients had 2 or more stones formed during the previous 2 years

Figure 9: Stone episodes (increase in stone size) (36 months)



Stone composition: calcium oxalate or a mixture of calcium oxalate and calcium phosphate; biochemical abnormality: hypocitraturia. At baseline, included patients had 2 or more stones formed during the previous 2 years

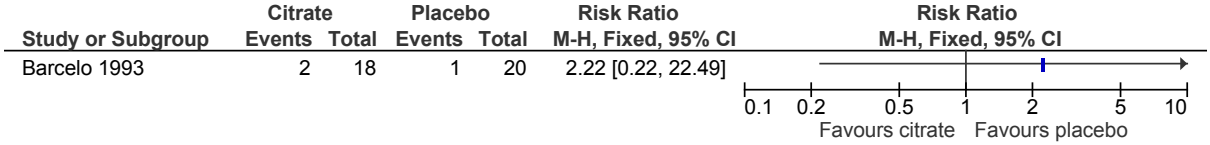
Figure 10: Stone interventions (procedures to remove stones) (36 months)



Stone composition: calcium oxalate or a mixture of calcium oxalate and calcium phosphate; biochemical abnormality: hypocitraturia. At baseline, included patients had 2 or more stones formed during the previous 2 years
Type of procedures: citrate group (SWL); placebo group (10 SWL, 1 basket, 1 open)

1

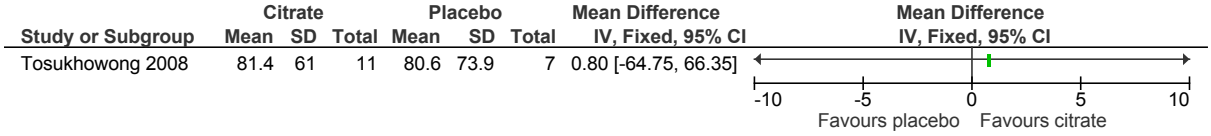
Figure 11: Minor adverse events (unspecified; causing withdrawal from study) (36 months)



Stone composition: calcium oxalate or a mixture of calcium oxalate and calcium phosphate; biochemical abnormality: hypocitraturia. At baseline, included patients had 2 or more stones formed during the previous 2 years

2

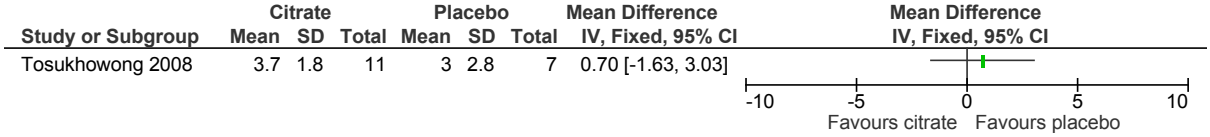
Figure 12: Kidney function (creatinine clearance – ml/min) (3 months)



Stone composition and biochemical abnormality not specified. At baseline, included patients had 2 or more stones formed during the previous 2 years

3

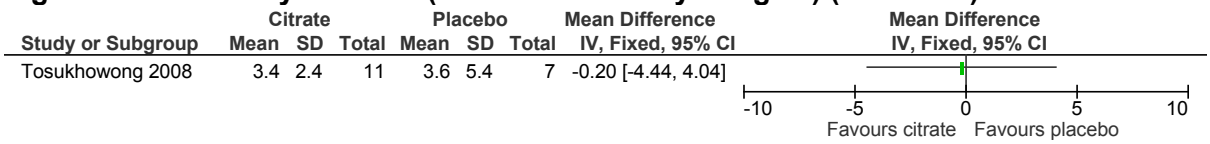
Figure 13: Kidney function (fractional excretion of magnesium - %) (3 months)



Stone composition and biochemical abnormality not specified. At baseline, included patients had 2 or more stones formed during the previous 2 years

4

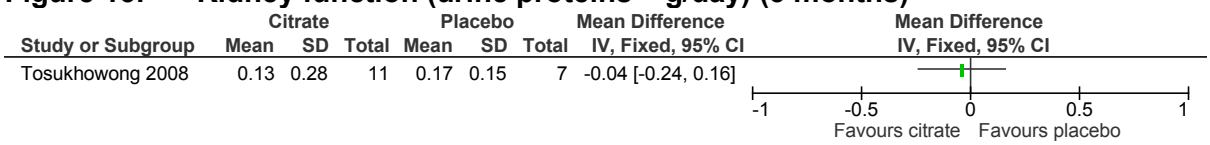
Figure 14: Kidney function (urine NAG activity – U/g Cr) (3 months)



Stone composition and biochemical abnormality not specified. At baseline, included patients had 2 or more stones formed during the previous 2 years

5

Figure 15: Kidney function (urine proteins – g/day) (3 months)

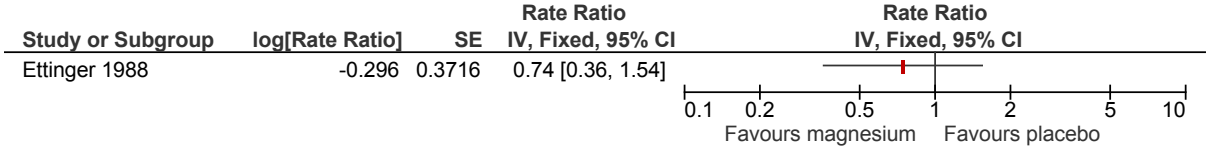


Stone composition and biochemical abnormality not specified. At baseline, included patients had 2 or more stones formed during the previous 2 years

1

2 E.3 Magnesium versus placbo in adults

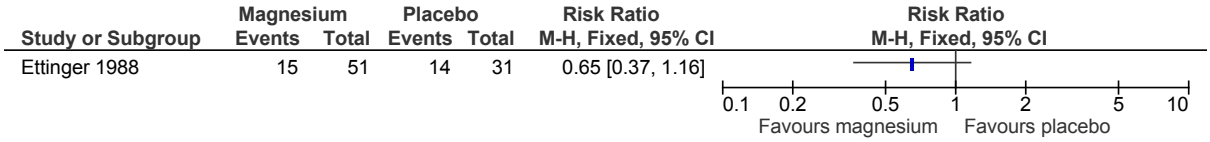
Figure 16: Recurrence rate (rate of calculous events per year of observation) (36 months)



Stone composition: exceeding 79% calcium oxalate; biochemical abnormality (magnesium/placebo groups_: hypercalciuria 13.8/9.7%, hyperuricosuria 8.1/9.7%, both 27.7/16.1 %, no metabolic abnormality 50.5/64.5% . At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

3

Figure 17: Recurrence (calculi observed) (36 months)

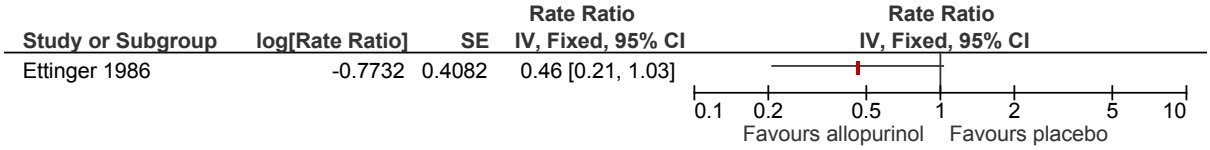


Stone composition: exceeding 79% calcium oxalate; biochemical abnormality (magnesium/placebo groups_: hypercalciuria 13.8/9.7%, hyperuricosuria 8.1/9.7%, both 27.7/16.1 %, no metabolic abnormality 50.5/64.5%. At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

4

E.4 Allopurinol versus placebo in adults

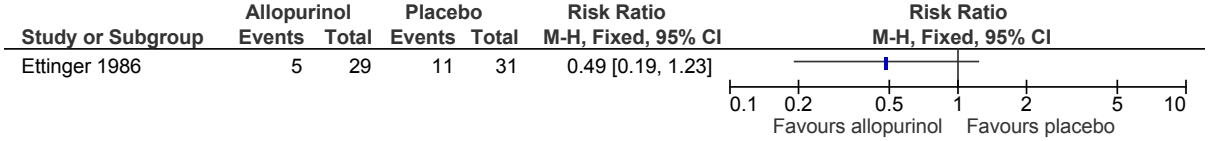
Figure 18: Recurrence rate (rate of calculous events per patient per year) (39 months)



Stone composition: more than 79% calcium oxalate; biochemical abnormality not specified
At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

5

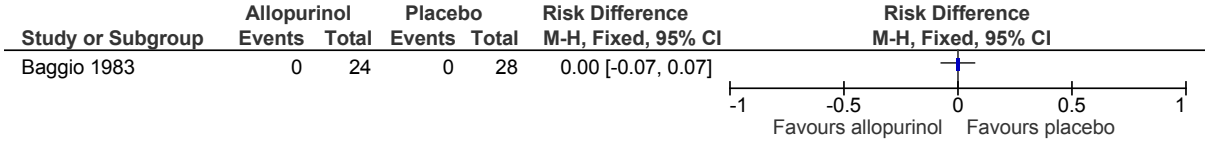
Figure 19: Recurrence (new stones) (39 months)



Stone composition: more than 79% calcium oxalate; biochemical abnormality not specified
At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

1

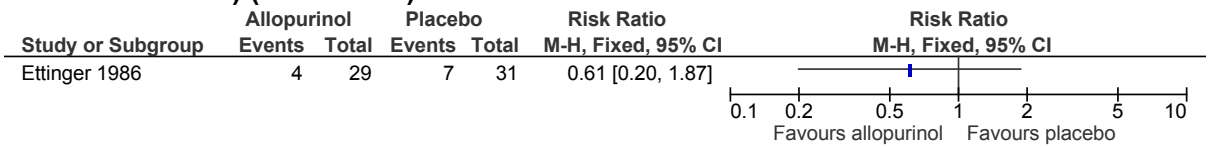
Figure 20: Recurrence (unspecified) (2 months)



Stone composition: calcium oxalate, calcium oxalate ($P0_4$) or unknown; biochemical abnormality: hypercalciuria 11.5%, hyperuricuria 9.6%, hyperoxaluria 30.8%
At baseline, included patients had passed at least one stone in the two preceding months.

2

Figure 21: Stone episodes (new calculous events – increase in stone size or new stones) (39 months)

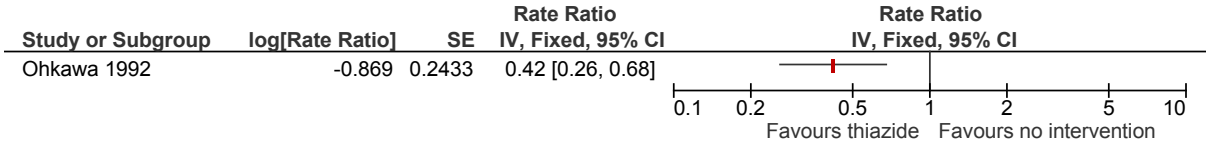


Stone composition: more than 79% calcium oxalate; biochemical abnormality not specified
At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

3

E.5 Thiazides versus no intervention in adults

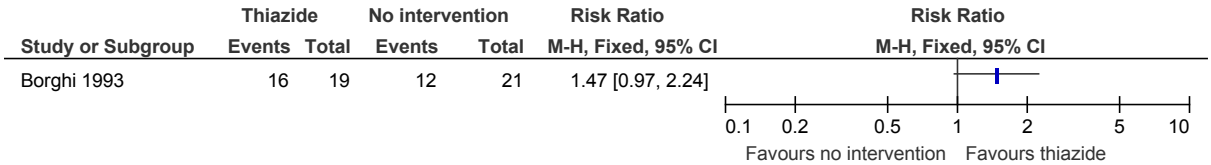
Figure 22: Recurrence rate (number of stones/patient/year) (2.21 years)



Stone composition: calcium oxalate and calcium phosphate; biochemical abnormality: hypercalciuria; at baseline included patients had single stones and multiple or recurrent stones

4

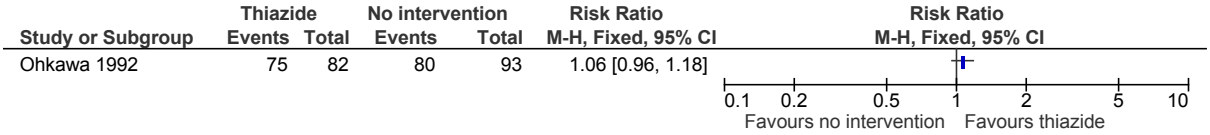
Figure 23: Recurrence (number of participants stone free) (3 years)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria
At baseline, included patients had formed at least one stone in the previous 3 years, but before treatment were calculi-free

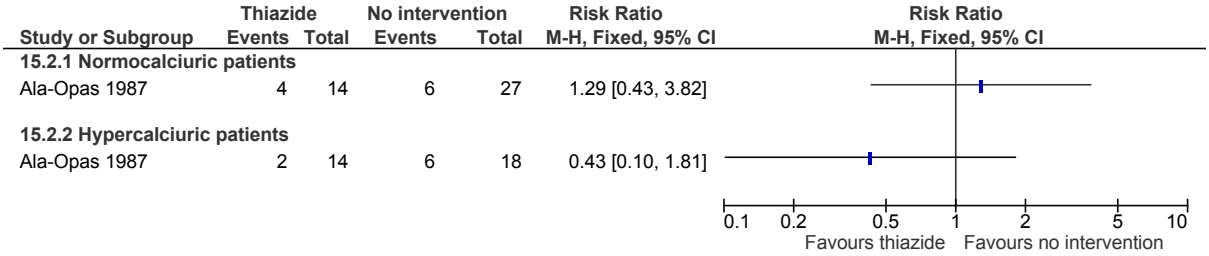
5

Figure 24: Recurrence (remission – patients without new stone formation) (2.21 years)



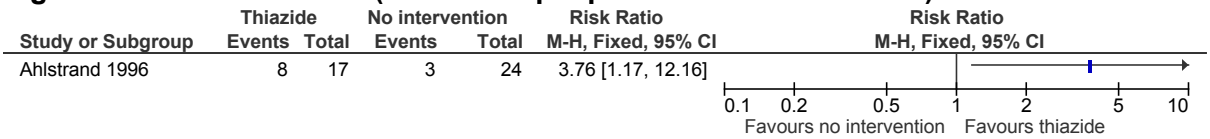
Stone composition: calcium oxalate and calcium phosphate; biochemical abnormality: hypercalciuria
At baseline included patients had single stones and multiple or recurrent stones

Figure 25: Recurrence (number of patients with recurrences) (2 years)



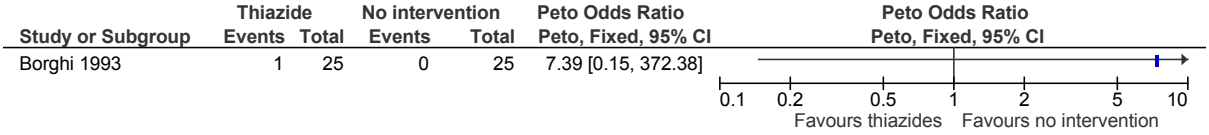
Stone composition: calcium; biochemical abnormality: all participants (hypercalciuria 43.8%)
Pre-treatment average frequency of stone formation adjusted to treatment period of 2 years: 0.466(0.187) (no intervention, normocalciuric); 0.784(0.943) (no intervention, hypercalciuric); 0.587(0.338)(thiazide, normocalciuric); 0.516(0.258)(thiazide, hypercalciuric)

Figure 26: Recurrence (number of people free from recurrence)



Stone composition: calcium; biochemical abnormality: hypercalciuria or hypomagnesiuria

Figure 27: Minor adverse events (study discontinuation due to clinical hypotension: dizziness and hypotension) (36 months)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria

At baseline, included patients had formed at least one stone in the previous 3 years, but before treatment were calculi-free

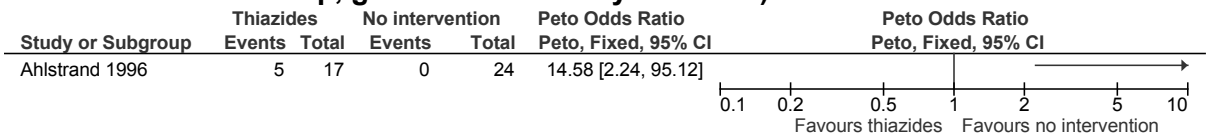
Figure 28: Minor adverse events (study discontinuation due to silent severe hypokalaemia) (36 months)

Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria

At baseline, included patients had formed at least one stone in the previous 3 years, but before treatment were calculi-free

1

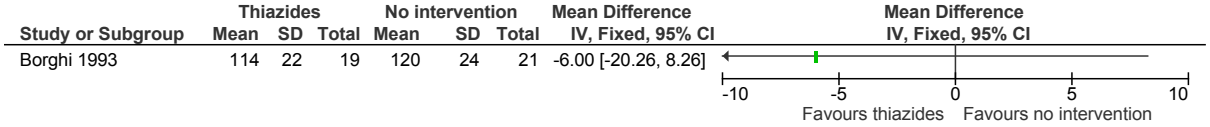
Figure 29: Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction)



Stone composition: calcium; biochemical abnormality: hypercalciuria or hypomagnesiuria

2

Figure 30: Kidney function (creatinine clearance – ml/min)



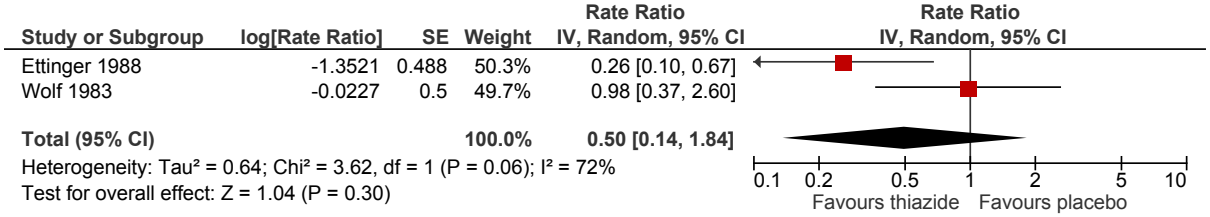
Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria

At baseline, included patients had formed at least one stone in the previous 3 years, but before treatment were calculi-free

3

4 E.6 Thiazides versus placebo in adults

Figure 31: Recurrence rate (rate of stones per patient year) (36 months)

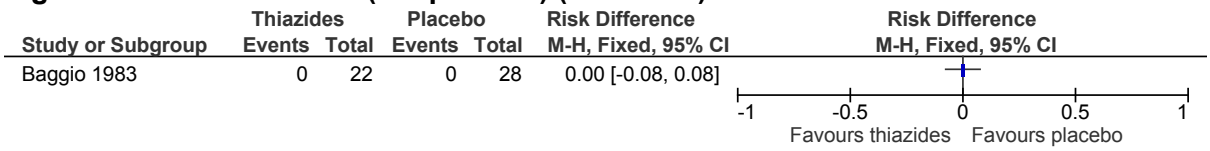


Ettinger 1998: Stone composition: exceeding 79% calcium oxalate; biochemical abnormality (thiazide/placebo groups): hypercalciuria 14.4/9.7%, hyperuricosuria 26.3/9.7%, both 23.1/16.1 %, no metabolic abnormality 38.9/64.5%. At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

Wolf 1983: Stone composition: calcium; biochemical abnormality: no well-defined metabolic cause of renal stone formation. At baseline, pre-treatment rate of stone formation over an average control period of 36 months was 0.40 stones/patient/year in thiazide group and 0.70 stones/patient/year in placebo group.

5

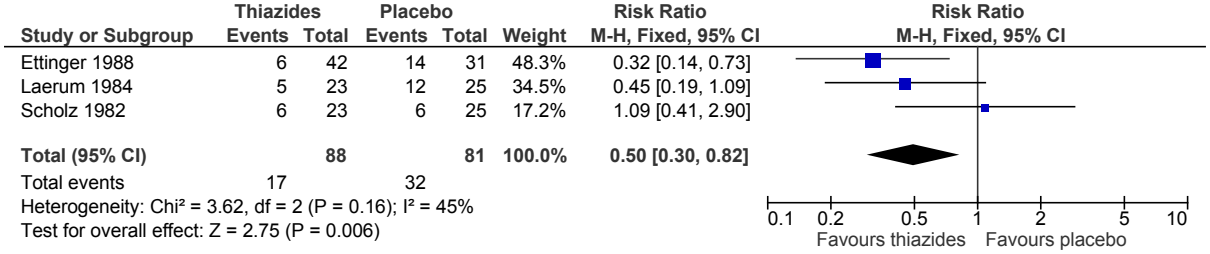
Figure 32: Recurrence (unspecified) (2 months)



Stone composition: calcium oxalate, calcium oxalate ($P0_4$) or unknown; biochemical abnormality; biochemical abnormality: hypercalciuria 18%, hyperuricuria 12%, hyperoxaluria 30%. At baseline, included patients had passed at least one stone in the two preceding months

1

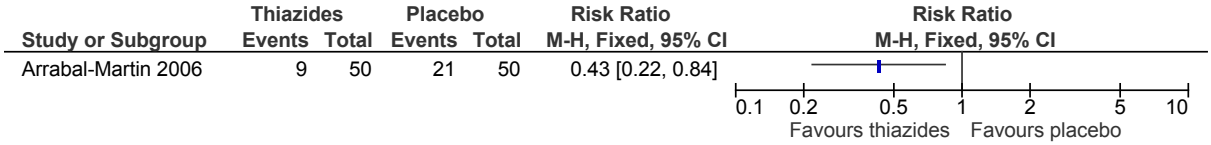
Figure 33: Recurrence (verified and probable new stone formation/spontaneous passage of newly formed stones/calculi observed) (1-3 years)



Ettinger 1998: Stone composition: exceeding 79% calcium oxalate; biochemical abnormality (thiazide/placebo groups): hypercalciuria 14.4/9.7%, hyperuricosuria 26.3/9.7%, both 23.1/16.1 %, no metabolic abnormality 38.9/64.5%. At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 yearsLaerum 1984: calcium (24 participants had calcium oxalate alone or combined with calcium phosphate); biochemical abnormality: hypercalciuria 27%, hyperuricosuria 25%
At baseline, included patients had two or more stones totally formed, with the most recent stone, associated with renal colic, having occurred during the last 2 years*Scholz 1982: stone composition: calcium; biochemical abnormality not specified; At baseline, stone formation was examined by X-ray – results not reported*
Time-point: Laerum 1984: 3 years; Scholz 1982: 1 year

2

Figure 34: Stone interventions (SWL) with previous SWL (36 months)

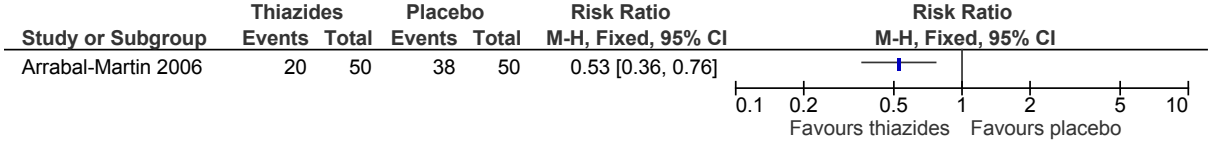


Stone composition: calcium; biochemical abnormality: hypercalciuria 38%, hypocitraturia 14%, hyperuricuria 4%, hyperoxaluria 4%, mixed 9%, no disorder 31%: not specified
At baseline, included patients had residual lithiasis 3 months after SWL (one to three fragments <4mm)

3

4

Figure 35: Stone episodes (unchanged or increased in size residual fragments) with previous SWL (36 months)



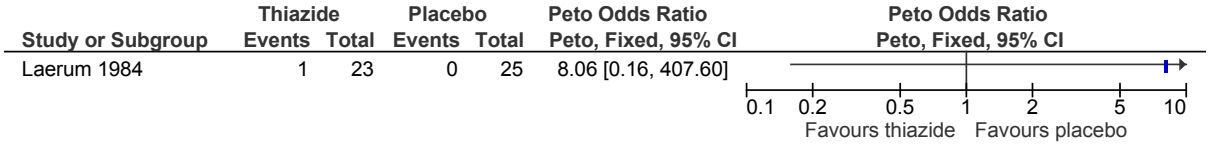
Stone composition: calcium; biochemical abnormality: hypercalciuria 38%, hypocitraturia 14%, hyperuricuria 4%, hyperoxaluria 4%, mixed 9%, no disorder 31%: not specified

At baseline, included patients had residual lithiasis 3 months after SWL (one to three fragments <4mm)

1

2

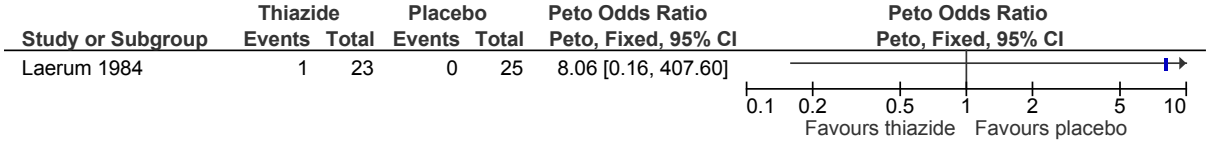
Figure 36: Minor adverse events (attack of gouty arthritis) (median 3 years)



Stone composition: calcium (24 participants had calcium oxalate alone or combined with calcium phosphate); biochemical abnormality: hypercalciuria 27%, hyperuricosuria 25%
At baseline, included patients had two or more stones totally formed, with the most recent stone, associated with renal colic, having occurred during the last 2 years

3

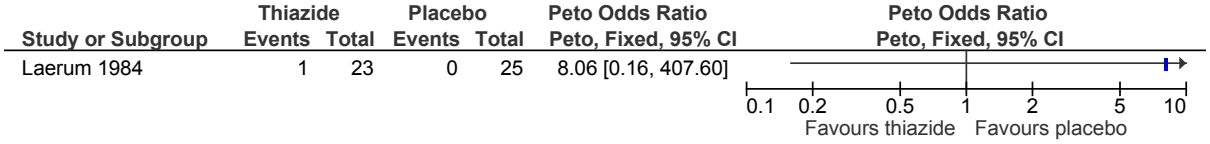
Figure 37: Minor adverse events (impotence – transient and characterised as mild) (median 3 years)



Stone composition: calcium (24 participants had calcium oxalate alone or combined with calcium phosphate); biochemical abnormality: hypercalciuria 27%, hyperuricosuria 25%
At baseline, included patients had two or more stones totally formed, with the most recent stone, associated with renal colic, having occurred during the last 2 years

4

Figure 38: Minor adverse events (hypopotassemia) (median 3 years)

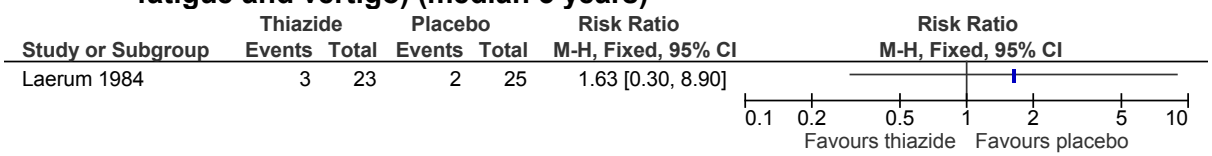


Stone composition: calcium (24 participants had calcium oxalate alone or combined with calcium phosphate); biochemical abnormality: hypercalciuria 27%, hyperuricosuria 25%
At baseline, included patients had two or more stones totally formed, with the most recent stone, associated with renal colic, having occurred during the last 2 years

5

6

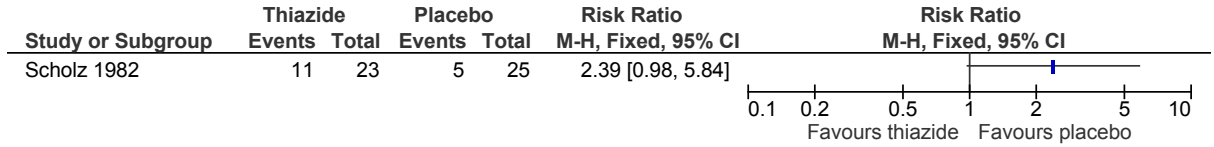
Figure 39: Minor adverse events (general discomfort as nausea, dyspepsia, fatigue and vertigo) (median 3 years)



Stone composition: calcium (24 participants had calcium oxalate alone or combined with calcium phosphate); biochemical abnormality: hypercalciuria 27%, hyperuricosuria 25%
At baseline, included patients had two or more stones totally formed, with the most recent stone, associated with renal colic, having occurred during the last 2 years

1

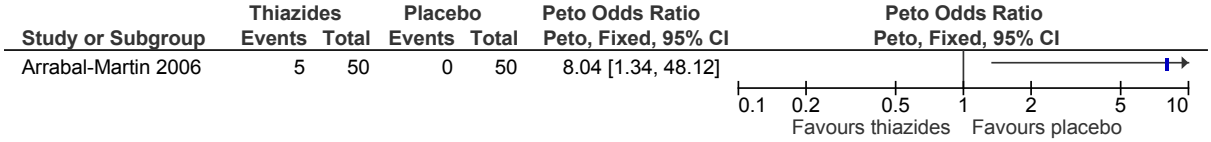
Figure 40: Minor adverse events (weariness, nausea and symptoms of low blood pressure) (12 months)



Stone composition: calcium; biochemical abnormality not specified At baseline, stone formation was examined by X-ray – results not reported

2

Figure 41: Minor adverse events (intracellular acidosis and hypocitraturia induced by hypopotassemia secondary to administration of thiazides) (36 months)



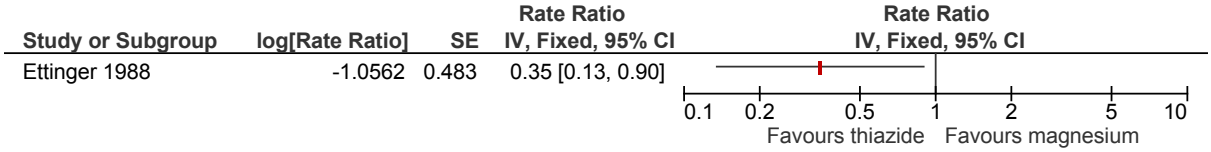
Stone composition: calcium; biochemical abnormality: hypercalciuria 38%, hypocitraturia 14%, hyperuricuria 4%, hyperoxaluria 4%, mixed 9%, no disorder 31%: not specified

At baseline, included patients had residual lithiasis 3 months after SWL (one to three fragments <4mm)

3

E.7 Thiazide versus magnesium in adults

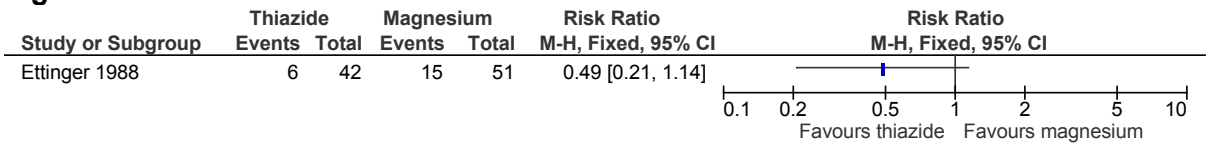
Figure 42: Recurrence rate (36 months)



Stone composition: exceeding 79% calcium oxalate; biochemical abnormality (thiazide/magnesium groups): hypercalciuria 14.4/13.8%, hyperuricosuria 26.3/8.1%, both 23.1/27.7%, no metabolic abnormality 38.9/50.5%. At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

4

Figure 43: Recurrence

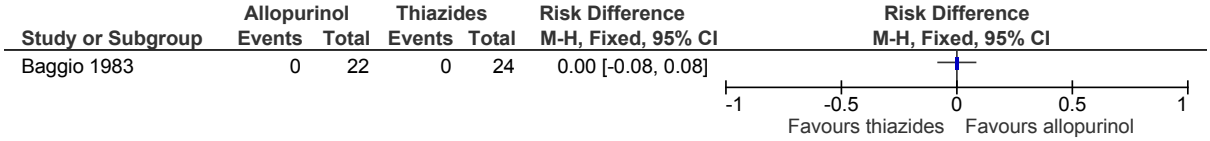


Stone composition: exceeding 79% calcium oxalate; biochemical abnormality (thiazide/magnesium groups): hypercalciuria 14.4/13.8%, hyperuricosuria 26.3/8.1%, both 23.1/27.7%, no metabolic abnormality 38.9/50.5%. At baseline, included patients had 2 or more calculi within the previous 5 years and at least 1 calculous within the previous 2 years

5

E.8 Thiazides versus allopurinol in adults

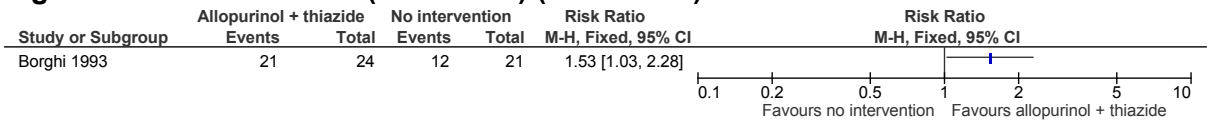
Figure 44: Recurrence (unspecified) (2 months)



Stone composition: calcium oxalate, calcium oxalate (PO_4) or unknown; biochemical abnormality: hypercalciuria 15.3%, hyperuricuria 15.2%, hyperoxaluria 28.3%. At baseline, included patients had passed at least one stone in the two preceding months

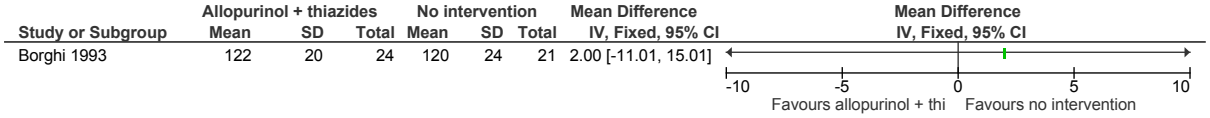
E.9 Allopurinol + thiazides versus no intervention in adults

Figure 45: Recurrence (stone-free) (36 months)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria. At baseline, included patients had formed at least one stone in the previous 3 years, but before treatment were calculi-free (intravenous pyelography and renal echography).

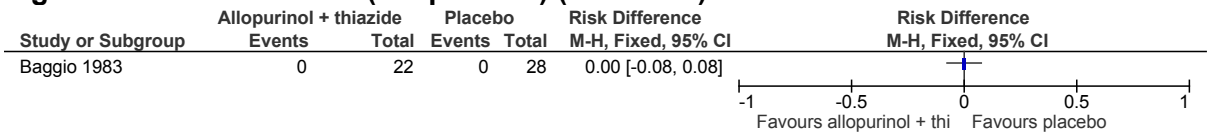
Figure 46: Kidney function (creatinine clearance – ml/min) (36 months)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria. At baseline, included patients had formed at least one stone in the previous 3 years, but before treatment were calculi-free (intravenous pyelography and renal echography).

E.10 Allopurinol + thiazides versus placebo in adults

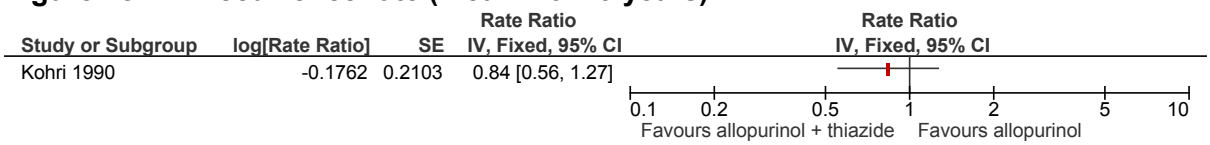
Figure 47: Recurrence (unspecified) (2 months)



Stone composition: calcium oxalate, calcium oxalate (PO_4) or unknown; biochemical abnormality: hypercalciuria 16%, hyperuricuria 14%, hyperoxaluria 34%. At baseline, included patients had passed at least one stone in the two preceding months

E.11 Allopurinol + thiazides versus allopurinol in adults

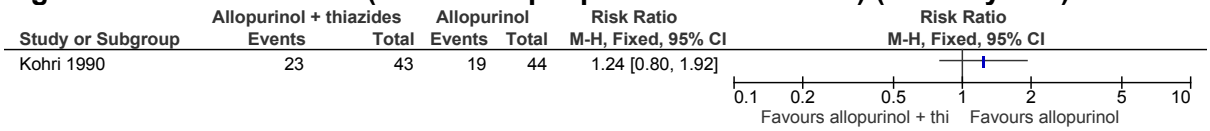
Figure 48: Recurrence rate (mean 4.6-4.9 years)



Stone composition: calcium oxalate or calcium phosphate; biochemical abnormality with or without hypercalciuria and/or hyperuricosuria. At baseline, the frequency of stone formation was patient-reported; one surgical or spontaneous pass was considered to be one episode

1

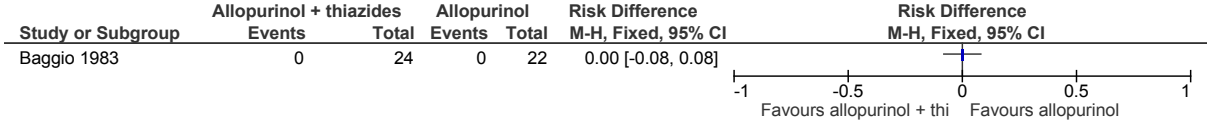
Figure 49: Recurrence (number of people with new stones) (4.6-4.9 years)



Stone composition: calcium oxalate or calcium phosphate; biochemical abnormality with or without hypercalciuria and/or hyperuricosuria. At baseline, the frequency of stone formation was patient-reported; one surgical or spontaneous pass was considered to be one episode

2

Figure 50: Recurrence (unspecified) (2 months)

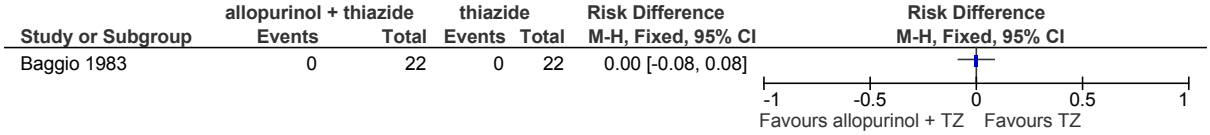


Stone composition: calcium oxalate, calcium oxalate ($P0_4$) or unknown; biochemical abnormality: hypercalciuria 13%, hyperuricuria 17.4%, hyperoxaluria 32.6%. At baseline, included patients had passed at least one stone in the two preceding months

3

E.12 Thiazides + allopurinol versus thiazides in adults

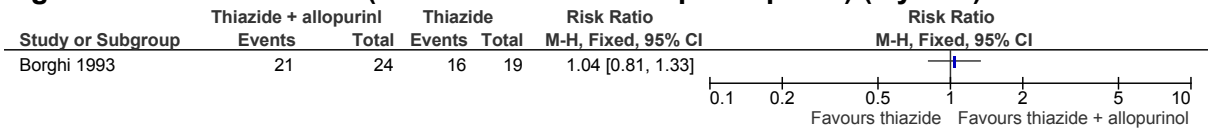
Figure 51: Recurrence (recurrence - undefined) (2 months)



Stone composition: calcium oxalate, calcium oxalate ($P0_4$) or unknown; biochemical abnormality: hypercalciuria 20.5%, hyperuricuria 20.5%, hyperoxaluria 31.8%. At baseline, included patients had passed at least one stone in the two preceding months

4

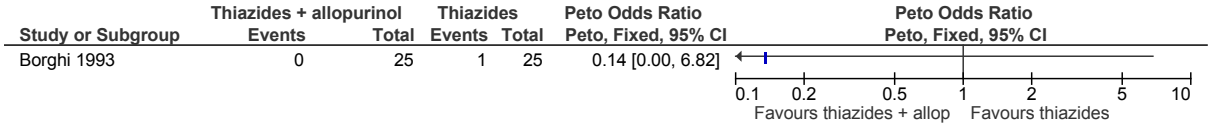
Figure 52: Recurrence (number of stone-free participants) (3 years)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria. At baseline, included patients were calculi-free

5

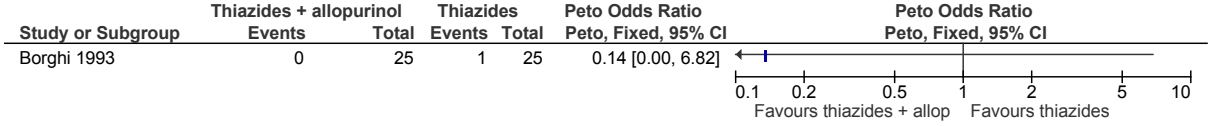
Figure 53: Minor adverse events (study discontinuation due to clinical hypotension: dizziness and hypotension) (36 months)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria. At baseline, included patients were calculi-free

1

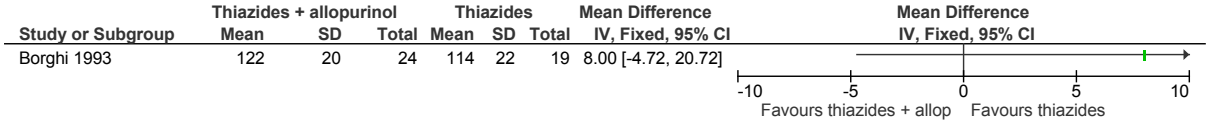
Figure 54: Minor adverse events (study discontinuation due to silent severe hypokalaemia) (36 months)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria. At baseline, included patients were calculi-free

2

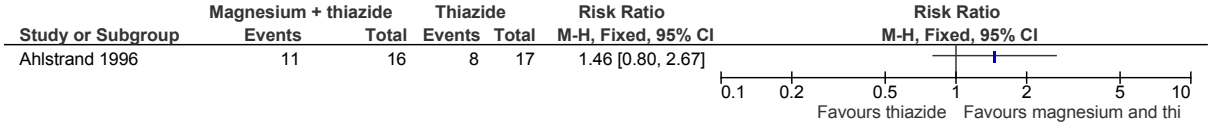
Figure 55: Kidney function (creatinine clearance – ml/min) (36 months)



Stone composition: calcium (pure calcium oxalate or <20% calcium phosphate); biochemical abnormality: hypercalciuria. At baseline, included patients were calculi-free

3 # E.13 Magnesium supplement (2460mg) + thiazides versus
4 thiazides in adults

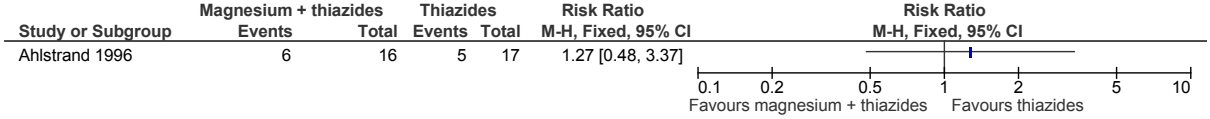
Figure 56: Recurrence (number of people free from recurrence)



Stone composition: calcium; biochemical abnormality: hypercalciuria or hypomagnesiuria; stone status at baseline not reported

5

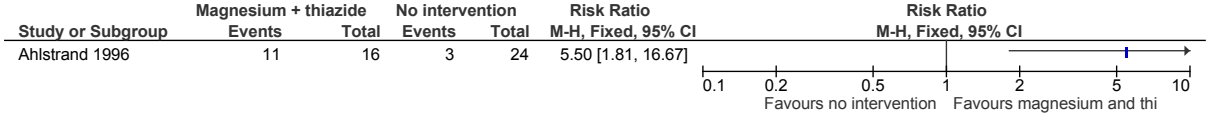
Figure 57: Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction)



Stone composition: calcium; biochemical abnormality: hypercalciuria or hypomagnesiuria; stone status at baseline not reported

E.14 Magnesium supplement (2460mg) + thiazides versus no intervention in adults

Figure 58: Recurrence (number of people free from recurrence)



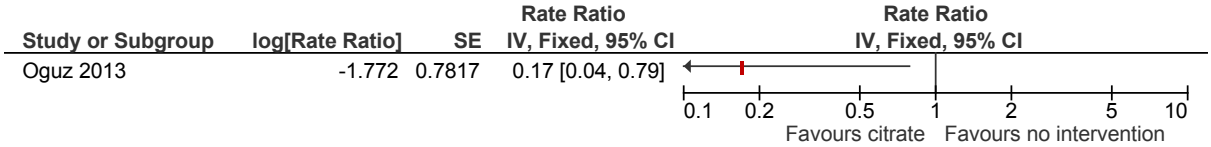
Stone composition: calcium; biochemical abnormality: hypercalciuria or hypomagnesiuria; stone status at baseline not reported

Figure 59: Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction)

Stone composition: calcium; biochemical abnormality: hypercalciuria or hypomagnesiuria; stone status at baseline not reported

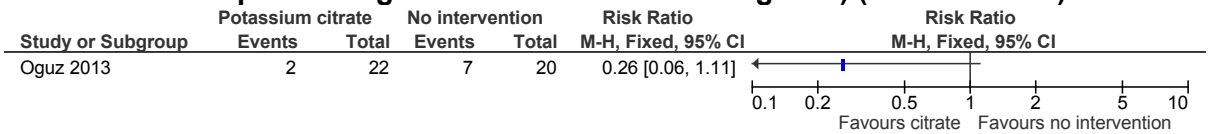
E.15 Potassium citrate versus no intervention in children (non-randomised studies)

Figure 60: Recurrence rate (stone formation rate in children after PNL, per patient per year) (12-42 months)



Stone composition: calcium oxalate; metabolic abnormality: hypocitraturia was detected in 54.5% of the citrate group and 55% of the no intervention group; hypercalciuria was detected in 50% of the citrate group and 35% of the no intervention group; hyperuricuria was detected in 22.7% of the citrate group and 20% of the no intervention group; hyperoxaluria was detected in 13.6% of the citrate group and 5% of the no intervention group

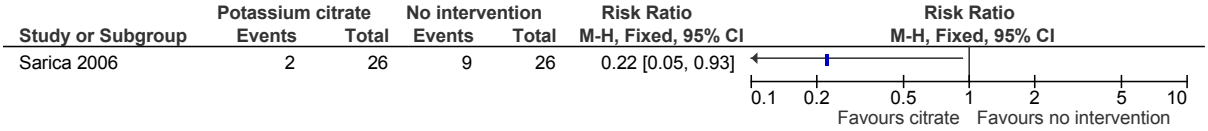
Figure 61: Recurrence (defined as new detection of stone or spontaneous passage of non-preexisting stone in children following PNL) (12-42 months)



Stone composition: calcium oxalate; metabolic abnormality: hypocitraturia was detected in 54.5% of the citrate group and 55% of the no intervention group; hypercalciuria was detected in 50% of the citrate group and 35% of the no intervention group; hyperuricuria was detected in 22.7% of the citrate group and 20% of the no intervention group; hyperoxaluria was detected in 13.6% of the citrate group and 5% of the no intervention group

1

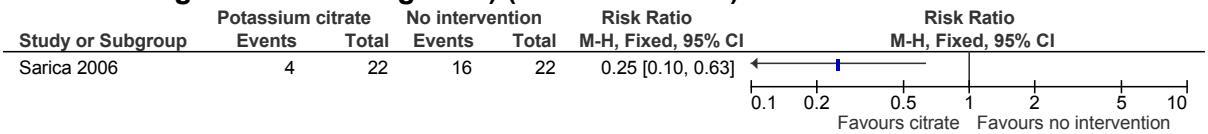
Figure 62: Recurrence (new stone formation in children stone-free following SWL) (12-36.6 months)



Stone composition: calcium-containing stones; evidence of metabolic abnormality was a study exclusion criterion. Of those experiencing recurrence, 50% had hypocitraturia and 50% had hyperoxaluria (whereby hypercitraturia was defined as <320 mg/1.73m^2 and hyperoxaluria was defined as >0.57 mg/kg)

2

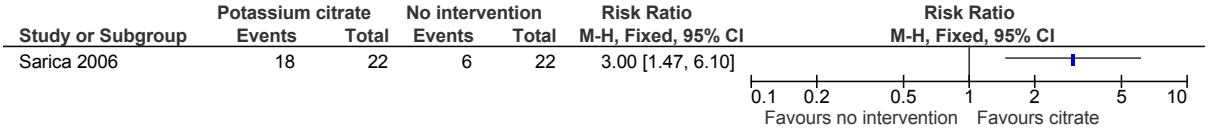
Figure 63: Recurrence (stone recurrence or regrowth in children with residual fragments following SWL) (12-36.6 months)



Stone composition: calcium-containing stones; evidence of metabolic abnormality was a study exclusion criterion. Of those experiencing regrowth, 66.7% had hypocitraturia and 25% had hyperoxaluria (whereby hypercitraturia was defined as <320 mg/1.73m^2 and hyperoxaluria was defined as >0.57 mg/kg)

3

Figure 64: Stone episodes (stone stability in children with residual fragments following SWL) (12-36.6 months)



Stone composition: calcium-containing stones; evidence of metabolic abnormality was a study exclusion criterion. Of those experiencing stone stability, 32.1% had hypocitraturia and 3.5% had hyperoxaluria (whereby hypercitraturia was defined as <320 mg/1.73m^2 and hyperoxaluria was defined as >0.57 mg/kg)

4

Appendix F: GRADE tables

Table 25: Clinical evidence profile: potassium citrate versus no intervention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Potassium citrate	No intervention	Relative (95% CI)	Absolute		
Recurrence (new stone formation of patients stone-free at baseline) (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/28 (0%)	28.6%	Peto OR 0.1 (0.02 to 0.45)	247 fewer per 1000 (from 133 fewer to 278 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence (stone free) - subgroups - Residual stones at baseline (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	8/18 (44.4%)	12.5%	RR 3.56 (0.88 to 14.35)	320 more per 1000 (from 15 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Recurrence (stone free) - subgroups - Stone-free at baseline (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	28/28 (100%)	71.4%	RR 1.39 (1.09 to 1.77)	278 more per 1000 (from 64 more to 550 more)	⊕⊕OO LOW	CRITICAL
Stone episodes (stone size unchanged in patients with residual fragments <5mm at baseline)) - subgroups (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	10/18 (55.6%)	25%	RR 2.22 (0.86 to 5.71)	305 more per 1000 (from 35 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Stone episodes (stone size increased in patients with residual fragments <5mm at baseline) (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/18 (0%)	62.5%	OR 0.05 (0.01 to 0.23)	548 fewer per 1000 (from 348 fewer to 609 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 26: Clinical evidence profile: potassium citrate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Potassium citrate	Placebo	Relative (95% CI)	Absolute		
Recurrence (new stone formation) (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/18 (27.8%)	70%	RR 0.4 (0.18 to 0.88)	420 fewer per 1000 (from 84 fewer to 574 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence (number remaining stone-free) (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/18 (72.2%)	20%	RR 3.61 (1.44 to 9.08)	522 more per 1000 (from 88 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Stone interventions (procedures to remove stones) (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/18 (5.6%)	60%	RR 0.09 (0.01 to 0.64)	546 fewer per 1000 (from 216 fewer to 594 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stone episodes (increase in stone size) (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/18 (0%)	15%	OR 0.13 (0.01 to 1.38)	128 fewer per 1000 (from 148 fewer to 46 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (unspecified; causing withdrawal from study)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/18 (11.1%)	5%	RR 2.22 (0.22 to 22.49)	61 more per 1000 (from 39 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

Kidney function (fractional excretion of magnesium - %) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11	7	-	MD 0.7 higher (1.63 lower to 3.03 higher)	⊕OOO VERY LOW	CRITICAL
Kidney function (creatinine clearance - ml/min) (follow-up 3 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious	none	11	7	-	MD 0.8 higher (64.75 lower to 66.35 higher)	⊕OOO VERY LOW	IMPORTANT
Kidney function (urine NAG activity - U/g Cr) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11	7	-	MD 0.2 lower (4.44 lower to 4.04 higher)	⊕OOO VERY LOW	IMPORTANT
Kidney function (urine proteins - g/day) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11	7	-	MD 0.04 lower (0.24 lower to 0.16 higher)	⊕OOO VERY LOW	IMPORTANT
Recurrence rate (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Rate Ratio 0.09 (0.04 to 0.20)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 27: Clinical evidence profile: magnesium supplement (650mg and 1300mg) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Magnesium supplement 650mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Recurrence rate (650mg; follow-up 36 months)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	0%	Rate Ratio 0.71 (0.3 to 1.7)	-	⊕OOO VERY LOW	CRITICAL
Recurrence rate (1300mg; follow-up 36 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	0%	Rate Ratio 0.78 (0.32 to 1.94)	-	⊕OOO VERY LOW	CRITICAL
Recurrence (calculi observed) (650mg and 1300mg doses combined; follow-up 36 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/51 (29.4%)	45.2%	RR 0.65 (0.37 to 1.16)	158 fewer per 1000 (from 285 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 28: Clinical evidence profile: allopurinol versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Allopurinol**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Recurrence rate (follow-up 39 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	-	0%	Rate Ratio 0.46 (0.16 to 1.33)	-	⊕⊕OO LOW	CRITICAL
Recurrence (unspecified) (follow-up 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/24 (0%)	0%	See comment	0 fewer per 1000 (from 73 fewer to 73 more)[1]	⊕⊕⊕O MODERATE	CRITICAL
Recurrence (new stones) (follow-up 39 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	5/29 (17.2%)	35.5%	RR 0.49 (0.19 to 1.23)	181 fewer per 1000 (from 288 fewer to 82 more)	⊕⊕OO LOW	CRITICAL
Stone episodes (number of people with stone size increase) (follow-up 39 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/29 (13.8%)	22.6%	RR 0.61 (0.2 to 1.87)	88 fewer per 1000 (from 181 fewer to 197 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 29: Clinical evidence profile: thiazides versus no intervention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Thiazides**	**No intervention**	**Relative (95% CI)**	**Absolute**		
Recurrence rate (follow-up 2.21 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	Rate Ratio 0.42 (0.26 to 0.68)	-	⊕⊕OO LOW	CRITICAL
Recurrence (number of patients with recurrences) - Normocalciuric patients (follow-up 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/14 (28.6%)	22.2%	RR 1.29 (0.43 to 3.82)	64 more per 1000 (from 127 fewer to 626 more)	⊕OOO VERY LOW	
Recurrence (number of patients with recurrences) - Hypercalciuric patients (follow-up 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/14 (14.3%)	33.3%	RR 0.43 (0.1 to 1.81)	190 fewer per 1000 (from 300 fewer to 270 more)	⊕OOO VERY LOW	
Recurrence (stone free) (follow-up 36 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	16/19 (84.2%)	57.1%	RR 1.47 (0.97 to 2.24)	268 more per 1000 (from 17 fewer to 708 more)	⊕⊕OO LOW	CRITICAL
Recurrence (patients without new stone formation) (follow-up 2.21 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/82 (91.5%)	86%	RR 1.06 (0.96 to 1.18)	52 more per 1000 (from 34 fewer to 155 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence (number of people free from recurrence) (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/17 (47.1%)	12.5%	RR 3.76 (1.17 to 12.16)	345 more per 1000 (from 21 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (study discontinuation due to clinical hypotension: dizziness and hypotension) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/25 (4%)	0%	Peto OR 7.39 (0.15 to 372.38)	40 more per 1000 (from 64 fewer to 144 more)[3]	⊕⊕OO LOW	CRITICAL
Minor adverse events (study discontinuation due to silent severe hypokalaemia) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/25 (4%)	0%	Peto OR 7.39 (0.15 to 372.38)	40 more per 1000 (from 64 more to 144 more)[3]	⊕⊕OO LOW	CRITICAL
Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction) (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/17 (29.4%)	0%	Peto OR 14.58 (2.24 to 95.12)	294 more per 1000 (from 74 more to 514 more)[3]	⊕OOO VERY LOW	CRITICAL
Kidney function (creatinine clearance - ml/min) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	19	21	-	MD 6.00 lower (20.26 lower to 8.26 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Table 30: Clinical evidence profile: thiazides versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazides	Placebo	Relative (95% CI)	Absolute		
Recurrence rate (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	0%	Rate Ratio 0.98 (0.37 to 2.6)	-	⊕OOO VERY LOW	CRITICAL
Recurrence (unspecified) (follow-up 2 to 36 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/22 (0%)	0%	See comment	0 fewer per 1000 (from 76 fewer to 76 more)[1]	⊕⊕OO LOW	CRITICAL
Recurrence (new stone defined as verified and probable new stone/ spontaneous passage of newly formed stones) (follow-up 1-3 years)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	11/46 (23.9%)	36%	RR 0.66 (0.35 to 1.26)	122 fewer per 1000 (from 234 fewer to 94 more)	⊕OOO VERY LOW	CRITICAL
Stone episodes/ interventions (SWL) (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/50 (18%)	42%	RR 0.43 (0.22 to 0.84)	239 fewer per 1000 (from 67 fewer to 328 fewer)	⊕⊕OO LOW	CRITICAL
Stone episodes/ interventions (unchanged or increase in stone fragment size) (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/50 (40%)	76%	RR 0.53 (0.36 to 0.76)	357 fewer per 1000 (from 182 fewer to 486 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Minor adverse events (attack of gouty arthritis) (follow-up 37-38 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/23 (4.3%)	0%	OR 8.06 (0.16 to 407.6)	44 more per 1000 (from 67 fewer to 154 more)[1]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (general discomfort as nausea, dyspepsia, fatigue and vertigo) (follow-up 37-38 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/23 (13%)	8%	RR 1.63 (0.3 to 8.9)	50 more per 1000 (from 56 fewer to 632 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (impotence - transient and characterised as mild) (follow-up 37-38 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/23 (4.3%)	0%	OR 8.06 (0.16 to 407.6)	44 more per 1000 (from 67 fewer to 154 more)[1]	⊕OOO VERY LOW	CRITICAL
Minor adverse events (hypopotassemia) (follow-up 38-40 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/23 (4.3%)	0%	Peto OR 8.06 (0.16 to 407.6)	-	⊕OOO VERY LOW	CRITICAL
Minor adverse events (weariness, nausea and symptoms of low blood pressure) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/23 (47.8%)	20%	RR 2.39 (0.98 to 5.84)	278 more per 1000 (from 4 fewer to 968 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (intracellular acidosis and hypocitraturia induced by hypopotassemia secondary to administration of thiazides)) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	5/50 (10%)	0%	Peto OR 8.04 (1.34 to 48.12)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 31: Clinical evidence profile: thiazides versus allopurinol

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazides	Allopurinol	Relative (95% CI)	Absolute		
Recurrence (unspecified) (follow-up 2 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/22 (0%)	0%	See comment	-	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 32: Clinical evidence profile: allopurinol + thiazides versus no intervention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Allopurinol + thiazides**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Recurrence (stone free) (follow-up 36 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	21/24 (87.5%)	57.1%	RR 1.53 (1.03 to 2.28)	303 more per 1000 (from 17 more to 731 more)	⊕⊕OO LOW	CRITICAL
Kidney function (creatinine clearance - ml/min) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	24	21	-	MD 2.00 higher (11.01 lower to 15.01 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 33: Clinical evidence profile: allopurinol + thiazides versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Allopurinol + thiazides**	**Placebo**	**Relative (95% CI)**	**Absolute**		

Recurrence (unspecified) (follow-up 2 months)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious inconsistency	none	0/22 (0%)	0%	See comment	-	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 34: Clinical evidence profile: allopurinol + thiazides versus allopurinol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Allopurinol + thiazides**	**Allopurinol**	**Relative (95% CI)**	**Absolute**		
Recurrence rate (follow-up mean 4.6-4.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	0%	Rate Ratio 0.84 (0.56 to 1.27)	-	⊕OOO VERY LOW	CRITICAL
Recurrence (number of people with stones formed during treatment)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	23/43 (53.5%)	43.2%	RR 1.24 (0.8 to 1.92)	104 more per 1000 (from 86 fewer to 397 more)	⊕OOO VERY LOW	CRITICAL
Recurrence (not specified) (follow-up 2 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/24 (0%)	0%	See comment	0 fewer per 1000 (from 81 fewer to 81 more)[1]	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 35: Clinical evidence profile: thiazides + allopurinol versus thiazides

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazides + allopurinol	Thiazides	Relative (95% CI)	Absolute		
Recurrence (unspecified) (follow-up 2 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/22 (0%)	0%	See comment[3]	0 fewer per 1000 (from 84 fewer to 43 more)[4]	⊕⊕OO LOW	CRITICAL
Recurrence (number of stone free participants) (follow-up 3 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/24 (0%)	0%	RR 1.04 (0.81 to 1.33)	34 more per 1000 (from 160 fewer to 278 more)	⊕⊕OO LOW	CRITICAL
Minor adverse events (study discontinuation due to clinical hypotension: dizziness and hypotension) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/25 (0%)	4%	Peto OR 7.39 (0.15 to 372.38)	40 fewer per 1000 (from 64 fewer to 144 more)[4]	⊕⊕OO LOW	CRITICAL
Minor adverse events (study discontinuation due to silent severe hypokalaemia) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/25 (0%)	4%	Peto OR 7.39 (0.15 to 372.38)	40 fewer per 1000 (from 64 fewer to 144 more)[4]	⊕⊕OO LOW	CRITICAL
Kidney function (creatinine clearance - ml/min) (follow-up 36 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	24	19	-	MD 8.00 higher (4.72 lower to 20.72 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Could not be calculated as there were no events in the intervention or comparison group
[4] Risk difference calculated in Review Manager

Table 36: Clinical evidence profile in adults: magnesium supplement (2460 mg) + thiazides versus thiazides

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Magnesium + thiazides**	**Thiazides**	**Relative (95% CI)**	**Absolute**		
Recurrence (number of people free from recurrence) (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/16 (68.8%)	47.1%	RR 1.46 (0.8 to 2.67)	217 more per 1000 (from 94 fewer to 787 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction) (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/16 (37.5%)	29.4%	RR 1.28 (0.48 to 3.37)	82 more per 1000 (from 153 fewer to 697 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 37: Clinical evidence profile in adults: magnesium supplement (2460 mg) + thiazides versus no intervention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Magnesium + thiazides**	**No intervention**	**Relative (95% CI)**	**Absolute**		
Recurrence (number of people free from recurrence) (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/17 (47.1%)	12.5%	RR 3.76 (1.17 to 12.16)	345 more per 1000 (from 21 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Minor adverse events (treatment discontinued due to side effects including orthostatic reactions, dizziness, gastrointestinal symptoms, muscle cramp, gout and erectile dysfunction) (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/16 (37.5%)	0%	Peto OR 17.6 (3.06 to 101.18)	375 more per 1000 (from 138	⊕OOO VERY LOW	CRITICAL

										more to 612 more)[3]		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Risk difference calculated in Review Manager

Table 38: Clinical evidence profile in children: potassium citrate versus no intervention (non-randomised studies)

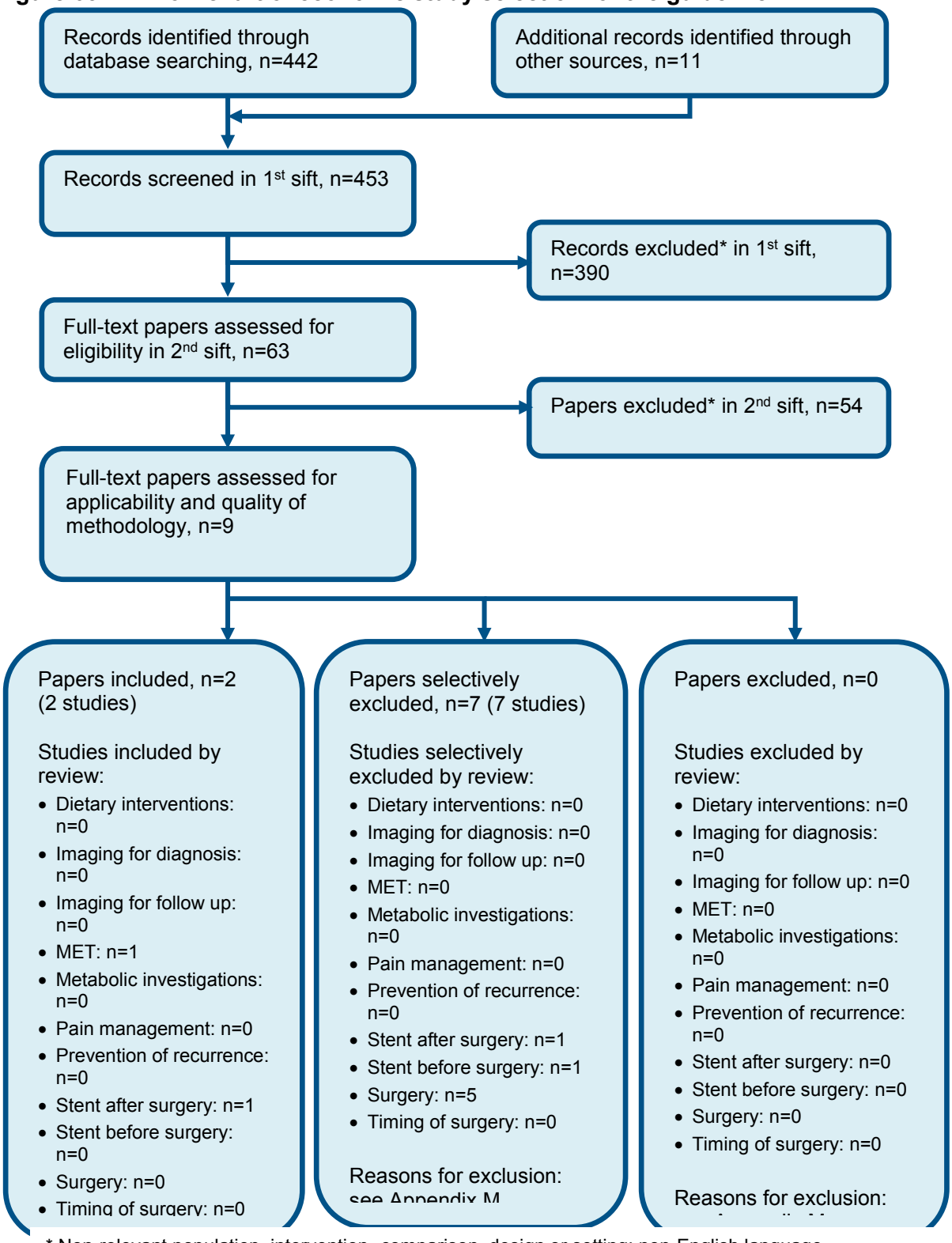
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Potassium citrate	No intervention	Relative (95% CI)	Absolute		
Recurrence rate (stone formation rate in children after PNL, per patient per year) (follow-up 12-42 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Rate Ratio 0.17 (0.04 to 0.79)	-	⊕OOO VERY LOW	CRITICAL
Recurrence (defined as new detection of stone or spontaneous passage of non-preexisting stone in children following PNL) (follow-up 12-42 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/22 (9.1%)	35%	RR 0.26 (0.06 to 1.11)	259 fewer per 1000 (from 329 fewer to 39 more)	⊕OOO VERY LOW	CRITICAL
Recurrence (new stone formation in children stone-free following SWL) (follow-up 12-36.6 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/26 (7.7%)	34.6%	RR 0.22 (0.05 to 0.93)	270 fewer per 1000 (from 24 fewer to 329 fewer)	⊕OOO VERY LOW	CRITICAL
Recurrence (stone recurrence or regrowth in children with residual fragments following SWL) (follow-up 12-36.6 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/22 (18.2%)	72.7%	RR 0.25 (0.1 to 0.63)	545 fewer per 1000 (from 269 fewer to 654 fewer)	⊕OOO VERY LOW	CRITICAL

Stone episodes (stone stability in children with residual fragments following SWL) (follow-up 12-36.6 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/22 (81.8%)	27.3%	RR 3 (1.47 to 6.1)	546 more per 1000 (from 128 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 65: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 39: Studies excluded from the clinical review

Study	Exclusion reason
Ahlstrand 1984[1]	Incorrect study design
Ahlstrand 1984[3]	Incorrect study design
Ahmed 2008[4]	Incorrect study design
Ahn 1997[5]	Not in English
Allie-Hamdulay 2005[8]	No relevant outcomes
Al-Mosawi 2005[6]	Incorrect comparison
Alon 2004[9]	No relevant outcomes
Amancio 2016[10]	Incorrect study design
Anon 2015[135]	Incorrect interventions
Anonymous 2011[11]	Incorrect study design
Aras 2008[12]	Incorrect comparison
Assimos 2017[14]	Incorrect study design
Bach 1980[15]	Not in English
Baxmann 2003[18]	Incorrect interventions
Berg 1990[20]	Not in English
Berg 1992[19]	Incorrect study design
Bergsland 2013[21]	Not guideline condition
Berthoux 1981[22]	Abstract only
Bevilacqua 2005[23]	Incorrect study design
Bevill 2017[24]	Incorrect study design
Brardi 2012[26]	Not in English
Brocks 1982[27]	Not in English
Butz 1982[29]	Not in English
Carvalho 2017[30]	Inappropriate comparison
Ceylan 2005[31]	Incorrect study design
Churchill 1985[32]	Incorrect study design
Cicerello 1994[33]	Incorrect comparison
Coe 1977[34]	Incorrect study design
Conte Visús 1994[35]	Not in English
Daudon 2003[36]	Incorrect comparison
Dos Santos 2016[37]	Incorrect study design
Elderwy 2014[39]	Incorrect interventions. Inappropriate comparison

Study	Exclusion reason
El-gamal 2012[38]	Incorrect comparison
Elmaci 2014[40]	Incorrect study design
Elomaa 1983[41]	Incorrect study design
Escribano 2009[42]	Systematic review is not relevant to review question or unclear PICO
Escribano 2014[43]	Systematic review: study designs inappropriate
Ettinger 1979[44]	Incorrect interventions
Ettinger 1997[46]	Incorrect comparison
Fernández Rodríguez 2001[49]	Not in English
Fernández-Rodríguez 2006[48]	Not in English
Ferroni 2017[50]	Incorrect comparison
Fink 2013[51]	Incorrect study design
Gheissari 2012[52]	Incorrect study design
Gökta 2012[53]	Incorrect comparison
Gurgoze 2011[54]	Incorrect study design
Hallson 1976[55]	Incorrect study design
Hauser 1990[56]	Incorrect study design
Heaney 2008[57]	Incorrect study design
Hofbauer 1994[58]	Incorrect comparison
Izol 2013[59]	Incorrect comparison
Jaeger 1986[60]	Not in English
Jiménez Verdejo 2001[61]	Not in English
Johansson 1982[62]	Incorrect study design
Kang 2007[64]	Incorrect comparison
Knoll 1988[65]	Incorrect study design
Koyuncu 2011[67]	Incorrect study design
Krishna reddy 2014[68]	Incorrect comparison
Lojanapiwat 2011[71]	Incorrect comparison
Mahmood 2008[72]	Incorrect study design
Malihi 2016[73]	Incorrect study design
Marangella 1983[74]	Incorrect study design
Martins 1996[75]	Crossover study. Not review population. Not guideline condition
Miano 1985[76]	Incorrect study design
Milosevic 2014[77]	Incorrect study design
Morimoto 1996[78]	Incorrect study design
Mortensen 1986[79]	Incorrect interventions
Naseri 2011[80]	Incorrect study design
Niroomand 2016[82]	Inappropriate comparison
Onal 2013[85]	Incorrect study design
Pak 1973[91]	Incorrect study design
Pak 1982[86]	Incorrect study design
Pak 1985[88]	Incorrect study design
Pak 1986[90]	Incorrect study design
Pak 1992[89]	Crossover study
Pak 1999[87]	Incorrect study design
Paulson 1972[92]	Incorrect study design

Study	Exclusion reason
Pearle 1999[94]	Incorrect study design
Pearle 2001[93]	Incorrect study design
Phillips[95]	Systematic review checked for references
Premgamone 2001[96]	Incorrect comparison
Preminger 1985[97]	Incorrect study design
Preminger 1988[98]	Incorrect study design
Qaseem 2014[99]	Incorrect study design
Robertson 1985[101]	No relevant outcomes
Sakhaee 1983[103]	Crossover study
Scholz 1980[105]	Not in English
Schwille 1988[108]	Incorrect study design
Schwille 1992[107]	Not in English
Scott 1989[109]	Incorrect study design
Sfoungaristos 2015[110]	Incorrect study design
Sharma 1992[111]	Incorrect study design
Shim 2014[112]	Incorrect comparison
Singh 2011[113]	Incorrect interventions
Singh 2012[114]	Incorrect interventions
Skolarikos 2015[115]	Incorrect study design
Smith 1973[116]	Incorrect study design
Smith 1977[117]	Unclear reporting of data
Smith 1983[118]	Unclear reporting of data
Tasian 2014[120]	Incorrect study design
Tekin 2002[121]	Incorrect study design
Thomas 2007[122]	Incorrect study design
Tiselius 1993[123]	Incorrect study design
Tomson 1995[124]	Incorrect study design
Ulmann 1984[126]	Not in English
Vigen 2011[127]	Incorrect study design
Wilhelm 2016[128]	Not in English
Wilson. 1984[129]	Incorrect study design
Wolf 1983[131]	Abstract only
Worcester 2008[132]	Incorrect study design
Yatzidis 1985[133]	Incorrect interventions
Yendt 1978[134]	Incorrect study design
Yuan 1987[136]	Not in English
Zöllner 1967[137]	Not in English

I.2 Excluded health economic studies

None

Appendix J: Research recommendations

J.1 Preventive treatments for patients with small residual kidney stone fragments following shockwave lithotripsy

Research question: What is the clinical and cost-effectiveness of empirical potassium citrate or bendroflumethiazide as preventative therapies for patients with small residual fragments following shockwave lithotripsy to renal and ureteric stones.

Why this is important:

Renal and ureteric stones affect a large proportion of the population at some time in their life and can be associated with extremely severe pain and significant morbidity. The incidence of kidney stones is increasing significantly as they are linked to poor diet, obesity, diabetes and hypertension. About half of stone formers will develop a further stone in the future. The most commonly used treatment for renal and ureteric stones is shockwave lithotripsy. This is a clinically effective and cost-effective treatment for the more common smaller stones. Sometimes following lithotripsy treatment, small fragments don't washout completely and these patients are at an increased risk of future stone related problems such as pain, infections, or the need for further interventions. Previous studies have given some evidence that inexpensive empirical preventative treatments might help avoid such problems but the evidence quality is low, some of the evidence is contradictory and such preventative treatments have not been widely adopted in this scenario. A study to compare the clinical effectiveness and cost effectiveness of these approaches is required.

Table 40: Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults with residual renal and ureteric stone fragments post shockwave lithotripsy (1-3 fragments less than 4mm in size) **Intervention(s):** o bendroflumethiazide 5mg o potassium citrate 10ml tds o no treatment **Comparison:** each other **Outcome(s):** Primary: Stone related events (spontaneous stone passage, flank pain, infections, new stone growth or the need for intervention) Secondary: Pain, disability, quality of life, EQ-5D-3L, cost per QALY, side effects, compliance FU: 36months
Importance to patients or the population	Renal and ureteric stones are very common and the source of significant morbidity. Shockwave lithotripsy provides a cost-effective low morbidity treatment for these stones and is the most commonly used intervention. Nevertheless, small residual fragments sometimes remain after treatment. Residual stones of 4mm or larger are usually offered further lithotripsy or ureteroscopy. Smaller fragments are often managed conservatively but there is evidence that such patients may be at an increased risk of future stone related events. Effective simple preventative strategies to reduce this risk would prevent morbidity to the patient.

Relevance to NICE guidance	This research will reduce the existing uncertainty regarding the effectiveness and cost-effectiveness of empirical preventative strategies in patients with residual fragments following lithotripsy.
Relevance to the NHS	A clear recommendation regarding empirical stone prevention in this group will offer clinicians clearer guidance on best care for patients with residual stone fragments following lithotripsy. The 2 agents tested are both very cheap so this has the potential to improve stone prevention, improve quality of life and reduce the associated healthcare costs.
National priorities	There is a strong link between diabetes, obesity and kidney stones and limiting the impact of these conditions is one of the top research priorities of the NHS. It is also a priority to test interventions and maximize effectiveness and cost-effectiveness.
Current evidence base	2 small RCTs show that potassium citrate reduces stone recurrence in patients with residual fragments compared to no intervention but the evidence quality is low. Several small RCTs have studied the effects of thiazides in such patients but the outcomes measures and effects are mixed. No cost effectiveness studies have been performed. There is therefore a need for a conclusive study into the effectiveness and cost effectiveness of empirical preventative therapies for patients with small residual renal or ureteric stone fragments following shockwave lithotripsy.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Randomised controlled trial with corresponding economic analysis.
Feasibility	The trial is feasible and should be straightforward to carry out. There are a large number of such patients and a UK kidney stone trial network has already been established. There may be difficulty getting an effective placebo because of the nature of potassium citrate solution so no treatment has been proposed as the control arm.
Other comments	Patients will need some blood tests to monitor their potassium levels
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

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